National Heart, Lung, and Blood Institute

National Asthma Education and Prevention Program

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma

Full Report 2007

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

CONTENTS

Acknowledgements and Financial Disclosures xi
Acronyms and Abbreviations xix
Preface xxii
Section 1, Introduction 1
Overall Methods Used To Develop This Report 2
Background 2
Systematic Evidence Review Overview 3
Inclusion/Exclusion Criteria 3
Search Strategies 3
Literature Review Process 3
Preparation of Evidence Tables 6
Ranking the Evidence 7
Panel Discussion 8
Report Preparation 8
References 9

Section 2, Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma 11
Key Points: Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma 11
Key Differences From 1997 and 2002 Expert Panel Reports 12
Introduction 12
Definition of Asthma 12
Pathophysiology and Pathogenesis of Asthma 14
Pathophysiologic Mechanisms in the Development of Airway Inflammation 16
Inflammatory Cells 16
Inflammatory Mediators 18
Immunoglobulin E 19
Implications of Inflammation for Therapy 19
Pathogenesis 20
Host Factors 20
Environmental Factors 22
Natural History of Asthma 23
Natural History of Persistent Asthma 24
Children 24
Adults 25
Summary 27
Effect of Interventions on Natural History of Asthma 27
Implications of Current Information About Pathophysiology and Pathogenesis, and Natural History for Asthma Management 28
References 28

Section 3, The Four Components of Asthma Management 35
Introduction 35
Section 3, Component 1: Measures of Asthma Assessment and Monitoring..... 36
Introduction 36
Overview of Assessing and Monitoring Asthma Severity, Control, and Responsiveness in Managing Asthma 36
Key Points: Overview of Measures of Asthma Assessment and Monitoring 36
Key Differences From 1997 and 2002 Expert Panel Reports 37
Diagnosis of Asthma 40
Key Points: Diagnosis of Asthma 40
Key Differences From 1997 and 2002 Expert Panel Reports 41
Medical History 41
Physical Examination 42
Pulmonary Function Testing (Spirometry) 43
Differential Diagnosis of Asthma 45
Initial Assessment: Characterization of Asthma and Classification of Asthma Severity 47
Key Points: Initial Assessment of Asthma 47
Key Differences From 1997 and 2002 Expert Panel Reports 48
Identify Precipitating Factors 48
Identify Comorbid Conditions That May Aggravate Asthma 49
Assess the Patient's Knowledge and Skills for Self-Management 49
Classify Asthma Severity 49
Assessment of Impairment 50
Assessment of Risk 51
Periodic Assessment and Monitoring of Asthma Control Essential for Asthma Management 52
Key Points: Periodic Assessment of Asthma Control 52
Key Differences From 1997 and 2002 Expert Panel Reports 54
Goals of Therapy: Asthma Control 55
Asthma Control 55
Measures for Periodic Assessment and Monitoring of Asthma Control 56
Monitoring Signs and Symptoms of Asthma 57
Monitoring Pulmonary Function 58
Spirometry 58
Peak Flow Monitoring 59
Peak Flow Versus Symptom-Based Monitoring Action Plan 60
Monitoring Quality of Life 61
Monitoring History of Asthma Exacerbations 63
Monitoring Pharmacotherapy for Adherence and Potential Side Effects 63
Monitoring Patient–Provider Communication and Patient Satisfaction 63
Monitoring Asthma Control With Minimally Invasive Markers and Pharmacogenetics 64
Pharmacogenetics in Managing Asthma 66
Methods for Periodic Assessment and Monitoring of Asthma Control 66
Clinician Assessment 67
Patient Self-Assessment 67
Population-Based Assessment 67
Referral to an Asthma Specialist for Consultation or Comanagement 68
References 82

Section 3, Component 2: Education for a Partnership in Asthma Care 93
Key Points: Education for a Partnership in Asthma Care 93
Key Points: Provider Education 95
Key Differences From 1997 and 2002 Expert Panel Reports 95
Introduction 96
Asthma Self-Management Education at Multiple Points of Care 97
Clinic/Office-Based Education 97
Adults—Teach Asthma Self-Management Skills To Promote Asthma Control 97
Written Asthma Action Plans, Clinician Review, and Self-Monitoring 98
Patient–Provider Partnership 99
Health Professionals Who Teach Self-Management 100
Education With Multiple Sessions 101
Children—Teach Asthma Self-Management Skills To Promote Asthma Control 101
Emergency Department/Hospital-Based Education 102
Adults 102
Emergency Department Asthma Education 103
Hospital-Based Asthma Education 104
Children 105
Educational Interventions by Pharmacists 106
Educational Interventions in School Settings 107
Community-Based Interventions 108
Asthma Education 108
Home-Based Interventions 109
Home-Based Asthma Education for Caregivers 109
Home-Based Allergen-Control Interventions 109
Other Opportunities for Asthma Education 111
Education for Children Using Computer-Based Technology 111
Education on Tobacco Avoidance for Women Who Are Pregnant and Members of Households With Infants and Young Children 112
Case Management for High-Risk Patients 113
Cost-Effectiveness 114
Tools for Asthma Self-Management 115
Role of Written Asthma Action Plans for Patients Who Have Asthma 115
Role of Peak Flow Monitoring 120
Goals of Asthma Self-Management Education and Key Educational Messages 121
Establish and Maintain a Partnership 124
Teach Asthma Self-Management 125
Jointly Develop Treatment Goals 131
Assess and Encourage Adherence to Recommended Therapy 131
Tailor Education to the Needs of the Individual Patient 133
Knowledge and Beliefs 133
Health Literacy 134
Cultural/Ethnic Considerations 135
Maintain the Partnership 135
Asthma Education Resources 140
Provider Education 141
Methods of Improving Clinician Behaviors 141
Implementing Guidelines—Recommended Practices 141
Communication Techniques 143
Methods of Improving System Supports 144
Clinical Pathways 144
Clinical Decision Supports 145
References 146

Section 3, Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma 165
Key Points: Control of Environmental Factors and Comorbid Conditions That Affect Asthma 165
Key Differences From 1997 Expert Panel Report 166
Introduction 167
Inhalant Allergens 167
Diagnosis—Determine Relevant Inhalant Sensitivity 167
Management—Reduce Exposure 169
Immunotherapy 172
Assessment of Devices That May Modify Indoor Air 174
Occupational Exposures 175
Irritants 175
Environmental Tobacco Smoke 175
Indoor/Outdoor Air Pollution and Irritants 176
Formaldehyde and Volatile Organic Compounds 176
Gas Stoves and Appliances 176
Comorbid Conditions 177
Allergic Bronchopulmonary Aspergillosis 177
Gastroesophageal Reflux Disease 178
Obesity 179
Obstructive Sleep Apnea 179
Rhinitis/Sinusitis 180
Stress, Depression, and Psychosocial Factors in Asthma 180
Other Factors 181
Medication Sensitivities 181
Aspirin 181
Beta-Blockers 182
Sulfite Sensitivity 182
Infections 182
Viral Respiratory Infections 182
Bacterial Infections 183
Influenza Infection 183
Female Hormones and Asthma 183
Diet 184
Primary Prevention of Allergic Sensitization and Asthma 184
References 190

Section 3, Component 4: Medications 213
Key Points: Medications 213
Key Differences From 1997 and 2002 Expert Panel Reports 215
Introduction 215
Overview of the Medications 216
Long-Term Control Medications 216
Inhaled Corticosteroids 216
Mechanism 216
Inhaled Corticosteroid Insensitivity 217
Efficacy of Inhaled Corticosteroids as Compared to Other Long-Term Control Medications as Monotherapy 217
Efficacy of Inhaled Corticosteroid and Adjunctive Therapy (Combination Therapy) 217
Dose-Response and Delivery Device 218
Variability in Response and Adjustable Dose Therapy 219
Safety of Inhaled Corticosteroids 220

Key Points: Safety of Inhaled Corticosteroids 220
Key Points: Inhaled Corticosteroids and Linear Growth in Children 222
Oral Systemic Corticosteroids 224
Cromolyn Sodium and Nedocromil 224
Immunomodulators 225
Omalizumab 225
Antibiotics 226
Others 226
Leukotriene Modifiers 227
Inhaled Long-Acting Beta$_2$-Agonists 229
Safety of Long-Acting Beta$_2$-Agonists 231
Key Points: Safety of Inhaled Long-Acting Beta$_2$-Agonists 231
Methylxanthines 234
Tiotropium Bromide 235
Quick-Relief Medications 235
Anticholinergics 235
Inhaled Short-Acting Beta$_2$-Agonists 235
Safety of Inhaled Short-Acting Beta$_2$-Agonists 236
Key Points: Safety of Inhaled Short-Acting Beta$_2$-Agonists 236
Systemic Corticosteroids 237
Route of Administration 238
Alternatives to CFC-Propelled MDIs 238
Spacers and Valved Holding Chambers 239
Complementary and Alternative Medicine 240
Key Points: Complementary and Alternative Medicine 240
Acupuncture 240
Chiropractic Therapy 241
Homeopathy and Herbal Medicine 241
Breathing Techniques 241
Relaxation Techniques 242
Yoga 242
References 252

Section 4, Managing Asthma Long Term: Overview 277
Key Points: Managing Asthma Long Term 277
Key Differences From 1997 and 2002 Expert Panel Reports 278
Introduction 279
Section 4, Managing Asthma Long Term in Children 0–4 Years of Age and 5–11 Years of Age 281
Diagnosis and Prognosis of Asthma in Children 281
Diagnosis of Asthma 281
Prognosis of Asthma 281
Prevention of Asthma Progression 282
Monitoring Asthma Progression 283
Treatment: Principles of Stepwise Therapy in Children 284
Achieving Control of Asthma 285
Selecting Initial Therapy 285
Adjusting Therapy 286
Maintaining Control of Asthma 288
Key Points: Inhaled Corticosteroids in Children 289
Key Points: Managing Asthma in Children 0–4 Years of Age 289

Treatment: Pharmacologic Issues for Children 0–4 Years of Age 290
FDA Approval 291
Delivery Devices 291
Treatment: Pharmacologic Steps for Children 0–4 Years of Age 291
Intermittent Asthma 292
Step 1 Care, Children 0–4 Years of Age 292
Persistent Asthma 293
Step 2 Care, Children 0–4 Years of Age 293
Step 3 Care, Children 0–4 Years of Age 294
Step 4 Care, Children 0–4 Years of Age 295
Step 5 Care, Children 0–4 Years of Age 296
Step 6 Care, Children 0–4 Years of Age 296
Key Points: Managing Asthma in Children 5–11 Years of Age 296
Treatment: Special Issues for Children 5–11 Years of Age 297
Pharmacologic Issues 297
School Issues 298
Sports and Exercise Issues 298
Treatment: Pharmacologic Steps for Children 5–11 Years of Age 299
Intermittent Asthma 299
Step 1 Care, Children 5–11 Years of Age 299
Persistent Asthma 300
Step 2 Care, Children 5–11 Years of Age 300
Step 3 Care, Children 5–11 Years of Age 301
Step 4 Care, Children 5–11 Years of Age 303
Step 5 Care, Children 5–11 Years of Age 303
Step 6 Care, Children 5–11 Years of Age 303
References 319

Section 4, Managing Asthma Long Term in Youths ≥ 12 Years of Age and Adults 326
Key Points: Managing Asthma Long Term in Youths ≥ 12 Years of Age and Adults 326
Section 4, Stepwise Approach for Managing Asthma in Youths ≥ 12 Years of Age and Adults 328
Treatment: Principles of Stepwise Therapy in Youths ≥ 12 Years of Age and Adults 328
Achieving Control of Asthma 329
Selecting Initial Therapy for Patients Not Currently Taking Long-Term Control Medications 329
Adjusting Therapy 329
Impairment Domain 330
Risk Domain 330
Maintaining Control of Asthma 331
Treatment: Pharmacologic Steps 333
Intermittent Asthma 333
Step 1 Care 333
Persistent Asthma 334
Step 2 Care, Long-Term Control Medication 335
Step 3 Care, Long-Term Control Medications 336
Step 4 Care, Long-Term Control Medications 338
Step 5 Care, Long-Term Control Medications 338
Step 6 Care, Long-Term Control Medications 339
Special Issues for Adolescents 339
Assessment Issues 339
Treatment Issues 340

School Issues 340
Sports Issues 340
Special Issues for Older Adults 341
Assessment Issues 341
Treatment Issues 341
References 353

Section 4, Managing Asthma Long Term—Special Situations 362
Introduction 362
Exercise-Induced Bronchospasm 362
Diagnosis 362
Management Strategies 363
Surgery and Asthma 364
Pregnancy and Asthma 364
Racial and Ethnic Disparity in Asthma 365
References 367

Section 5, Managing Exacerbations of Asthma 372
Key Points: Managing Exacerbations of Asthma 372
Key Differences From 1997 and 2002 Expert Panel Reports 373
Introduction 373
General Considerations 375
Treatment Goals 377
Home Management of Asthma Exacerbations 380
Pre-hospital Management of Asthma Exacerbations 383
Emergency Department and Hospital Management of Asthma Exacerbations 384
Assessment 384
Treatment 391
Repeat Assessment 395
Hospitalization 395
Impending Respiratory Failure 396
Patient Discharge 398
References 405

For More Information 415

List of Boxes And Figures

FIGURE 1–1. LITERATURE RETRIEVAL AND REVIEW PROCESS: BREAKDOWN BY COMMITTEE 4
FIGURE 1–2. LITERATURE RETRIEVAL AND REVIEW PROCESS: OVERALL SUMMARY 6

BOX 2–1. CHARACTERISTICS OF CLINICAL ASTHMA....12
FIGURE 2–1. THE INTERPLAY AND INTERACTION BETWEEN AIRWAY INFLAMMATION AND THE CLINICAL SYMPTOMS AND PATHOPHYSIOLOGY OF ASTHMA 13
FIGURE 2–2. FACTORS LIMITING AIRFLOW IN ACUTE AND PERSISTENT ASTHMA....15
BOX 2–2. FEATURES OF AIRWAY REMODELING....16
FIGURE 2–3. AIRWAY INFLAMMATION....17
FIGURE 2–4. HOST FACTORS AND ENVIRONMENTAL EXPOSURES 20
FIGURE 2–5. CYTOKINE BALANCE....21

BOX 3–1. KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF ASTHMA....42
BOX 3–2. IMPORTANCE OF SPIROMETRY IN ASTHMA DIAGNOSIS....43
BOX 3–3. DIFFERENTIAL DIAGNOSTIC POSSIBILITIES FOR ASTHMA 46
BOX 3–4. INSTRUMENTS FOR ASSESSING ASTHMA-SPECIFIC AND GENERIC QUALITY OF LIFE 62
FIGURE 3–1. SUGGESTED ITEMS FOR MEDICAL HISTORY* 69
FIGURE 3–2. SAMPLE QUESTIONS* FOR THE DIAGNOSIS AND INITIAL ASSESSMENT OF ASTHMA 70
FIGURE 3-3a. SAMPLE SPIROMETRY VOLUME TIME AND FLOW VOLUME CURVES 71
FIGURE 3–3b. REPORT OF SPIROMETRY FINDINGS PRE- AND POSTBRONCHODILATOR....71
FIGURE 3–4a. CLASSIFYING ASTHMA SEVERITY IN CHILDREN 0–4 YEARS OF AGE 72
FIGURE 3–4b. CLASSIFYING ASTHMA SEVERITY IN CHILDREN 5–11 YEARS OF AGE 73
FIGURE 3–4c. CLASSIFYING ASTHMA SEVERITY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS....74
FIGURE 3–5a. ASSESSING ASTHMA CONTROL IN CHILDREN 0–4 YEARS OF AGE....75
FIGURE 3–5b. ASSESSING ASTHMA CONTROL IN CHILDREN 5–11 YEARS OF AGE 76
FIGURE 3–5c. ASSESSING ASTHMA CONTROL IN YOUTHS ≥12 YEARS OF AGE AND ADULTS....77
FIGURE 3–6. SAMPLE QUESTIONS FOR ASSESSING AND MONITORING ASTHMA CONTROL....78
FIGURE 3–7. COMPONENTS OF THE CLINICIAN'S FOLLOWUP ASSESSMENT: SAMPLE ROUTINE CLINICAL ASSESSMENT QUESTIONS*....79
FIGURE 3–8. VALIDATED INSTRUMENTS FOR ASSESSMENT AND MONITORING OF ASTHMA 80
FIGURE 3–9. SAMPLE* PATIENT SELF-ASSESSMENT SHEET FOR FOLLOWUP VISITS....81
FIGURE 3–10a. ASTHMA ACTION PLAN 117
FIGURE 3–10b. ASTHMA ACTION PLAN 118

FIGURE 3–10c. ASTHMA ACTION PLAN 119
FIGURE 3–11. HOW TO USE YOUR PEAK FLOW METER 122
FIGURE 3–12. KEY EDUCATIONAL MESSAGES: TEACH AND REINFORCE AT EVERY OPPORTUNITY 124
FIGURE 3–13. DELIVERY OF ASTHMA EDUCATION BY CLINICIANS DURING PATIENT CARE VISITS 126
FIGURE 3–14. HOW TO USE YOUR METERED-DOSE INHALER 128
FIGURE 3–15. HOW TO CONTROL THINGS THAT MAKE YOUR ASTHMA WORSE 129
FIGURE 3–16a. SCHOOL ASTHMA ACTION PLAN 137
FIGURE 3–16b. SCHOOL ASTHMA ACTION PLAN 139
BOX 3–5. THE STRONG ASSOCIATION BETWEEN SENSITIZATION TO ALLERGENS AND ASTHMA: A SUMMARY OF THE EVIDENCE 168
BOX 3–6. RATIONALE FOR ALLERGY TESTING FOR PERENNIAL INDOOR ALLERGENS 169
FIGURE 3–17. ASSESSMENT QUESTIONS* FOR ENVIRONMENTAL AND OTHER FACTORS THAT CAN MAKE ASTHMA WORSE 186
FIGURE 3–18. COMPARISON OF SKIN TESTS WITH IN VITRO TESTS 187
FIGURE 3–19. PATIENT INTERVIEW QUESTIONS* FOR ASSESSING THE CLINICAL SIGNIFICANCE OF POSITIVE ALLERGY TESTS 187
FIGURE 3–20. SUMMARY OF MEASURES TO CONTROL ENVIRONMENTAL FACTORS THAT CAN MAKE ASTHMA WORSE 188
FIGURE 3–21. EVALUATION AND MANAGEMENT OF WORK-AGGRAVATED ASTHMA AND OCCUPATIONAL ASTHMA 189
FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS 243
FIGURE 3–23. QUICK-RELIEF MEDICATIONS 247
FIGURE 3–24. AEROSOL DELIVERY DEVICES 249

BOX 4–1. SAMPLE PATIENT RECORD. MONITORING THE RISK DOMAIN IN CHILDREN: RISK OF ASTHMA PROGRESSION (INCREASED EXACERBATIONS OR NEED FOR DAILY MEDICATION, OR LOSS OF LUNG FUNCTION), AND POTENTIAL ADVERSE EFFECTS OF CORTICOSTEROID THERAPY 283
FIGURE 4–1a. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE 305
FIGURE 4–1b. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE 306
FIGURE 4–2a. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 0–4 YEARS OF AGE 307
FIGURE 4–2b. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 5–11 YEARS OF AGE 308
FIGURE 4–3a. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 0–4 YEARS OF AGE 309
FIGURE 4–3b. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 5–11 YEARS OF AGE 310
FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN* 311
FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN 314
FIGURE 4–4c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS IN CHILDREN* 317

FIGURE 4–5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS 343
FIGURE 4–6. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE AND ADULTS 344
FIGURE 4–7. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS 345
FIGURE 4–8a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS 346
FIGURE 4–8b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS 349
FIGURE 4–8c.USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS 351

FIGURE 5–1. CLASSIFYING SEVERITY OF ASTHMA EXACERBATIONS IN THE URGENT OR EMERGENCY CARE SETTING 374
FIGURE 5–2a. RISK FACTORS FOR DEATH FROM ASTHMA 376
FIGURE 5–2b. SPECIAL CONSIDERATIONS FOR INFANTS 377
FIGURE 5–3. FORMAL EVALUATION OF ASTHMA EXACERBATION SEVERITY IN THE URGENT OR EMERGENCY CARE SETTING 379
FIGURE 5–4. MANAGEMENT OF ASTHMA EXACERBATIONS: HOME TREATMENT 381
FIGURE 5–5. DOSAGES OF DRUGS FOR ASTHMA EXACERBATIONS 385
FIGURE 5–6. MANAGEMENT OF ASTHMA EXACERBATIONS: EMERGENCY DEPARTMENT AND HOSPITAL-BASED CARE 387
FIGURE 5–7a. EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN 401
FIGURE 5–7b. EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN: HOW TO USE YOUR METERED-DOSE INHALER 402
FIGURE 5–8. CHECKLIST FOR HOSPITAL DISCHARGE OF PATIENTS WHO HAVE ASTHMA 404

ACKNOWLEDGMENTS AND FINANCIAL DISCLOSURES

External Review and Comment Overview

In response to a recommendation by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee, an Expert Panel was convened by the National Heart, Lung, and Blood Institute (NHLBI) to update the asthma guidelines.

Several measures were taken in the development of these asthma guidelines to enhance transparency of the evidence review process and to better manage any potential or perceived conflict of interest. In addition to using a methodologist to guide preparation of the Evidence Tables, several layers of external content review were also embedded into the guidelines development process. Expert Panel members and consultant reviewers completed financial disclosure forms that are summarized below. In addition to review by consultants, an early draft of the guidelines was circulated to a panel of guidelines end-users (the Guidelines Implementation Panel) appointed specifically for their review and feedback on ways to enhance guidelines utilization by primary care clinicians, health care delivery organizations, and third-party payors. Finally, a draft of the guidelines was posted on the NHLBI Web Site for review and comment by the NAEPP Coordinating Committee and to allow opportunity for public review and comment before the guidelines were finalized and released.

NAEPP COORDINATING COMMITTEE

Agency for Healthcare Research and Quality
Denise Dougherty, Ph.D.

Allergy and Asthma Network Mothers of Asthmatics
Nancy Sander

American Academy of Allergy, Asthma, and Immunology
Michael Schatz, M.D., M.S.

American Academy of Family Physicians
Kurtis S. Elward, M.D., M.P.H., F.A.A.F.P.

American Academy of Pediatrics
Gary S. Rachelefsky, M.D.

American Academy of Physician Assistants
Tera Crisalida, P.A.-C., M.P.A.S.

American Association for Respiratory Care
Thomas J. Kallstrom, R.R.T., F.A.A.R.C., AE-C

American College of Allergy, Asthma, and Immunology
William Storms, M.D.

American College of Chest Physicians
John Mitchell, M.D., F.A.C.P.

American College of Emergency Physicians
Richard M. Nowak, M.D., M.B.A., F.A.C.E.P.

American Lung Association
Noreen M. Clark, Ph.D.

American Medical Association
Paul V. Williams, M.D.

American Nurses Association
Karen Huss, D.N.Sc., R.N., A.P.R.N.B.C., F.A.A.N., F.A.A.A.A.I.

American Pharmacists Association
Dennis M. Williams, Pharm.D.

American Public Health Association
Pamela J. Luna, Dr.P.H., M.Ed.

American School Health Association
Lani S. M. Wheeler, M.D., F.A.A.P., F.A.S.H.A.

American Society of Health-System Pharmacists
Kathryn V. Blake, Pharm.D.

American Thoracic Society
Stephen C. Lazarus, M.D.

Asthma and Allergy Foundation of America
Mo Mayrides

Council of State and Territorial Epidemiologists
Sarah Lyon-Callo, M.A., M.S.

National Association of School Nurses
Donna Mazyck, R.N., M.S., N.C.S.N.

National Black Nurses Association, Inc.
Susan B. Clark, R.N., M.N.

National Center for Chronic Disease Prevention, Centers for Disease Control and Prevention (CDC)
Sarah Merkle, M.P.H.

National Center for Environmental Health, CDC
Paul M. Garbe, M.D.

National Center for Health Statistics, CDC
Lara Akinbami, M.D.

National Institute for Occupational Safety and Health, CDC
Margaret Filios, S.M., R.N.

National Heart, Lung, and Blood Institute
National Institutes of Health (NIH)
Elizabeth Nabel, M.D.

National Heart, Lung, and Blood Institute
NIH, Ad Hoc Committee on Minority Populations
Ruth I. Quartey, Ph.D.

National Institute of Allergy and Infectious Diseases (NIAID), NIH
Peter J. Gergen, M.D., M.P.H.

National Institute of Environmental Health Sciences, NIH
Charles A. Wells, Ph.D.

National Medical Association
Michael Lenoir, M.D.

National Respiratory Training Center
Pamela Steele, M.S.N., C.P.N.P., AE-C

Society for Academic Emergency Medicine
Rita Cydulka, M.D., M.S.

Society for Public Health Education
Judith C. Taylor-Fishwick, M.Sc., AE-C

U.S. Department of Education
Dana Carr

U.S. Environmental Protection Agency Indoor Environments Division
David Rowson, M.S.

U.S. Environmental Protection Agency Office of Research and Development
Hillel S. Koren, Ph.D.

U.S. Food and Drug Administration
Robert J. Meyer, M.D.

THIRD EXPERT PANEL ON THE DIAGNOSIS AND MANAGEMENT OF ASTHMA

William W. Busse, M.D., Chair
University of Wisconsin Medical School
Madison, Wisconsin

Homer A. Boushey, M.D.
University of California–San Francisco
San Francisco, California

Carlos A. Camargo, Jr., M.D., Dr.P.H.
Massachusetts General Hospital
Boston, Massachusetts

David Evans, Ph.D., A.E.-C,
Columbia University
New York, New York

Michael B. Foggs, M.D.
Advocate Health Centers
Chicago, Illinois

Susan L. Janson, D.N.Sc., R.N., A.N.P., F.A.A.N.
University of California–San Francisco
San Francisco, California

H. William Kelly, Pharm.D.
University of New Mexico Health Sciences Center
Albuquerque, New Mexico

Robert F. Lemanske, M.D.
University of Wisconsin Hospital and Clinics
Madison, Wisconsin

Fernando D. Martinez, M.D.
University of Arizona Medical Center
Tucson, Arizona

Robert J. Meyer, M.D.
U.S. Food and Drug Administration
Silver Spring, Maryland

Harold S. Nelson, M.D.
National Jewish Medical and Research Center
Denver, Colorado

Thomas A. E. Platts-Mills, M.D., Ph.D.
University of Virginia School of Medicine
Charlottesville, Virginia

Michael Schatz, M.D., M.S.
Kaiser-Permanente–San Diego
San Diego, California

Gail Shapiro, M.D.†
University of Washington
Seattle, Washington

Stuart Stoloff, M.D.
University of Nevada School of Medicine
Carson City, Nevada

Stanley J. Szefler, M.D.
National Jewish Medical and Research Center
Denver, Colorado

Scott T. Weiss, M.D., M.S.
Brigham and Women's Hospital
Boston, Massachusetts

Barbara P. Yawn, M.D., M.Sc.
Olmstead Medical Center
Rochester, Minnesota

†Deceased

Development of the resource document and the guidelines report was funded by the NHLBI, NIH. Expert Panel members completed financial disclosure forms, and the Expert Panel members disclosed relevant financial interests to each other prior to their discussions. Expert Panel members participated as volunteers and were compensated only for travel expenses related to the Expert Panel meetings. Financial disclosure information covering the 3-year period during which the guidelines were developed is provided for each Panel member below.

Dr. Busse has served on the Speakers' Bureaus of GlaxoSmithKline, Merck, Novartis, and Pfizer; and on the Advisory Boards of Altana, Centocor, Dynavax, Genentech/Novartis, GlaxoSmithKline, Isis, Merck, Pfizer, Schering, and Wyeth. He has received funding/grant support for research projects from Astellas, AstraZeneca, Centocor, Dynavax, GlaxoSmithKline, Novartis, and Wyeth. Dr. Busse also has research support from the NIH.

Dr. Boushey has served as a consultant for Altana, Protein Design Lab, and Sumitomo. He has received honoraria from (Boehringer-Ingelheim, Genentech, Merck, Novartis, and Sanofi-Aventis, and funding/grant support for research projects from the NIH.

Dr. Camargo has served on the Speakers' Bureaus of AstraZeneca, GlaxoSmithKline, Merck, and Schering-Plough; and as a consultant for AstraZeneca, Critical Therapeutics, Dey Laboratories, GlaxoSmithKline, MedImmune, Merck, Norvartis, Praxair, Respironics, Schering-Plough, Sepracor, and TEVA. He has received funding/grant support for research projects from a variety of Government agencies and not-for-profit foundations, as well as AstraZeneca, Dey Laboratories, GlaxoSmithKline, MedImmune, Merck, Novartis, and Respironics.

Dr. Evans has received funding/grant support for research projects from the NHLBI.

Dr. Foggs has served on the Speakers' Bureaus of GlaxoSmithKline, Merck, Pfizer, Sepracor, and UCB Pharma; on the Advisory Boards of Alcon, Altana, AstraZeneca, Critical Therapeutics, Genentech, GlaxoSmithKline, and IVAX; and as consultant for Merck and Sepracor. He has received funding/grant support for research projects from GlaxoSmithKline.

Dr. Janson has served on the Advisory Board of Altana, and as a consultant for Merck. She has received funding/grant support for research projects from the NHLBI.

Dr. Kelly has served on the Speakers' Bureaus of AstraZeneca and GlaxoSmithKline; and on the Advisory Boards of AstraZeneca, MAP Pharmaceuticals, Merck, Novartis, and Sepracor.

Dr. Lemanske has served on the Speakers' Bureaus of GlaxoSmithKline and Merck, and as a consultant for AstraZeneca, Aventis, GlaxoSmithKline, Merck, and Novartis. He has received honoraria from Altana, and funding/grant support for research projects from the NHLBI and NIAID.

Dr. Martinez has served on the Advisory Board of Merck and as a consultant for Genentech, GlaxaSmithKline, and Pfizer. He has received honoraria from Merck.

Dr. Meyer has no relevant financial interests.

Dr. Nelson has served on the Speakers' Bureaus of AstraZeneca, GlaxoSmithKline, Pfizer, and Schering-Plough; and as a consultant for Abbott Laboratories, Air Pharma, Altana Pharma US, Astellas, AstraZeneca, Curalogic, Dey Laboratories, Dynavax Technologies, Genentech/Novartis, GlaxoSmithKline, Inflazyme Pharmaceuticals, MediciNova, Protein Design Laboratories, Sanofi-Aventis, Schering-Plough, and Wyeth Pharmaceuticals. He has received funding/grant support for research projects from Altana, Astellas, AstraZeneca, Behringer, Critical Therapeutics, Dey Laboratories, Epigenesis, Genentech, GlaxoSmithKline, Hoffman LaRoche, IVAX, Medicinova, Novartis, Sanofi-Aventis, Schering-Plough, Sepracor, TEVA, and Wyeth.

Dr. Platts-Mills has served on the Advisory Committee of Indoor Biotechnologies. He has received funding/grant support for a research project from Pharmacia Diagnostics.

Dr. Schatz has served on the Speakers' Bureaus of AstraZeneca, Genentech, GlaxoSmithKline, and Merck; and as a consultant for GlaxoSmithKline on an unbranded asthma initiative. He has received honoraria from AstraZeneca, Genentech, GlaxoSmithKline and Merck. He has received funding/grant support for research projects from GlaxoSmithKline and Merck and Sanofi-Adventis.

Dr. Shapiro[†] served on the Speakers' Bureaus of AstraZeneca, Genentech, GlaxoSmithKline, IVAX Laboratories, Key Pharmaceuticals, Merck, Pfizer Pharmaceuticals, Schering Corporation, UCB Pharma, and 3M; and as a consultant for Altana, AstraZeneca, Dey Laboratories, Genentech/Novartis, GlaxoSmithKline, ICOS, IVAX Laboratories, Merck, Sanofi-Aventis, and Sepracor. She received funding/grant support for research projects from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squibb, Dey Laboratories, Fujisawa Pharmaceuticals, Genentech, GlaxoSmithKline, Immunex, Key, Lederle, Lilly Research, MedPointe Pharmaceuticals, Medtronic Emergency Response Systems, Merck, Novartis, Pfizer, Pharmaxis, Purdue Frederick, Sanofi-Aventis, Schering, Sepracor, 3M Pharmaceuticals, UCB Pharma, and Upjohn Laboratories.

Dr. Stoloff has served on the Speakers' Bureaus of Alcon, Altana, AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Pfizer, Sanofi-Aventis, and Schering; and as a consultant for Alcon, Altana, AstraZeneca, Dey, Genentech, GlaxoSmithKline, Merck, Novartis, Pfizer, Sanofi-Aventis, and Schering.

Dr. Szefler has served on the Advisory Boards of Altana, AstraZeneca, Genentech, GlaxoSmithKline, Merck, Novartis, and Sanofi-Aventis; and as a consultant for Altana, AstraZeneca, Genentech, GlaxoSmithKline, Merck, Novartis, and Sanofi-Aventis. He has received funding/grant support for a research project from Ross.

Dr. Weiss has served on the Advisory Board of Genentech, and as a consultant for Genentech and GlaxoSmithKline. He has received funding/grant support for research projects from GlaxoSmithKline.

Dr. Yawn has served on the Advisory Boards of Altana, AstraZeneca, Merck, Sanofi-Aventis, and Schering-Plough. She has received honoraria from Pfizer and Schering-Plough, and funding/grant support for research projects from the Agency for Healthcare Research and Quality, the CDC, the NHLBI, Merck, and Schering-Plough.

[†]Deceased

CONSULTANT REVIEWERS

The Expert Panel acknowledges the following consultants for their review of an early draft of the report. Financial disclosure information covering a 12-month period prior to the review of the guidelines is provided below for each consultant.

Andrea J. Apter, M.D., M.Sc.
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

Noreen M. Clark, Ph.D.
University of Michigan School of Public Health
Ann Arbor, Michigan

Anne Fuhlbrigge, M.D., M.S.
Brigham and Women's Hospital
Boston, Massachusetts

Elliott Israel, M.D.
Brigham and Women's Hospital
Boston, Massachusetts

Meyer Kattan, M.D.
Mount Sinai Medical Center
New York, New York

Jerry A. Krishnan. M.D., Ph.D.
The Johns Hopkins School of Medicine
Baltimore, Maryland

James T. Li, M.D., Ph.D., F.A.A.A.A.I.
Mayo Clinic
Rochester, Minnesota

Dennis R. Ownby, M.D.
Medical College of Georgia
Augusta, Georgia

Gary S. Rachelefshy, M.D.
University of California–Los Angeles, School of Medicine
Los Angeles, California

Brian H. Rowe, M.D., M.Sc., C.C.F.P. (E.M.), F.C.C.P.
University of Alberta Hospital
Edmonton, Alberta, Canada

E. Rand Sutherland, M.D., M.P.H.
National Jewish Medical and Research Center
Denver, Colorado

Sandra R. Wilson, Ph.D.
Palo Alto Medical Foundation
Palo Alto, California

Robert A. Wood, M.D.
The Johns Hopkins School of Medicine
Baltimore, Maryland

Robert Zeiger, M.D.
Kaiser Permanente Medical Center
San Diego, California

Dr. Apter owns stock in Johnson & Johnson. She has received funding/grant support for research projects from the NHLBI.

Dr. Clark has no relevant financial interests.

Dr. Fulhlbrigge has served on the Speakers' Bureau of GlaxoSmithKline, the Advisory Boards of GlaxoSmithKline and Merck, the Data Systems Monitoring Board for a clinical trial sponsored by Sepracor, and as a consultant for GlaxoSmithKline. She has received honoraria from GlaxoSmithKline and Merck, and funding/grant support for a research project from Boehringer Ingelheim.

Dr. Israel has served on the Speakers' Bureau of Genentech and Merck, and as a consultant for Asthmatx, Critical Therapeutics, Genentech, Merck, Novartis Pharmaceuticals, Protein Design Labs, Schering-Plough Company, and Wyeth. He has received funding/grant support for research projects from Asthmatx, Boehringer Ingelheim, Centocor, Genentech, GlaxoSmithKline, and Merck.

Dr. Kattan has served on the Speakers' Bureau of AstraZeneca.

Dr. Krishnan has received funding/grant support for a research project from Hill-Rom, Inc.

Dr. Li has received funding/grant support for research projects from the American Lung Association, GlaxoSmithKline, Pharming, and ZLB Behring.

Dr. Ownby has none.

Dr. Rachelefsky has served on the Speakers' Bureaus of AstraZeneca, GlaxoSmithKline, IVAX, Medpointe, Merck, and Schering-Plough. He has received honoraria from AstraZeneca, GlaxoSmithKline, IVAX, Medpointe, Merck, and Schering-Plough.

Dr. Rowe has served on the Advisory Boards of Abbott, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline. He has received honoraria from Abbott, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline. He has received funding/grant support for research projects from Abbott, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Trudell.

Dr. Sutherland has served on the Speakers' Bureau of Novartis/Genentech and the Advisory Board of Dey Laboratories. He has received honoraria from IVAX and funding/grant support for research projects from GlaxoSmithKline and the NIH.

Dr. Wilson has served as a consultant for the Department of Urology, University of California, San Francisco (UCSF); Asthmatx, Inc.; and the Stanford-UCSF Evidence-Based Practice Center. She has received funding/grant support for research projects from the NHLBI and from a subcontract to Stanford University from Blue Shield Foundation.

Dr. Wood has served on the Speakers' Bureaus of Dey Laboratories, GlaxoSmithKline, and Merck; on the Advisory Board of Dey Laboratories; and as a consultant to Dey Laboratories. He has received honoraria from Dey Laboratories, GlaxoSmithKline, and Merck, and funding/grant support for a research project from Genentech.

Dr. Zeiger has served on the Data Monitoring Board of Genentech, Advisory Board of GlaxoSmithKline, and as a consultant for Aerocrine, AstraZeneca, and Genentech. He has received honoraria from AstraZeneca and funding/grant support for a research project from Sanofi-Aventis.

National Heart, Lung, and Blood Institute Staff

Robinson (Rob) Fulwood, Ph.D., M.S.P.H.
Chief, Enhanced Dissemination and Utilization Branch
Division for the Application of Research Discoveries

James P. Kiley, Ph.D.
Director
Division of Lung Diseases

Gregory J. Morosco, Ph.D., M.P.H.
Associate Director for Prevention, Education, and Control
Director
Division for the Application of Research Discoveries

Diana K. Schmidt, M.P.H.
Coordinator
National Asthma Education and Prevention Program
Division for the Application of Research Discoveries

Virginia S. Taggart, M.P.H.
Program Director
Division of Lung Diseases

American Institutes for Research Staff

Heather Banks, M.A., M.A.T.
Senior Editor

Patti Louthian
Senior Desktop Publisher

Karen L. Soeken, Ph.D.
Methodologist

Mary Tierney, M.D.
Project Manager

ACRONYMS AND ABBREVIATIONS

AAI	acute asthma index
A. artemisiifolia	*Ambrosia artemisiifolia*
ABG	arterial blood gas
ABPA	allergic bronchopulmonary aspergillosis
ACE	angiotensin converting enzyme
ACIP	Advisory Committee on Immunization Practices (CDC)
ACT	Asthma Control Test
AHRQ	Agency for Healthcare Research and Quality
ALT	alanine aminotransferase (enzyme test of liver function)
Amb a 1	*Ambrosia artemisiifolia*
AQLQ	asthma-related quality of life questionnaire
ATAQ	Asthma Therapy Assessment Questionnaire
ATS	American Thoracic Society
BDP	beclomethasone dipropionate
Bla g1	*Blattella germanica 1* (cockroach allergen)
BMD	bone mineral density
BPT	bronchial provocation test
CAMP	Childhood Asthma Management Program
CBC	complete blood count
CC	Coordinating Committee
CDC	Centers for Disease Control and Prevention
CFC	chlorofluorocarbon (inhaler propellant being phased out because it harms atmosphere)
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase (an enzyme)
CPAP	continuous positive airway pressure
CT	computer tomography
Der f	*Dermatophagoides farinae* (American house-dust mite)
Der p	*Dermatophagoides pteronyssinus* (European house-dust mite)
DEXA	dual energy x-ray absorptiometry
DHHS	U.S. Department of Health and Human Services
DPI	dry powder inhaler
EBC	exhaled breath concentrate
ECP	eosinophilic cationic protein
ED	emergency department
EIB	exercise-induced bronchospasm
EMS	emergency medical services
eNO	exhaled nitric oxide
EPR	Expert Panel Report EPR 1991, EPR 1997 (EPR—2), EPR—Update 2002, EPR—3: Full Report 2007 (this 2007 guidelines update)
ER	emergency room
ERS	European Respiratory Society
ETS	environmental tobacco smoke

FC□RI	high-affinity IgE receptor
FDA	U.S. Food and Drug Administration
FEF	forced expiratory flow
$FEF_{25–75}$	forced expiratory flow between 25 percent and 75 percent of the vital capacity
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FEV_6	forced expiratory volume in 6 seconds
FiO_2	fractional inspired oxygen
FRC	functional residual capacity
FVC	forced vital capacity
GERD	gastroesophageal reflux disease
GINA	Global Initiative for Asthma
GIP	Guidelines Implementation Panel (at NHLBI)
GM-CSF	granulocyte-macrophage colony-stimulating factor
HEPA	high-efficiency particulate air (a type of filter)
HFA	hydrofluoroalkane (inhaler propellant)
HMO	health maintenance organization
HPA	hypothalamic-pituitary-adrenal (usually used with “axis”)
HRT	hormone replacement therapy
ICS	inhaled corticosteroid(s)
ICU	intensive care unit
IFN-□	interferon-gamma
IgE	immunoglobulin E (and similar types, such as IgG)
IL-4, IL-12, etc.	interleukin-4, interleukin-12 (and similar)
IL-4R	interleukin-4 receptor (and similar)
INR	international normalized ratio
IVIG	intravenous immunoglobulin
IVMg	intravenous magnesium sulfate
LABA/LABAs	long-acting $beta_2$-agonist(s)
LTRA	leukotriene receptor antagonist
Mab or MAb	monoclonal antibody
MDC	macrophage-derived chemokines
MDI	metered-dose inhaler
MDI/DED	metered-dose inhaler (MDI) with delivery enhancement device (DED)
MeSH	Medical Subject Headings (in MEDLINE)
MIP	macrophage inflammatory protein
NAEPP	National Asthma Education and Prevention Program
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey (with roman numeral)
NHIS	National Health Information Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NK	natural killer cells

NO or NO_2	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
OSA	obstructive sleep apnea
PCO_2	partial pressure of carbon dioxide
PCP	primary care provider (or physician)
PD20	20 percent of provocative dose
PEF	peak expiratory flow
PEFR	PEF rate
PI	pulmonary index
PI_{max}	maximal pulmonary inspiration
PICU	pediatric intensive care unit
PIV	parainfluenza virus
PM10	particulate matter ≤10 micrometers
RANTES	Regulated on Activation, Normal T Expressed and Secreted
RCT	randomized controlled trial
RR	relative risk
RSV	respiratory syncytial virus
RV	residual volume
SABA/SABAs	short-acting $beta_2$-agonist(s) (inhaled)
SaO_2	oxygen saturation
SMART	Salmeterol Multicenter Asthma Research Trial
START	Inhaled Steroid Treatment as Regular Therapy in Early Asthma study
TAA	triamcinolone acetonide
TAO	troleandomycin (antibiotic)
Th1, Th2	T cell helper 1, T cell helper 2
TLC	total lung capacity
TNF-□	tumor necrosis factor-alpha
TRUST	The Regular Use of Salbutamol Trial
USDA	U.S. Department of Agriculture
VC	vital capacity
VCD	vocal cord dysfunction
VHC	valved holding chamber
VOC	volatile organic compounds (e.g., benzene)

PREFACE

The Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma was developed by an expert panel commissioned by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee (CC), coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.

Using the 1997 EPR 2 guidelines and the 2004 update of EPR 2 as the framework, the expert panel organized the literature review and final guidelines report around four essential components of asthma care, namely: assessment and monitoring, patient education, control of factors contributing to asthma severity, and pharmacologic treatment. Subtopics were developed for each of these four broad categories.

The 2007 EPR 3 guidelines have been developed under the leadership of Dr. William Busse, Panel Chair. The NHLBI sincerely appreciates the work of Dr. Busse and all the members of the expert panel as well as an expert consultant group in developing this report. Sincere appreciation is also extended to the NAEPP CC and the Guidelines Implementation Panel as well as other stakeholder groups (professional societies, voluntary health, government, consumer/patient advocacy organizations, and industry) for their invaluable comments during the public review period that helped to enhance the scientific credibility and practical utility of this document.

Ultimately, the broad change in clinical practice depends on the influence of local primary care physicians and other health professionals who not only provide state-of-the-art care to their patients, but also communicate to their peers the importance of doing the same. The NHLBI and its partners will forge new initiatives based on these guidelines to stimulate adoption of the recommendations at all levels, but particularly with primary care clinicians at the community level. We ask for the assistance of every reader in reaching our ultimate goal: improving asthma care and the quality of life for every asthma patient with asthma.

Gregory Morosco, Ph.D., M.P.H.
Director
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

James Kiley, Ph.D.
Director
Division of Lung Diseases
National Heart, Lung, and Blood Institute

SECTION 1, INTRODUCTION

Asthma is a chronic inflammatory disease of the airways. In the United States, asthma affects more than 22 million persons. It is one of the most common chronic diseases of childhood, affecting more than 6 million children (current asthma prevalence, National Health Interview Survey (NHIS), National Center for Health Statistics, Centers for Disease Control and Prevention, 2005) (NHIS 2005). There have been important gains since the release of the first National Asthma Education and Prevention Program (NAEPP) clinical practice guidelines in 1991. For example, the number of deaths due to asthma has declined, even in the face of an increasing prevalence of the disease (NHIS 2005); fewer patients who have asthma report limitations to activities; and an increasing proportion of people who have asthma receive formal patient education (Department of Health and Human Services, Healthy People 2010 midcourse review). Hospitalization rates have remained relatively stable over the last decade, with lower rates in some age groups but higher rates among young children 0–4 years of age. There is some indication that improved recognition of asthma among young children contributes to these rates. However, the burden of avoidable hospitalizations remains. Collectively, people who have asthma have more than 497,000 hospitalizations annually (NHIS 2005). Furthermore, ethnic and racial disparities in asthma burden persist, with significant impact on African American and Puerto Rican populations. The challenge remains to help all people who have asthma, particularly those at high risk, receive quality asthma care.

Advances in science have led to an increased understanding of asthma and its mechanisms as well as improved treatment approaches. To help health care professionals bridge the gap between current knowledge and practice, the NAEPP of the National Heart, Lung, and Blood Institute (NHLBI) has previously convened three Expert Panels to prepare guidelines for the diagnosis and management of asthma. The NAEPP Coordinating Committee (CC), under the leadership of Claude Lenfant, M.D., Director of the NHLBI, convened the first Expert Panel in 1989. The charge to that Panel was to develop a report that would provide a general approach to diagnosing and managing asthma based on current science. Published in 1991, the “Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma” (EPR 1991) organized the recommendations for the treatment of asthma around four components of effective asthma management:

- Use of objective measures of lung function to assess the severity of asthma and to monitor the course of therapy
- Environmental control measures to avoid or eliminate factors that precipitate asthma symptoms or exacerbations
- Patient education that fosters a partnership among the patient, his or her family, and clinicians
- Comprehensive pharmacologic therapy for long-term management designed to reverse and prevent the airway inflammation characteristic of asthma as well as pharmacologic therapy to manage asthma exacerbations

The NAEPP recognizes that the value of clinical practice guidelines lies in their presentation of the best and most current evidence available. Thus, the Expert Panels have been convened periodically to update the guidelines, and new NAEPP reports were prepared: The “Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma” (EPR—2 1997) and

"Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002" (EPR—Update 2002). The "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Full Report, 2007" (EPR—3: Full Report 2007) is the latest report from the NAEPP and updates the 1997 and 2002 reports. The EPR—3: Full Report 2007 is organized as follows: Section 1—Introduction/Methodology; Section 2—Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma; Section 3—The Four Components of Asthma Management; Section 4—Managing Asthma Long Term; and Section 5—Managing Exacerbations of Asthma. Key points and key differences are presented at the beginning of each section and subsection in order to highlight major issues.

This report presents recommendations for the diagnosis and management of asthma that will help clinicians and patients make appropriate decisions about asthma care. Of course, the clinician and patient need to develop individual treatment plans that are tailored to the specific needs and circumstances of the patient. The NAEPP, and all who participated in the development of this latest report, hope that the patient who has asthma will be the beneficiary of the recommendations in this document. This report is not an official regulatory document of any Government agency. It will be used as the source to develop clinical practice tools and educational materials for patients and the public.

OVERALL METHODS USED TO DEVELOP THIS REPORT

Background

In June 2004, the Science Base Committee of the NAEPP recommended to the NAEPP CC that its clinical practice guidelines for the diagnosis and management of asthma be updated. In September, under the leadership of Dr. Barbara Alving, M.D. (Chair of the NAEPP CC, and Acting Director of the NHLBI), a panel of experts was selected to update the clinical practice guidelines by using a systematic review of the scientific evidence for the treatment of asthma and consideration of literature on implementing the guidelines.

In October 2004, the Expert Panel assembled for its first meeting. Using EPR—2 1997 and EPR—Update 2002 as the framework, the Expert Panel organized the literature searches and subsequent report around the four essential components of asthma care, namely:
(1) assessment and monitoring, (2) patient education, (3) control of factors contributing to asthma severity, and (4) pharmacologic treatment. Subtopics were developed for each of these four broad categories.

The steps used to develop this report include: (1) completing a comprehensive search of the literature; (2) conducting an indepth review of relevant abstracts and articles; (3) preparing evidence tables to assess the weight of current evidence with respect to past recommendations and new and unresolved issues; (4) conducting thoughtful discussion and interpretation of findings; (5) ranking strength of evidence underlying the current recommendations that are made; (6) updating text, tables, figures, and references of the existing guidelines with new findings from the evidence review; (7) circulating a draft of the updated guidelines through several layers of external review, as well as posting it on the NHLBI Web site for review and comment by the public and the NAEPP CC, and (8) preparing a final-report based on consideration of comments raised in the review cycle.

Systematic Evidence Review Overview

INCLUSION/EXCLUSION CRITERIA

The literature review was conducted in three cycles over an 18-month period (September 2004 to March 2006). Search strategies for the literature review initially were designed to cast a wide net but later were refined by using publication type limits and additional terms to produce results that more closely matched the framework of topics and subtopics selected by the Expert Panel. The searches included human studies with abstracts that were published in English in peer-reviewed medical journals in the MEDLINE database. Two timeframes were used for the searches, dependent on topic: January 1, 2001, through March 15, 2006, for pharmacotherapy (medications), peak flow monitoring, and written action plans, because these topics were recently reviewed in the EPR—Update 2002; and January 1, 1997, through March 15, 2006, for all other topics, because these topics were last reviewed in the EPR—2 1997.

SEARCH STRATEGIES

Panel members identified, with input from a librarian, key text words for each of the four components of care. A separate search strategy was developed for each of the four components and various key subtopics when deemed appropriate. The key text words and Medical Subject Headings (MeSH) terms that were used to develop each search string are found in an appendix posted on the NHLBI Web site.

LITERATURE REVIEW PROCESS

The systematic review covered a wide range of topics. Although the overarching framework for the review was based on the four essential components of asthma care, multiple subtopics were associated with each component. To organize a review of such an expanse, the Panel was divided into 10 committees, with about 4–7 reviewers in each (all reviewers were assigned to 2 or more committees). Within each committee, teams of two (“topic teams”) were assigned as leads to cover specific topics. A system of independent review and vote by each of the two team reviewers was used at each step of the literature review process to identify studies to include in the guidelines update. The initial step in the literature review process was to screen titles from the searches for relevancy in updating content of the guidelines, followed by reviews of abstracts of the relevant titles to identify those studies meriting full-text review based on relevance to the guidelines and study quality.

Figure 1–1 summarizes the literature retrieval and review process by committee.

Figure 1–2 summarizes the overall literature retrieval and review process. The combined number of titles screened from cycles 1, 2, and 3 was 15,444. The number of abstracts and articles reviewed for all three cycles was 4,747. Of these, 2,863 were voted to the abstract Keep list following the abstract-review step. A database of these abstracts is posted on the NHLBI Web site. Of these abstracts, 2,122 were advanced for full-text review, which resulted in 1,654 articles serving as a bibliography of references used to update the guidelines, available on the NHLBI Web site. Articles were selected from this bibliography for evidence tables and/or citation in the text. In addition, articles reporting new and particularly relevant findings and published after March 2006 were identified by Panel members during the writing period (March 2006–December 2006) and by comments received from the public review in February 2007.

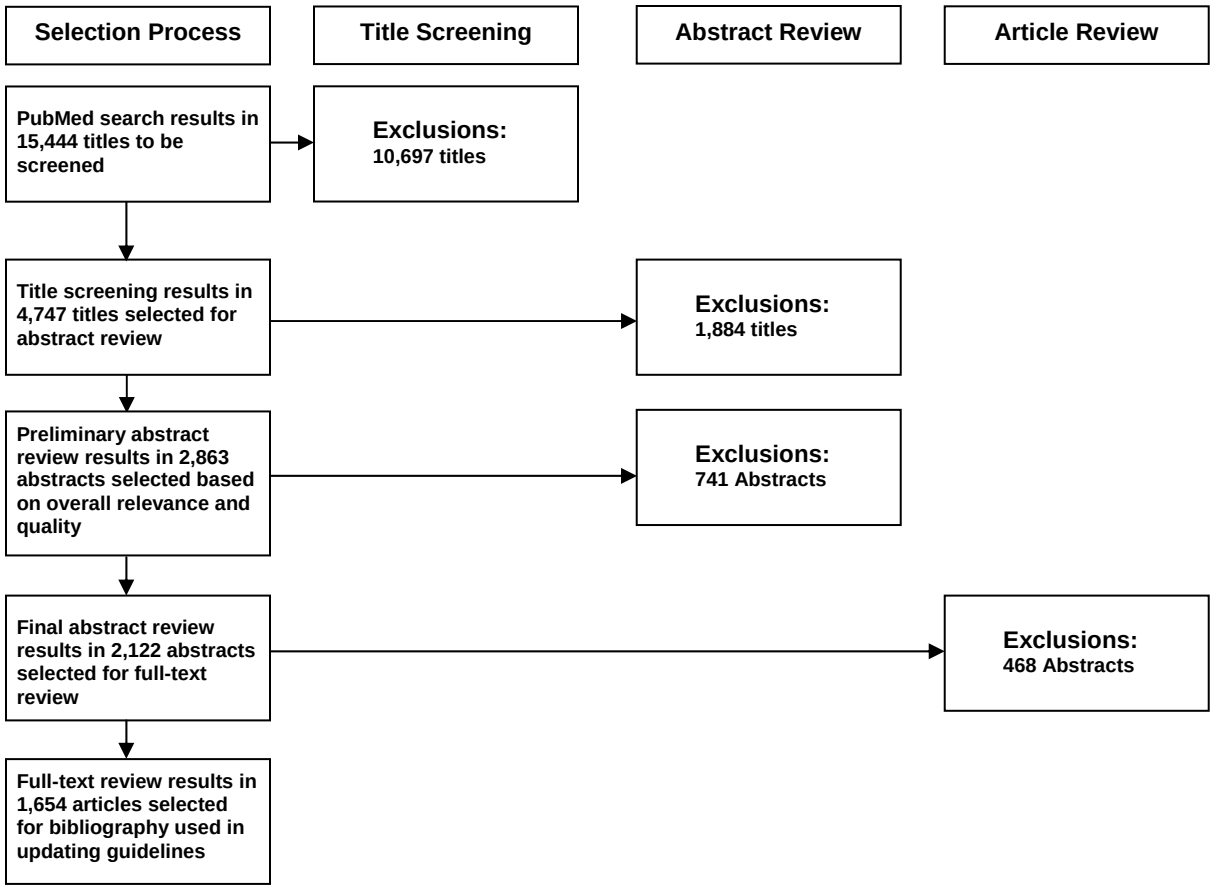
FIGURE 1–1. LITERATURE RETRIEVAL AND REVIEW PROCESS: BREAKDOWN BY COMMITTEE

Committee	Citations	Abstracts	Full Text	Evidence Tables		
	Screened for relevance to asthma guidelines	Reviewed by 2 independent reviewers; vote based on relevance to guidelines and quality of study	Reviewed by primary reviewer with secondary review of articles rejected by primary reviewer			
Topics Covered	**Number**	**Number**	**Number**	**Table Number**	**Table Title**	**Number of Cites**
Assessment and Monitoring	3,996	758	214	1	Predictors of Exacerbation	31
				2	Usefulness of Peak Flow Measurement	14
Patient and Provider Education	1,860	873	442	3	Asthma Self-Management Education for Adults	24
				4	Asthma Self-Management Education for Children	27
				5	Asthma Self-Management Education in Community Settings	35
				6	Cost-Effectiveness of Asthma Self-Management Education	12
				7	Methods for Improving Clinician Behaviors: Implementing Guidelines	6
				8	Methods for Improving Systems Support	4
Control of Factors Affecting Asthma	2,574	1,108	195	9	Allergen Avoidance	11
				10	Immunotherapy	8

FIGURE 1–1. LITERATURE RETRIEVAL AND REVIEW PROCESS: BREAKDOWN BY COMMITTEE (CONTINUED)

Committee	Citations Screened for relevance to asthma guidelines	Abstracts Reviewed by 2 independent reviewers; vote based on relevance to guidelines and quality of study	Full Text Reviewed by primary reviewer with secondary review of articles rejected by primary reviewer	Evidence Tables		
Topics Covered	**Number**	**Number**	**Number**	**Table Number**	**Table Title**	**Number of Cites**
Pharmacologic Therapy: Inhaled Corticosteroids	724	463	155	11	Combination Therapy	27
				12	Dosing Strategies	37
Pharmacologic Therapy: Immunomodulators	141	63	28	13	Anti-IgE	17
Pharmacologic Therapy: Leukotriene Receptor Antagonists	364	130	56	14	Monotherapy/Effectiveness Studies	21
Pharmacologic Therapy: Bronchodilators	921	438	183	15	Safety of Long-Acting Beta$_2$-Agonists	18
				16	Levalbuterol	7
Pharmacologic Therapy: Special Situations	3,187	222	107		No tables	
Complementary and Alternative Medicine	171	134	81		No tables	
Managing Exacerbations	1,407	616	261	17	Increasing the Dose of Inhaled Corticosteroids	5
				18	IV Aminophylline	2
				19	Magnesium Sulfate	5
				20	Heliox	5

FIGURE 1–2. LITERATURE RETRIEVAL AND REVIEW PROCESS: OVERALL SUMMARY



PREPARATION OF EVIDENCE TABLES

Evidence tables were prepared for selected topics. It was not feasible to generate evidence tables for every topic in the guidelines. Furthermore, many topics did not have a sufficient body of evidence or a sufficient number of high-quality studies to warrant the preparation of a table.

The Panel decided to prepare evidence tables on those topics for which an evidence table would be particularly useful to assess the weight of the evidence—e.g., topics with numerous articles, conflicting evidence, or which addressed questions raised frequently by clinicians. Summary findings on topics without evidence tables, however, also are included in the updated guidelines text.

Evidence tables were prepared with the assistance of a methodologist who served as a consultant to the Expert Panel. Within their respective committees, Expert Panel members selected the topics and articles for evidence tables. The evidence tables included all articles that received a “yes” vote from both the primary and secondary reviewer during the systematic literature review process. The methodologist abstracted the articles to the tables, using a template developed by the Expert Panel. The Expert Panel subsequently reviewed and

approved the final evidence tables. A total of 20 tables, comprising 316 articles are included in the current update (see figure 1–1). Evidence tables are posted on the NHLBI Web site.

RANKING THE EVIDENCE

The Expert Panel agreed to specify the level of evidence used to justify the recommendations being made. Panel members only included ranking of evidence for recommendations they made based on the scientific literature in the current evidence review. They did not assign evidence rankings to recommendations pulled through from the EPR—2 1997 on topics that are still important to the diagnosis and management of asthma but for which there was little new published literature. These "pull through" recommendations are designated by EPR—2 1997 in parentheses following the first mention of the recommendation. For recommendations that have been either revised or further substantiated on the basis of the evidence review conducted for the EPR—3: Full Report 2007, the level of evidence is indicated in the text in parentheses following first mention of the recommendation. The system used to describe the level of evidence is as follows (Jadad et al. 2000):

- **Evidence Category A: Randomized controlled trials (RCTs), rich body of data.** Evidence is from end points of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.

- **Evidence Category B: RCTs, limited body of data.** Evidence is from end points of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, category B pertains when few randomized trials exist; they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.

- **Evidence Category C: Nonrandomized trials and observational studies.** Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.

- **Evidence Category D: Panel consensus judgment.** This category is used only in cases where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel consensus is based on clinical experience or knowledge that does not meet the criteria for categories A through C.

In addition to specifying the level of evidence supporting a recommendation, the Expert Panel agreed to indicate the strength of the recommendation. When a certain clinical practice "is recommended," this indicates a strong recommendation by the panel. When a certain clinical practice "should, or may, be considered," this indicates that the recommendation is less strong. This distinction is an effort to address nuances of using evidence ranking systems. For example, a recommendation for which clinical RCT data are not available (e.g., conducting a medical history for symptoms suggestive of asthma) may still be strongly supported by the Panel. Furthermore, the range of evidence that qualifies a definition of "B" or "C" is wide, and the Expert Panel considered this range and the potential implications of a recommendation as they decided how strongly the recommendation should be presented.

PANEL DISCUSSION

The first opportunity for discussion of findings occurred within the "topic teams." Teams then presented a summary of their findings during a conference call to all members of their respective committee. A full discussion ensued on each topic, and the committee arrived at a consensus position. Teams then presented their findings and the committee position to the full Expert Panel at an in-person meeting, thereby engaging all Panel members in critical analysis of the evidence and interpretation of the data.

A series of conference calls for each of the 10 committees as well as four in-person Expert Panel meetings (held in October 2004, April 2005, December 2005, and May 2006) were scheduled to facilitate discussion of findings and to dovetail with the three cycles of literature review that occurred over the 18-month period. Potential conflicts of interest were disclosed at the initial meeting.

REPORT PREPARATION

Development of the EPR—3: Full Report 2007 was an iterative process of interpreting the evidence, drafting summary statements, and reviewing comments from the various external reviews before completing the final report. In the summer and fall of 2005, the various topic teams, through conference calls and subsequent electronic mail, began drafting their assigned sections of the report. Members of the respective committees reviewed and revised team drafts, also by using conference calls and electronic mail. During the calls, votes were taken to ensure agreement with final conclusions and recommendations.

During the December 2005 meeting, Panel members reviewed and discussed all committee drafts.

During the May 2006 meeting, the Panel conducted a thorough review and discussion of the report and reached consensus on the recommendations. For controversial topics, votes were taken to ensure that each individual's opinion was considered. In July, using conference calls and electronic mail, the Panel completed a draft of the EPR—3: Full Report 2007 for submission in July/August to a panel of expert consultants for their review and comments. In response to their comments, a revised draft of the EPR—3: Full Report 2007 was developed and circulated in November to the NAEPP Guidelines Implementation Panel (GIP) for their comment. This draft was also posted on the NHLBI Web site for public comment in February 2007. The Expert Panel considered 721 comments from 140 reviewers. Edits were made to the documents, as appropriate, before the full EPR—3: Full Report 2007 was finalized and published. The EPR—3: Full Report 2007 will be used to develop clinical practice guidelines and practice-based tools as well as educational materials for patients and the public.

In summary, the NAEPP "Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Full Report 2007" represents the NAEPP's ongoing effort to keep recommendations for clinical practice up to date and based upon a systematic review of the best available scientific evidence by a Panel of experts, as well as peer review and critique by the collective expertise of external research/science consultants, the NAEPP CC members, guidelines implementation specialists, and public comment. The relationship between guidelines and clinical research is a dynamic one, and the NAEPP recognizes that the task of keeping guidelines' recommendations up to date is an increasing challenge. In 1991, many recommendations were based on expert opinion because there were only limited randomized clinical trials in adults, and almost none in children, that adequately tested clinical interventions

grounded in research findings about the disease process in asthma. The large gaps in the literature defined pressing clinical research questions that have now been vigorously addressed by the scientific community, as the size of the literature reviewed for the current report attests. The NAEPP is grateful to all of the Expert Panel members for meeting the challenge with tremendous dedication and to Dr. William Busse for his outstanding leadership. The NAEPP would particularly like to acknowledge the contributions of Dr. Gail Shapiro, who served on NAEPP Expert Panels from 1991 until her death in August 2006. Dr. Shapiro provided valuable continuity to the Panel's deliberations while simultaneously offering a fresh perspective that was rooted in observations from her clinical practice and was supported and substantiated by her clinical research and indepth understanding of the literature. Dr. Shapiro had a passion for improving asthma care and an unwavering commitment to develop evidence-based recommendations that would also be practical. Dr. Shapiro inspired in others the essence of what NAEPP hopes to offer with this updated Expert Panel Report: a clear vision for clinicians and patients to work together to achieve asthma control.

References

EPR. Expert panel report: guidelines for the diagnosis and management of asthma (EPR 1991). NIH Publication No. 91-3642. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1991.

EPR—2. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

EPR—Update 2002. Expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics 2002 (EPR—Update 2002). NIH Publication No. 02-5074. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003.

Jadad AR, Moher M, Browman GP, Booker L, Sigouin C, Fuentes M, Stevens R. Systematic reviews and meta-analyses on treatment of asthma: critical evaluation. *BMJ* 2000;320(7234):537–40.

NHIS. National health interview survey (NHIS 2005). Hyattsville, MD: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2005. Available at http://www.cdc.gov/nchs/about/major/nhis/reports_2005.htm.

SECTION 2, DEFINITION, PATHOPHYSIOLOGY AND PATHOGENESIS OF ASTHMA, AND NATURAL HISTORY OF ASTHMA

KEY POINTS: DEFINITION, PATHOPHYSIOLOGY AND PATHOGENESIS OF ASTHMA, AND NATURAL HISTORY OF ASTHMA

- Asthma is a chronic inflammatory disorder of the airways. This feature of asthma has implications for the diagnosis, management, and potential prevention of the disease.
- The immunohistopathologic features of asthma include inflammatory cell infiltration:
  - Neutrophils (especially in sudden-onset, fatal asthma exacerbations; occupational asthma, and patients who smoke)
  - Eosinophils
  - Lymphocytes
  - Mast cell activation
  - Epithelial cell injury
- Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity.
- In some patients, persistent changes in airway structure occur, including sub-basement fibrosis, mucus hypersecretion, injury to epithelial cells, smooth muscle hypertrophy, and angiogenesis.
- Gene-by-environment interactions are important to the expression of asthma.
- Atopy, the genetic predisposition for the development of an immunoglobulin E (IgE)-mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma.
  - Viral respiratory infections are one of the most important causes of asthma exacerbation and may also contribute to the development of asthma.

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- The critical role of inflammation has been further substantiated, but evidence is emerging for considerable variability in the pattern of inflammation, thus indicating phenotypic differences that may influence treatment responses.
- Gene-by-environmental interactions are important to the development and expression of asthma. Of the environmental factors, allergic reactions remain important. Evidence also suggests a key and expanding role for viral respiratory infections in these processes.
- The onset of asthma for most patients begins early in life with the pattern of disease persistence determined by early, recognizable risk factors including atopic disease, recurrent wheezing, and a parental history of asthma.
- Current asthma treatment with anti-inflammatory therapy does not appear to prevent progression of the underlying disease severity.

Introduction

Asthma is a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness and an underlying inflammation. This interaction can be highly variable among patients and within patients over time. This section presents a definition of asthma, a description of the processes on which that definition is based—the pathophysiology and pathogenesis of asthma, and the natural history of asthma.

Definition of Asthma

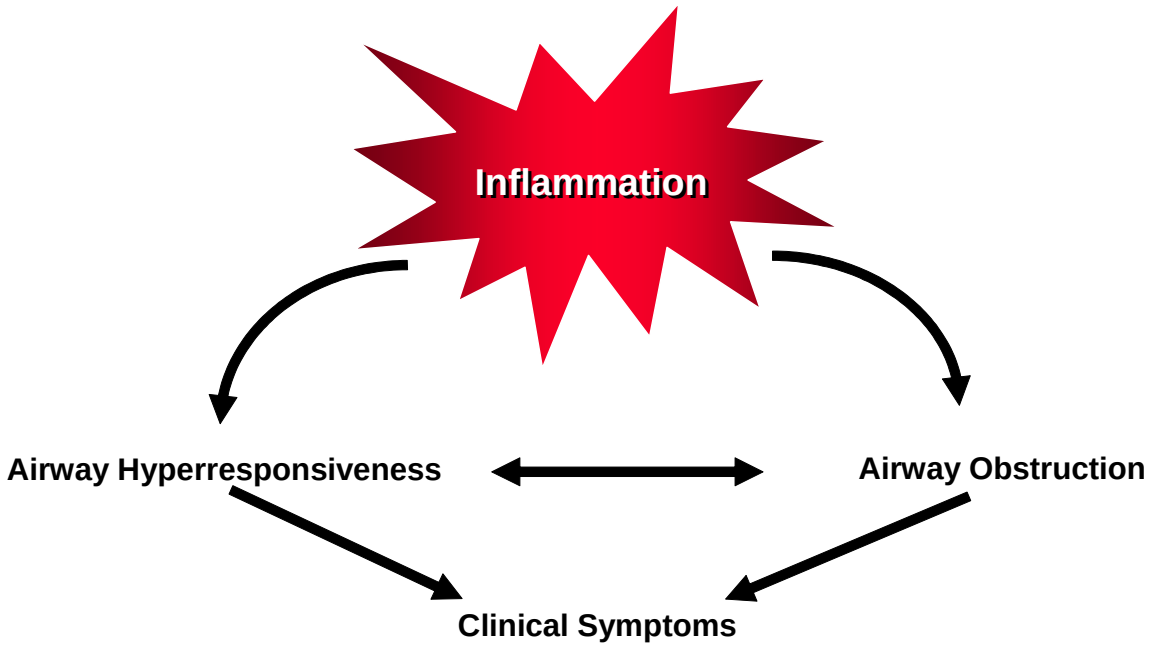
Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation (box 2–1). The interaction of these features of asthma determines the clinical manifestations and severity of asthma (figure 2–1) and the response to treatment.

BOX 2–1. CHARACTERISTICS OF CLINICAL ASTHMA

- Symptoms
- Airway obstruction
- Inflammation
- Hyperresponsiveness

The concepts underlying asthma pathogenesis have evolved dramatically in the past 25 years and are still undergoing evaluation as various phenotypes of this disease are defined and greater insight links clinical features of asthma with genetic patterns (Busse and Lemanske 2001; EPR—2 1997). Central to the various phenotypic patterns of asthma is the presence of underlying airway inflammation, which is variable and has distinct but overlapping patterns that reflect different aspects of the disease, such as intermittent versus persistent or acute versus chronic manifestations. Acute symptoms of asthma usually arise from bronchospasm and require and respond to bronchodilator therapy. Acute and chronic inflammation can affect not only the airway caliber and airflow but also underlying bronchial hyperresponsiveness, which enhances susceptibility to bronchospasm (Cohn et al. 2004).

FIGURE 2–1. THE INTERPLAY AND INTERACTION BETWEEN AIRWAY INFLAMMATION AND THE CLINICAL SYMPTOMS AND PATHOPHYSIOLOGY OF ASTHMA



Treatment with anti-inflammatory drugs can, to a large extent, reverse some of these processes; however, the successful response to therapy often requires weeks to achieve and, in some situations, may be incomplete (Bateman et al. 2004; O'Byrne and Parameswaran 2006). For some patients, the development of chronic inflammation may be associated with permanent alterations in the airway structure—referred to as airway remodeling—that are not prevented by or fully responsive to currently available treatments (Holgate and Polosa 2006). Therefore, the paradigm of asthma has been expanded over the last 10 years from bronchospasm and airway inflammation to include airway remodeling in some persons (Busse and Lemanske 2001).

The concept that asthma may be a continuum of these processes that can lead to moderate and severe persistent disease is of critical importance to understanding the pathogenesis, pathophysiology, and natural history of this disease (Martinez 2006). Although research since the first NAEPP guidelines in 1991 (EPR 1991) has confirmed the important role of inflammation in asthma, the specific processes related to the transmission of airway inflammation to specific pathophysiologic consequences of airway dysfunction and the clinical manifestations of asthma have yet to be fully defined. Similarly, much has been learned about the host–environment factors that determine airways' susceptibility to these processes, but the relative contributions of either and the precise interactions between them that leads to the initiation or persistence of disease have yet to be fully established. Nonetheless, current science regarding the mechanisms of asthma and findings from clinical trials have led to therapeutic approaches that allow most people who have asthma to participate fully in activities they choose. As we learn more about the pathophysiology, phenotypes, and genetics of asthma, treatments will become available to ensure adequate asthma control for all persons and, ideally, to reverse and even prevent the asthma processes.

As a guide to describing asthma and identifying treatment directions, a working definition of asthma put forth in the previous Guidelines remains valid: *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma* (EPR 1991; EPR—2 1997).

This working definition and its recognition of key features of asthma have been derived from studying how airway changes in asthma relate to the various factors associated with the development of airway inflammation (e.g., allergens, respiratory viruses, and some occupational exposures) and recognition of genetic regulation of these processes. From these descriptive approaches has evolved a more comprehensive understanding of asthma pathogenesis, the processes involved in the development of persistent airway inflammation, and the significant implications that these immunological events have for the development, diagnosis, treatment, and possible prevention of asthma.

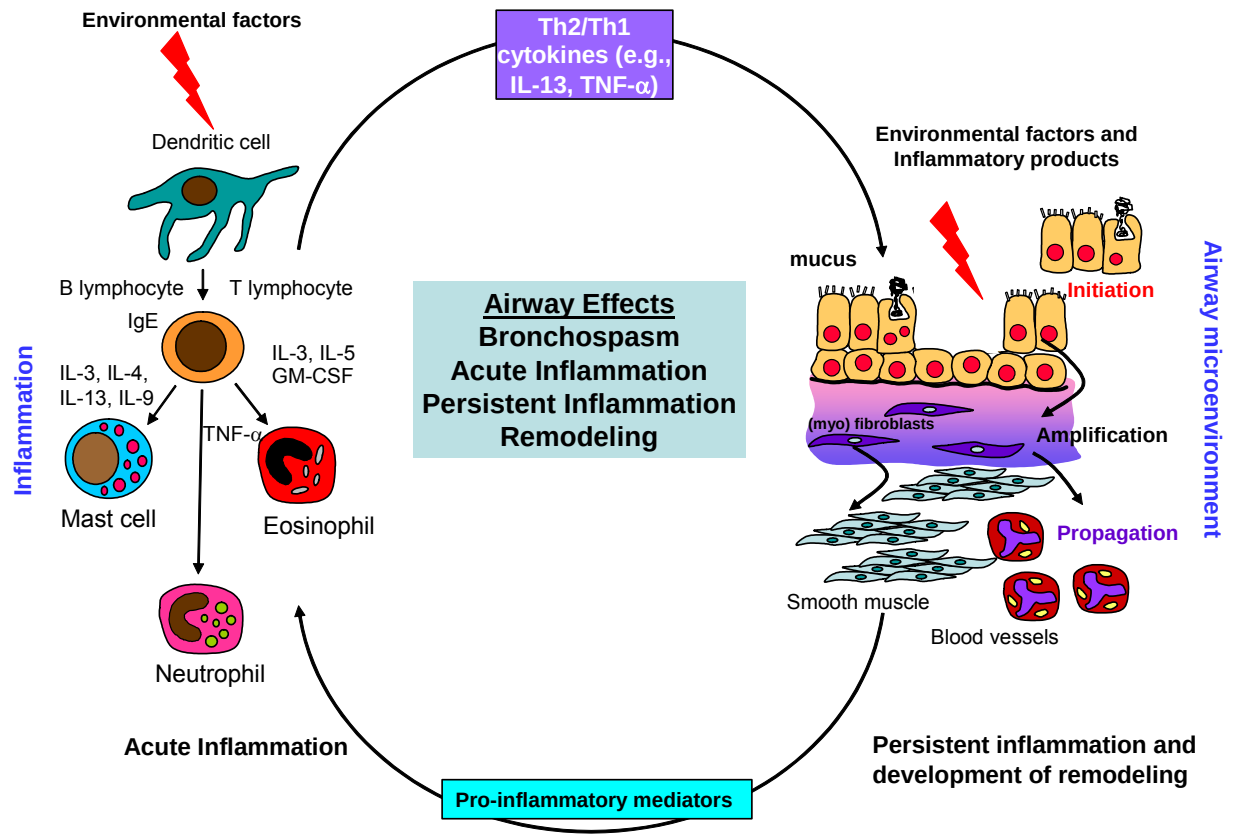
Pathophysiology and Pathogenesis of Asthma

Airflow limitation in asthma is recurrent and caused by a variety of changes in the airway. These include:

- **Bronchoconstriction.** In asthma, the dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle (Busse and Lemanske 2001). Aspirin and other nonsteroidal anti-inflammatory drugs (see section 3, component 3) can also cause acute airflow obstruction in some patients, and evidence indicates that this non-IgE-dependent response also involves mediator release from airway cells (Stevenson and Szczeklik 2006). In addition, other stimuli (including exercise, cold air, and irritants) can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to underlying airway inflammation. Stress may also play a role in precipitating asthma exacerbations. The mechanisms involved have yet to be established and may include enhanced generation of pro-inflammatory cytokines.

- **Airway edema.** As the disease becomes more persistent and inflammation more progressive, other factors further limit airflow (figure 2–2). These include edema, inflammation, mucus hypersecretion and the formation of inspissated mucus plugs, as well as structural changes including hypertrophy and hyperplasia of the airway smooth muscle. These latter changes may not respond to usual treatment.

FIGURE 2–2. FACTORS LIMITING AIRFLOW IN ACUTE AND PERSISTENT ASTHMA



Key: GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL-3, interleukin 3 (and similar); TNF-α, tumor necrosis factor-alpha

Source: Adapted and reprinted from The Lancet, 368, Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults, 780–93. Copyright (2006), with permission from Elsevier.

- **Airway hyperresponsiveness.** Airway hyperresponsiveness—an exaggerated bronchoconstrictor response to a wide variety of stimuli—is a major, but not necessarily unique, feature of asthma. The degree to which airway hyperresponsiveness can be defined by contractile responses to challenges with methacholine correlates with the clinical severity of asthma. The mechanisms influencing airway hyperresponsiveness are multiple and include inflammation, dysfunctional neuroregulation, and structural changes; inflammation appears to be a major factor in determining the degree of airway hyperresponsiveness. Treatment directed toward reducing inflammation can reduce airway hyperresponsiveness and improve asthma control.

- **Airway remodeling.** In some persons who have asthma, airflow limitation may be only partially reversible. Permanent structural changes can occur in the airway (figure 2–2); these are associated with a progressive loss of lung function that is not prevented by or fully

reversible by current therapy. Airway remodeling involves an activation of many of the structural cells, with consequent permanent changes in the airway that increase airflow obstruction and airway responsiveness and render the patient less responsive to therapy (Holgate and Polosa 2006). These structural changes can include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and hypersecretion (box 2–2). Regulation of the repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response.

BOX 2–2. FEATURES OF AIRWAY REMODELING

- Inflammation
- Mucus hypersecretion
- Subepithelial fibrosis
- Airway smooth muscle hypertrophy
- Angiogenesis

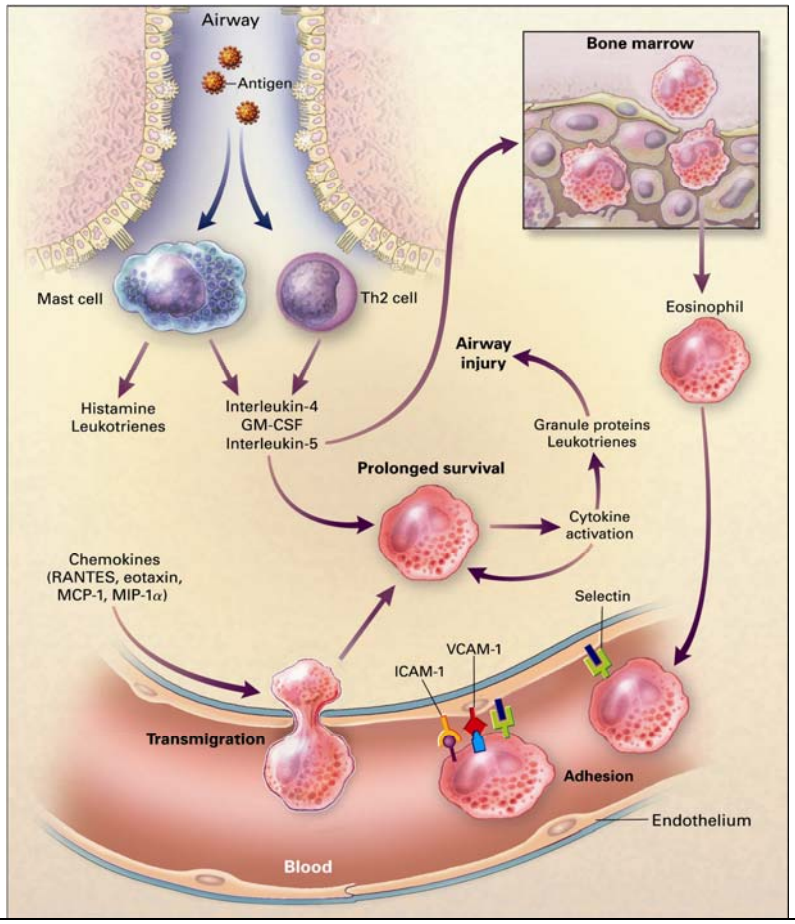
PATHOPHYSIOLOGIC MECHANISMS IN THE DEVELOPMENT OF AIRWAY INFLAMMATION

Inflammation has a central role in the pathophysiology of asthma. As noted in the definition of asthma, airway inflammation involves an interaction of many cell types and multiple mediators with the airways that eventually results in the characteristic pathophysiological features of the disease: bronchial inflammation and airflow limitation that result in recurrent episodes of cough, wheeze, and shortness of breath. The processes by which these interactive events occur and lead to clinical asthma are still under investigation. Moreover, although distinct phenotypes of asthma exist (e.g., intermittent, persistent, exercise-associated, aspirin-sensitive, or severe asthma), airway inflammation remains a consistent pattern. The pattern of airway inflammation in asthma, however, does not necessarily vary depending upon disease severity, persistence, and duration of disease. The cellular profile and the response of the structural cells in asthma are quite consistent.

Inflammatory Cells

Lymphocytes. An increased understanding of the development and regulation of airway inflammation in asthma followed the discovery and description of subpopulations of lymphocytes, T helper 1 cells and T helper 2 cells (Th1 and Th2), with distinct inflammatory mediator profiles and effects on airway function (figure 2–3). After the discovery of these distinct lymphocyte subpopulations in animal models of allergic inflammation, evidence emerged that, in human asthma, a shift, or predilection, toward the Th2-cytokine profile resulted in the eosinophilic inflammation characteristic of asthma (Cohn et al. 2004). In addition, generation of Th2 cytokines (e.g., interleukin-4 (IL-4), IL-5, and IL-13) could also explain the overproduction of IgE, presence of eosinophils, and development of airway hyperresponsiveness. There also may be a reduction in a subgroup of lymphocytes, regulatory T cells, which normally inhibit Th2 cells, as well as an increase in natural killer (NK) cells that release large amounts of Th1 and Th2 cytokines (Akbari et al. 2006; Larche et al. 2003). T lymphocytes, along with other airway resident cells, also can determine the development and degree of airway remodeling. Although it is an oversimplification of a complex process to describe asthma as a Th2 disease, recognizing the importance of *n* families of cytokines and chemokines has advanced our understanding of the development of airway inflammation (Barnes 2002; Zimmermann et al. 2003).

FIGURE 2–3. AIRWAY INFLAMMATION



Inhaled antigen activates mast cells and Th2 cells in the airway. They in turn induce the production of mediators of inflammation (such as histamine and leukotrienes) and cytokines including interleukin-4 and interleukin-5. Interleukin-5 travels to the bone marrow and causes terminal differentiation of eosinophils. Circulating eosinophils enter the area of allergic inflammation and begin migrating to the lung by rolling, through interactions with selectins, and eventually adhering to endothelium through the binding of integrins to members of the immunoglobulin superfamily of adhesion proteins: vascular-cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). As the eosinophils enter the matrix of the airway through the influence of various chemokines and cytokines, their survival is prolonged by interleukin-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF). On activation, the eosinophil releases inflammatory mediators, such as leukotrienes and granule proteins, to injure airway tissues. In addition, eosinophils can generate GM-CSF to prolong and potentiate their survival and contribution to persistent airway inflammation. MCP-1, monocyte chemotactic protein; and MIP-1α, macrophage inflammatory protein.

Reprinted by permission from Busse WW, Lemanske RF. Advances in Immunology *N Engl J Med* 2001; 344: 350-62. Copyright © 2001 Massachusetts Medical Society. All rights reserved.

Mast cells. Activation of mucosal mast cells releases bronchoconstrictor mediators (histamine, cysteinyl-leukotrienes, prostaglandin D_2) (Boyce 2003; Galli et al. 2005; Robinson 2004). Although allergen activation occurs through high-affinity IgE receptors and is likely the most relevant reaction, sensitized mast cells also may be activated by osmotic stimuli to account for exercise-induced bronchospasm (EIB). Increased numbers of mast cells in airway smooth muscle may be linked to airway hyperresponsiveness (Brightling et al. 2002). Mast cells also

can release a large number of cytokines to change the airway environment and promote inflammation even though exposure to allergens is limited.

Eosinophils. Increased numbers of eosinophils exist in the airways of most, but not all, persons who have asthma (Chu and Martin 2001; Sampson 2000; Williams 2004). These cells contain inflammatory enzymes, generate leukotrienes, and express a wide variety of pro-inflammatory cytokines. Increases in eosinophils often correlate with greater asthma severity. In addition, numerous studies show that treating asthma with corticosteroids reduces circulating and airway eosinophils in parallel with clinical improvement. However, the role and contribution of eosinophils to asthma is undergoing a reevaluation based on studies with an anti-IL-5 treatment that has significantly reduced eosinophils but did not affect asthma control (Leckie et al. 2000). Therefore, although the eosinophil may not be the only primary effector cell in asthma, it likely has a distinct role in different phases of the disease.

Neutrophils. Neutrophils are increased in the airways and sputum of persons who have severe asthma, during acute exacerbations, and in the presence of smoking. Their pathophysiological role remains uncertain; they may be a determinant of a lack of response to corticosteroid treatment (Fahy et al. 1995). The regulation of neutrophil recruitment, activation, and alteration in lung function is still under study, but leukotriene B_4 may contribute to these processes (Jatakanon et al. 1999; Wenzel et al. 1997; Wenzel 2006).

Dendritic cells. These cells function as key antigen-presenting cells that interact with allergens from the airway surface and then migrate to regional lymph nodes to interact with regulatory cells and ultimately to stimulate Th2 cell production from naïve T cells (Kuipers and Lambrecht 2004).

Macrophages. Macrophages are the most numerous cells in the airways and also can be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response (Peters-Golden 2004).

Resident cells of the airway. Airway smooth muscle is not only a target of the asthma response (by undergoing contraction to produce airflow obstruction) but also contributes to it (via the production of its own family of pro-inflammatory mediators). As a consequence of airway inflammation and the generation of growth factors, the airway smooth muscle cell can undergo proliferation, activation, contraction, and hypertrophy—events that can influence airway dysfunction of asthma.

Epithelial cells. Airway epithelium is another airway lining cell critically involved in asthma (Polito and Proud 1998). The generation of inflammatory mediators, recruitment and activation of inflammatory cells, and infection by respiratory viruses can cause epithelial cells to produce more inflammatory mediators or to injure the epithelium itself. The repair process, following injury to the epithelium, may be abnormal in asthma, thus furthering the obstructive lesions that occur in asthma.

Inflammatory Mediators

Chemokines are important in recruitment of inflammatory cells into the airways and are mainly expressed in airway epithelial cells (Zimmermann et al. 2003). Eotaxin is relatively selective for eosinophils, whereas thymus and activation-regulated chemokines (TARCs) and macrophage-derived chemokines (MDCs) recruit Th2 cells. There is an increasing appreciation

for the role this family of mediators has in orchestrating injury, repair, and many aspects of asthma.

Cytokines direct and modify the inflammatory response in asthma and likely determine its severity. Th2-derived cytokines include IL-5, which is needed for eosinophil differentiation and survival, and IL-4 which is important for Th2 cell differentiation and with IL-13 is important for IgE formation. Key cytokines include IL-1β and tumor necrosis factor-α (TNF-α), which amplify the inflammatory response, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which prolongs eosinophil survival in airways. Recent studies of treatments directed toward single cytokines (e.g., monoclonal antibodies against IL-5 or soluble IL-4 receptor) have not shown benefits in improving asthma outcomes.

Cysteinyl-leukotrienes are potent bronchoconstrictors derived mainly from mast cells. They are the only mediator whose inhibition has been specifically associated with an improvement in lung function and asthma symptoms (Busse 1996; Leff 2001). Recent studies have also shown leukotriene B_4 can contribute to the inflammatory process by recruitment of neutrophils (Gelfand and Dakhama 2006).

Nitric oxide (NO) is produced predominantly from the action of inducible NO synthase in airway epithelial cells; it is a potent vasodilator (Deykin et al. 2002; Strunk et al. 2003). Measurements of fractional exhaled NO (FeNO) may be useful for monitoring response to asthma treatment because of the purported association between FeNO and the presence of inflammation in asthma (Green et al. 2002).

Immunoglobulin E

IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic diseases and the development and persistence of inflammation. IgE attaches to cell surfaces via a specific high-affinity receptor. The mast cell has large numbers of IgE receptors; these, when activated by interaction with antigen, release a wide variety of mediators to initiate acute bronchospasm and also to release pro-inflammatory cytokines to perpetuate underlying airway inflammation (Boyce 2003; Sporik et al. 1995). Other cells, basophils, dendritic cells, and lymphocytes also have high-affinity IgE receptors.

The development of monoclonal antibodies against IgE has shown that the reduction of IgE is effective in asthma treatment (Busse et al. 2001; Holgate et al. 2005). These clinical observations further support the importance of IgE to asthma.

Implications of Inflammation for Therapy

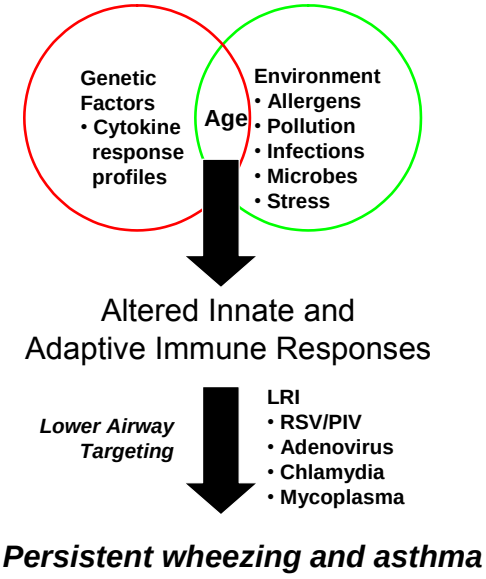
Recent scientific investigations have focused on translating the increased understanding of the inflammatory processes in asthma into therapies targeted at interrupting these processes (Barnes 2002). Some investigations have yielded promising results, such as the development leukotriene modifiers and anti-IgE monoclonal antibody therapy. Other studies, such as those directed at IL-4 or IL-5 cytokines, underscore the relevance of multiple factors regulating inflammation in asthma and the redundancy of these processes. All of these clinical studies also indicate that phenotypes of asthma exist, and these phenotypes may have very specific patterns of inflammation that require different treatment approaches. Current studies are investigating novel therapies targeted at the cytokines, chemokines, and inflammatory cells farther upstream in the inflammatory process. For example, drugs designed to inhibit the Th2 inflammatory pathway may cause a broad spectrum of effects such as airway

hyperresponsiveness and mucus hypersecretion. Further research into the mechanisms responsible for the varying asthma phenotypes and appropriately targeted therapy may enable improved control for all manifestations of asthma, and, perhaps, prevention of disease progression.

PATHOGENESIS

What initiates the inflammatory process in the first place and makes some persons susceptible to its effects is an area of active investigation. There is not yet a definitive answer to this question, but new observations suggest that the origins of asthma primarily occur early in life. The expression of asthma is a complex, interactive process that depends on the interplay between two major factors—host factors (particularly genetics) and environmental exposures that occur at a crucial time in the development of the immune system (figure 2–4).

FIGURE 2–4. HOST FACTORS AND ENVIRONMENTAL EXPOSURES

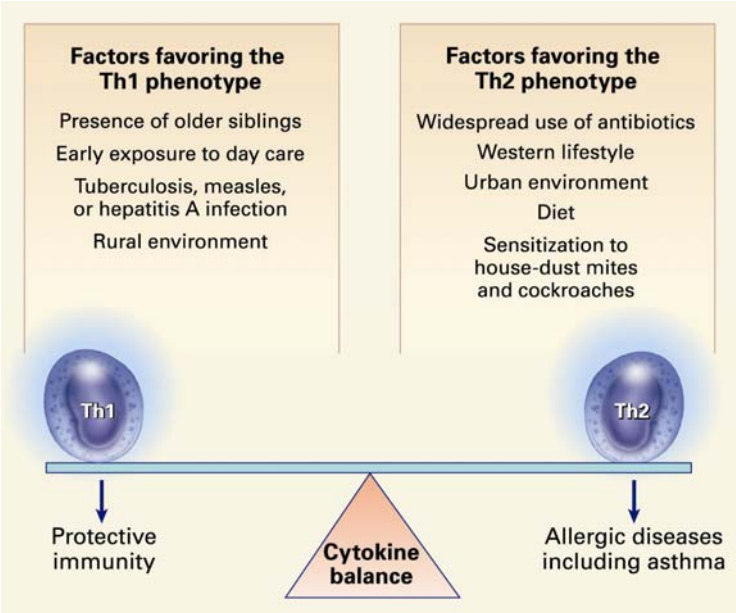


Key: LRI, lower respiratory illnesses; RSV, respiratory syncytial virus; PIV, parainfluenza virus

Host Factors

Innate immunity. There is considerable interest in the role of innate and adaptive immune responses associated with both the development and regulation of inflammation (Eder et al. 2006). In particular, research has focused on an imbalance between Th1 and Th2 cytokine profiles and evidence that allergic diseases, and possibly asthma, are characterized by a shift toward a Th2 cytokine-like disease, either as overexpression of Th2 or underexpression of Th1 (figure 2–5). Airway inflammation in asthma may represent a loss of normal balance between two "opposing" populations of Th lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce IL-2 and interferon-γ (IFN-γ), which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, -5, -6, -9, and -13) that can mediate allergic inflammation. The current "hygiene hypothesis" of asthma illustrates how this cytokine imbalance may explain some of the

FIGURE 2–5. CYTOKINE BALANCE



Numerous factors, including alterations in the number or type of infections early in life, the widespread use of antibiotics, adoption of the Western lifestyle, and repeated exposure to allergens, may affect the balance between Th1-type and Th2-type cytokine responses and increase the likelihood that the immune response will be dominated by Th2 cells and thus will ultimately lead to the expression of allergic diseases such as asthma.

Reprinted by permission from Busse WW, Lemanske RF. Advances in Immunology *N Engl J Med* 2001; 344: 350-62. Copyright © 2001 Massachusetts Medical Society. All rights reserved.

dramatic increases in asthma prevalence in westernized countries. This hypothesis is based on the assumption that the immune system of the newly born is skewed toward Th2 cytokine generation. Following birth, environmental stimuli such as infections will activate Th1 responses and bring the Th1/Th2 relationship to an appropriate balance. Evidence indicates that the incidence of asthma is reduced in association with certain infections (*M. tuberculosis,* measles, or hepatitis A), exposure to other children (e.g., presence of older siblings and early enrollment in childcare), and less frequent use of antibiotics (Eder et al. 2006; Gern et al. 1999; Gern and Busse 2002; Horwood et al. 1985; Sears et al. 2003). Furthermore, the absence of these lifestyle events is associated with the persistence of a Th2 cytokine pattern. Under these conditions, the genetic background of the child who has a cytokine imbalance toward Th2 will set the stage to promote the production of IgE antibodies to key environmental antigens, such as house-dust mite, cockroach, *Alternaria*, and possibly cat. Therefore, a gene-by-environment interaction occurs in which the susceptible host is exposed to environmental factors that are capable of generating IgE, and sensitization occurs. Precisely why the airways of some individuals are susceptible to these allergic events has not been established.

There also appears to be a reciprocal interaction between the two subpopulations in which Th1 cytokines can inhibit Th2 generation and vice versa. Allergic inflammation may be the result of an excessive expression of Th2 cytokines. Alternatively, recent studies have suggested the possibility that the loss of normal immune balance arises from a cytokine dysregulation in which Th1 activity in asthma is diminished. The focus on actions of cytokines and chemokines to regulate and activate the inflammatory profile in asthma has provided

ongoing and new insight into the pattern of airway injury that may lead to new therapeutic targets.

Genetics. It is well recognized that asthma has an inheritable component to its expression, but the genetics involved in the eventual development of asthma remain a complex and incomplete picture (Holgate 1999; Ober 2005). To date, many genes have been found that either are involved in or linked to the presence of asthma and certain of its features. The complexity of their involvement in clinical asthma is noted by linkages to certain phenotypic characteristics, but not necessarily the pathophysiologic disease process or clinical picture itself. The role of genetics in IgE production, airway hyperresponsiveness, and dysfunctional regulation of the generation of inflammatory mediators (such as cytokines, chemokines, and growth factors) has appropriately captured much attention. In addition, studies are investigating genetic variations that may determine the response to therapy. The relevance of polymorphisms in the beta-adrenergic and corticosteroid receptors in determining responsiveness to therapies is of increasing interest, but the widespread application of these genetic factors remains to be fully established.

Sex. In early life, the prevalence of asthma is higher in boys. At puberty, however, the sex ratio shifts, and asthma appears predominantly in women (Horwood et al. 1985). How specifically sex and sex hormones, or related hormone generation, are linked to asthma has not been established, but they may contribute to the onset and persistence of the disease.

Environmental Factors

Two major environmental factors have emerged as the most important in the development, persistence, and possibly severity of asthma: airborne allergens and viral respiratory infections. In the susceptible host, and at a critical time of development (e.g., immunological and physiological), both respiratory infections and allergens have a major influence on asthma development and its likely persistence. It is also apparent that allergen exposure, allergic sensitization, and respiratory infections are not separate entities but function interactively in the eventual development of asthma.

Allergens. The role of allergens in the development of asthma has yet to be fully defined or resolved, but it is obviously important. Sensitization and exposure to house-dust mite and *Alternaria* are important factors in the development of asthma in children. Early studies showed that animal danders, particularly dog and cat, were associated with the development of asthma. Recent data suggest that, under some circumstances, dog and cat exposure in early life may actually protect against the development of asthma. The determinant of these diverse outcomes has not been established. Studies to evaluate house-dust mite and cockroach exposure have shown that the prevalence of sensitization and subsequent development of asthma are linked (Huss et al. 2001; Sporik et al. 1990; Wahn et al. 1997). Exposure to cockroach allergen, for example, a major allergen in inner-city dwellings, is an important cause of allergen sensitization, a risk factor for the development of asthma (Rosenstreich et al. 1997). In addition, allergen exposure can promote the persistence of airway inflammation and likelihood of an exacerbation.

Respiratory infections. During infancy, a number of respiratory viruses have been associated with the inception or development of the asthma. In early life, respiratory syncytial virus (RSV) and parainfluenza virus in particular, cause bronchiolitis that parallels many features of childhood asthma (Gern and Busse 2002; Sigurs et al. 2000). A number of long-term prospective studies of children admitted to hospital with documented RSV have shown that

approximately 40 percent of these infants will continue to wheeze or have asthma in later childhood (Sigurs et al. 2000). Symptomatic rhinovirus infections in early life also are emerging as risk factors for recurrent wheezing. On the other hand, evidence also indicates that certain respiratory infections early in life—including measles and even RSV (Stein et al. 1999) or repeated viral infections (other than lower respiratory tract infections) (Illi et al. 2001; Shaheen et al. 1996)—can protect against the development of asthma. The "hygiene hypothesis" of asthma suggests that exposure to infections early in life influences the development of a child's immune system along a "nonallergic" pathway, leading to a reduced risk of asthma and other allergic diseases. Although the hygiene hypothesis continues to be investigated, this association may explain observed associations between large family size, later birth order, daycare attendance, and a reduced risk of asthma (Eder et al. 2006; Illi et al. 2001).

The influence of viral respiratory infections on the development of asthma may depend on an interaction with atopy. The atopic state can influence the lower airway response to viral infections, and viral infections may then influence the development of allergic sensitization. The airway interactions that may occur when individuals are exposed simultaneously to both allergens and viruses are of interest but are not defined at present.

Other environmental exposures. Tobacco smoke, air pollution, occupations, and diet have also been associated with an increased risk for the onset of asthma, although the association has not been as clearly established as with allergens and respiratory infections (Malo et al. 2004; Strachan and Cook 1998a; Strachan and Cook 1998b).

In utero exposure to environmental tobacco smoke increases the likelihood for wheezing in the infant, although the subsequent development of asthma has not been well defined. In adults who have asthma, cigarette smoking has been associated with an increase in asthma severity and decreased responsiveness to inhaled corticosteroids (ICSs) (Dezateux et al. 1999).

The role of air pollution in the development of asthma remains controversial and may be related to allergic sensitization (American Thoracic Society 2000). One recent epidemiologic study showed that heavy exercise (three or more team sports) outdoors in communities with high concentration of ozone was associated with a higher risk of asthma among school-age children (McConnell et al. 2002). The relationship between increased levels of pollution and increases in asthma exacerbations and emergency care visits has been well documented.

An association of low intake of antioxidants and omega-3 fatty acids has been noted in observational studies, but a direct link as a causative factor has not been established.

Increasing rates of obesity have paralleled increasing rates in asthma prevalence, but the interrelation is uncertain (Ford 2005). Obesity may be a risk factor for asthma due to the generation of unique inflammatory mediators that lead to airway dysfunction.

In summary, our understanding of asthma pathogenesis and underlying mechanisms now includes the concept that gene-by-environmental interactions are critical factors in the development of airway inflammation and eventual alteration in the pulmonary physiology that is characteristic of clinical asthma.

Natural History of Asthma

If the persistence and severity of asthma involves a progression of airway inflammation to airway remodeling and some eventual irreversible airway obstruction, then an important

question is whether anti-inflammatory medication (i.e., ICSs), given early in the course of disease might interrupt this process and prevent permanent declines in lung function. For early initiation of ICSs to be more beneficial than delayed initiation, two assumptions must be valid: (1) as a group, people who have mild or moderate persistent asthma experience a progressive decline in lung function that is measurable and clinically significant, and (2) treatment with ICSs prevents or slows this decline, in addition to providing long-term control of asthma. Reviews were conducted in 2002 (EPR—Update 2002) and for the current report to evaluate the literature on the effect of intervention with ICSs in altering the progression of disease.

NATURAL HISTORY OF PERSISTENT ASTHMA

Children

It is well established that asthma is a variable disease. Asthma can vary among individuals, and its progression and symptoms can vary within an individual's experience over time. The course of asthma over time, either remission or increasing severity, is commonly referred to as the natural history of the disease. It has been postulated that the persistence or increase of asthma symptoms over time is accompanied by a progressive decline in lung function. Recent research suggests that this may not be the case. Rather, the course of asthma may vary markedly between young children, older children and adolescents, and adults, and this variation is probably more dependent on age than on symptoms.

A prospective cohort study in which followup began at birth revealed that, in children whose asthma-like symptoms began before 3 years of age, deficits in lung growth associated with the asthma occurred by 6 years of age (Martinez et al. 1995). Continued followup on lung function measures taken at 11–16 years of age found that, compared to the group of children who experienced no asthma symptoms for the first 6 years of life, the group of children whose asthma symptoms began before 3 years of age experienced significant deficits in lung function at 11–16 years of age; however, no further loss in forced expiratory volume in 1 second (FEV_1) occurred compared to children who did not have asthma (Morgan et al. 2005). The group whose asthma symptoms began after 3 years of age did not experience deficits in lung function.

A longitudinal study of children 8–10 years of age found that bronchial hyperresponsiveness was associated with declines in lung function growth in both children who have active symptoms of asthma and children who did not have such symptoms (Xuan et al. 2000). Thus, symptoms neither predicted nor determined lung function deficits in this age group.

A study by Sears and colleagues (2003) assessed lung function repeatedly from ages 9 to 26 in almost 1,000 children from a birth cohort in Dunedin, New Zealand. They found that children who had asthma had persistently lower levels of FEV_1/forced vital capacity (FVC) ratio during the followup. Regardless of the severity of their symptoms, however, their levels of lung function paralleled those of children who did not have asthma, and no further losses of lung function were observed after age 9.

Baseline data from the Childhood Asthma Management Program (CAMP) study support the finding that the individual's age at the time of asthma onset influences declines in lung function growth. At the time of enrollment of children who had mild or moderate persistent asthma at 5–12 years of age, an inverse association between lung function and duration of asthma was noted (Zeiger et al. 1999). Although the analysis did not distinguish between age of onset and duration of asthma, it can be inferred that, because the average duration of asthma was 5 years and the average age of the children was 9 years, most children who had the longer duration of

asthma started experiencing symptoms before 3 years of age. The data suggest that these children had the lowest lung function levels. After 4–6 years of followup, the children in the CAMP study, on average, did not experience deficits in lung growth (as defined by postbronchodilator FEV_1), regardless of their symptom levels or the treatment they received (CAMP 2000). However, a followup analysis of the CAMP data showed that a subgroup of the children experienced progressive (at least 1 percent a year) reductions in lung growth, regardless of treatment group (Covar et al. 2004). Predictors of this progressive reduction, at baseline of the study, were male sex and younger age.

The CAMP study noted that when measures other than FEV_1 are used to assess lung function measures over time in childhood asthma, progressive declines are observed: the FEV_1/FVC ratio before bronchodilator use was smaller at the end of the treatment period than at the start in all three treatment groups; the decline in the ICS group was less than that of the placebo group (0.2 percent versus 1.8 percent) (CAMP 2000). In a comparison of lung function measures of CAMP study participants with lung function measures of children who did not have asthma, by year from ages 5 through 18, the FEV_1/FVC ratio was significantly lower for the children who had asthma compared to those who did not have asthma at age 5 (mean difference 7.3 percent for boys and 7.1 percent for girls), and the difference increased with age (9.8 percent for boys and 9.9 percent for girls) (Strunk et al. 2006).

Cumulatively, these studies suggest that most of the deficits in lung function growth observed in children who have asthma occur in children whose symptoms begin during the first 3 years of life, and the onset of symptoms after 3 years of age usually is not associated with significant deficits in lung function growth. Thus, a promising target for interventions designed to prevent deficits in lung function, and perhaps the development of more severe symptoms later in life, would be children who have symptoms before 3 years of age and seem destined to develop persistent asthma. However, it is important to distinguish this group from the majority of children who wheeze before 3 years of age and do not experience any more symptoms after 6 years of age (Martinez et al. 1995). Until recently, no validated algorithms were available to predict which children among those who had asthma-like symptoms early in life would go on to have persistent asthma. Data obtained from long-term longitudinal studies of children who were enrolled at birth have generated such a predictive index. The studies first identified an index of risk factors for developing persistent asthma symptoms among children younger than 3 years of age who had more than three episodes of wheezing during the previous year. The index was then applied to a birth cohort that was followed through 13 years of age. Seventy-six percent of the children who were diagnosed with asthma after 6 years of age had a positive asthma predictive index before 3 years of age; 97 percent of the children who did not have asthma after 6 years of age had a negative asthma predictive index before 3 years of age (Castro-Rodriguez et al. 2000). The index was subsequently refined and tested in a clinical trial to examine if treating children who had a positive asthma predictive index would prevent development of persistent wheezing (Guilbert et al. 2006). The asthma predictive index generated by these studies identifies the following risk factors for developing persistent asthma among children younger than 3 years of age who had four or more episodes of wheezing during the previous year: either (1) one of the following: parental history of asthma, a physician diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens, or (2) two of the following: evidence of sensitization to foods, $\geq$4 percent peripheral blood eosinophilia, or wheezing apart from colds.

Adults

Accelerated loss of lung function appears to occur in adults who have asthma. In a study of adults who have asthma and who received 2 weeks of high-dose prednisone if airflow

obstruction persisted after 2 weeks of bronchodilator therapy, the degree of persistent airflow obstruction correlated with both the severity and the duration of their asthma (Finucane et al. 1985).

Two large, prospective epidemiological studies evaluated the rate of decline in pulmonary function in adults who had asthma. In an 18-year prospective study of 66 nonsmokers who had asthma, 26 smokers who had asthma, and 186 control participants who had no asthma, spirometry was performed at 3-year intervals (Peat et al. 1987). Seventy-three percent of the study group underwent at least six spirometric evaluations. The slope for decline in lung function (FEV_1) was approximately 40 percent greater for the participants who had asthma than for those who had no asthma. This did not appear to result from extreme measurement produced by a few participants, because fewer than 25 percent of the participants who had asthma were measured with a slope less steep than the mean for those who did not have asthma. In another study, three spirometry evaluations were performed in 13,689 adults (778 had asthma, and 12,911 did not have asthma) over a 15-year period (Lange et al. 1998). The average decline in FEV_1 was significantly greater (38 mL per year) in those who had asthma than in those who did not have asthma (22 mL per year). Although, in this study, asthma was defined simply by patient report, the researchers noted that, because the 6 percent prevalence rate for asthma did not increase in this cohort as they increased in age, it is likely that the subjects who reported having asthma did indeed have asthma rather than chronic obstructive pulmonary disease (COPD). It is not possible to determine from these studies whether the loss of pulmonary function occurred in those who had mild or moderate asthma or only in those who had severe asthma. Nevertheless, the data support the likelihood of potential accelerated loss of pulmonary function in adults who have asthma.

New studies have addressed this issue since the “Expert Panel Review—Update 2002” (EPR—Update 2002). James and colleagues (2005) reanalyzed the data from the study of decline in lung function from Busselton, Australia (Peat et al. 1987), after adding a new survey in 1994–1995. Subjects (N = 9,317) had participated as adults (19 years or older) in one or more of the cross-sectional Busselton Health Surveys between 1966 and 1981 or in the followup study of 1994–1995. Using the whole data sample, James and colleagues found that subjects who had asthma showed significantly lower lung function during the whole followup period, but most of the differences were due to deficits in lung function present at the beginning of followup (when subjects were age 19). Once the effect of smoking was taken into account, the excess decline in FEV_1 attributable to asthma was 3.78 mL per year for women and 3.69 mL per year for men. Although these results were statistically significant, their clinical relevance is debatable. Sherrill and coworkers (2003) reanalyzed the data from the Tucson Epidemiologic Study of Airway Obstructive Disease. A total of 2,926 subjects, with longitudinal data for lung function assessed in up to 12 surveys spanning a period of up to 20 years, were included. They found that, unlike subjects who had a diagnosis of COPD, in those who had diagnosis of longstanding asthma, FEV_1 did not decline at a more rapid rate than normal. This was also true for subjects who had asthma and COPD. Griffith and colleagues (2001) studied decline in lung function in 5,242 participants in the Cardiovascular Health Study who were over age 65 at enrollment. Each participant had up to three lung function measurements over a 7-year interval. Subjects who had asthma had lower levels of FEV_1 than those who reported no asthma. However, after adjustment for emphysema and chronic bronchitis, there were no significant increases in the rate of decline in FEV_1 in participants who had asthma.

Summary

Taken together, these longitudinal epidemiological studies and clinical trials indicate that the progression of asthma, as measured by declines in lung function, varies in different age groups. Declines in lung function growth observed in children appear to occur by 6 years of age and occur predominantly in those children whose asthma symptoms started before 3 years of age. Children 5–12 years of age who have mild or moderate persistent asthma, on average, do not appear to experience declines in lung function through 11–17 years of age, although a subset of these children experience progressive reductions in lung growth as measured by FEV_1. Furthermore, there is emerging evidence of reductions in the FEV_1/FVC ratio, apparent in young children who have mild or moderate asthma compared to children who do not have asthma, that increase with age. There is also evidence of progressively declining lung function in adults who have asthma, but the clinical significance and the extent to which these declines contribute to the development of fixed airflow obstruction are unknown.

EFFECT OF INTERVENTIONS ON NATURAL HISTORY OF ASTHMA

Data on the effect of interventions on the progression of asthma, as measured by declines in lung function, airway hyperresponsiveness, or the severity of symptoms, were evaluated for EPR—Update 2002 and the current update. The Expert Panel does not recommend using ICSs for the purpose of modifying the underlying disease process (e.g., preventing persistent asthma). Evidence to date indicates that daily long-term control medication does not alter the underlying severity of the disease. Although a preliminary study suggests that appropriate control of childhood asthma may prevent more serious asthma or irreversible obstruction in later years (Agertoft and Pedersen 1994), these observations were not verified in a recent long-term randomized control trial (RCT) in 1,041 children 5–12 years of age (CAMP 2000). This study does not support the assumption that, on average, children 5–12 years of age who have mild or moderate persistent asthma have a progressive decline in lung function. Children in the placebo group did not experience a decline in postbronchodilator FEV_1 over the 5-year treatment period, and they had postbronchodilator FEV_1 levels similar to children in the ICS and nedocromil treatment groups at the end of the study. Observational prospective data from other studies of large groups of children suggest that the timing of the CAMP intervention was too late, as most loss of lung function in childhood asthma appears to occur in the first 3–5 years of life (Martinez et al. 1995). However, in a recent randomized, controlled prospective study, children 2–3 years of age who were at high risk of developing persistent asthma were treated for 2 years with ICSs and observed for 1 additional year after treatment was discontinued. That study demonstrated that the intervention group had lung function and asthma symptom levels similar to the placebo group at the end of the study (Guilbert et al. 2006).

Two recent studies addressed the possibility that ICSs may prevent the putative declines in lung function believed to occur shortly after the beginning of the disease in adults who have late-onset asthma. A retrospective study (Selroos et al. 2004) reported the results of an observational study of adults who had mild-to-moderate asthma and were treated for 5 years with an ICS. One group, treated early in the disease (less than 2 years after diagnosis), had better outcomes in terms of lung function than those who started treatment more than 2 years after diagnosis. The group in which treatment was started more than 2 years after diagnosis, however, had lower levels of lung function at the beginning of the trial. Therefore, it is not possible to determine from these data what the results would have been in a randomized trial. Two recent long-term observational studies report an association between ICS therapy and reduced decline in FEV_1 in adults who have asthma (Dijkstra et al. 2006; Lange et al. 2006). However, long-term RCTs will be necessary to confirm a causal relationship.

The START study (Pauwels et al. 2003) enrolled 7,241 subjects, 5–66 years of age, who had mild asthma of less than 2 years' duration, according to each subject's report. Participants were randomized to a low-dose ICS or placebo and were followed prospectively for 3 years. The study found a slightly better level of postbronchodilator lung function in participants in the active arm than in the placebo arm, but the difference was more prominent after 1 year of treatment (+1.48 percent predicted FEV_1) than at the end of the treatment period (+0.88 percent predicted FEV_1), suggesting no effect in the putative progressive loss in lung function in these subjects.

With respect to the potential role of ICSs in changing the natural course of asthma, the relevant clinical question is: Are ICSs associated with less disease burden *after* discontinuation of therapy? The best available evidence in children 5–12 years of age (CAMP 2000) and 2–3 years of age (Guilbert et al. 2006) demonstrated that, although ICSs provide superior control and prevention of symptoms and exacerbations during treatment, symptoms and airway hyperresponsiveness worsen when treatment is withdrawn (EPR—Update 2002; Guilbert et al. 2006). This evidence suggests that currently available therapy controls but does not modify the underlying disease process.

IMPLICATIONS OF CURRENT INFORMATION ABOUT PATHOPHYSIOLOGY AND PATHOGENESIS, AND NATURAL HISTORY FOR ASTHMA MANAGEMENT

Airway inflammation is a major factor in the pathogenesis and pathophysiology of asthma. The importance of inflammation to central features of asthma continues to expand and underscore this characteristic as a primary target of treatment. It has also become apparent, however, that airway inflammation is variable in many aspects including intensity, cellular/mediator pattern, and response to therapy. As knowledge of the various phenotypes of inflammation become apparent, it is likely that treatment also will also have greater specificity and, presumably, effectiveness.

It is also apparent that asthma, and its persistence, begin early in life. Although the factors that determine persistent versus intermittent asthma have yet to be ascertained, this information will become important in determining the type of treatment, its duration, and its effect on various outcomes of asthma. Early studies have indicated that although current treatment is effective in controlling symptoms, reducing airflow limitations, and preventing exacerbations, present treatment does not appear to prevent the underlying severity of asthma.

Despite these unknowns, the current understanding of basic mechanisms in asthma has greatly improved appreciation of the role of treatment. The Expert Panel's recommendations for asthma treatment, which are directed by knowledge of basic mechanisms, should result in improved control of asthma and a greater understanding of therapeutic effectiveness.

References

Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88(5):373–81.

Akbari O, Faul JL, Hoyte EG, Berry GJ, Wahlstrom J, Kronenberg M, DeKruyff RH, Umetsu DT. CD4+ invariant T-cell-receptor+ natural killer T cells in bronchial asthma. *N Engl J Med* 2006;354(11):1117–29.

American Thoracic Society. What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. *Am J Respir Crit Care Med* 2000;161(2 Pt 1):665–73.

Barnes PJ. Cytokine modulators as novel therapies for asthma. *Annu Rev Pharmacol Toxicol* 2002;42:81–98.

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004;170(8):836–44.

Boyce JA. Mast cells: beyond IgE. *J Allergy Clin Immunol* 2003;111(1):24–32; quiz 33. Review.

Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. *N Engl J Med* 2002;346(22):1699–1705.

Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108(2):184–90.

Busse WW. The role of leukotrienes in asthma and allergic rhinitis. *Clin Exp Allergy* 1996;26(8):868–79. Review.

Busse WW, Lemanske RF Jr. Asthma. *N Engl J Med* 2001;344(5):350–62.

Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1403–06.

Childhood Asthma Management Program Research Group (CAMP). Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054–63.

Chu HW, Martin RJ. Are eosinophils still important in asthma? *Clin Exp Allergy* 2001;31(4):525–28.

Cohn L, Elias JA, Chupp GL. Asthma: mechanisms of disease persistence and progression. *Annu Rev Immunol* 2004;22:789–815. Review.

Covar RA, Spahn JD, Murphy JR, Szefler SJ; Childhood Asthma Management Program Research Group. Progression of asthma measured by lung function in the childhood asthma management program. *Am J Respir Crit Care Med* 2004;170(3):234–41. Epub March 2004.

Deykin A, Massaro AF, Drazen JM, Israel E. Exhaled nitric oxide as a diagnostic test for asthma: online versus offline techniques and effect of flow rate. *Am J Respir Crit Care Med* 2002;165(12):1597–1601.

Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. *Am J Respir Crit Care Med* 1999;159(2):403–10.

Dijkstra A, Vonk JM, Jongepier H, Koppelman GH, Schouten JP, ten Hacken NH, Timens W, Postma DS. Lung function decline in asthma: association with inhaled corticosteroids, smoking and sex. *Thorax* 2006;61(2):105–10. Epub November 2005.

Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;355(21):2226–2235. Review.

EPR. "Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma (EPR 1991)". NIH Publication No. 91-3642. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1991.

EPR—2. "Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma (EPR—2 1997)". NIH Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

EPR—Update 2002. "Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002 (EPR—Update 2002)". NIH Publication No. 02-5074. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003.

Fahy JV, Kim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol* 1995;95(4):843–52.

Finucane KE, Greville HW, Brown PJ. Irreversible airflow obstruction. Evolution in asthma. *Med J Aust* 1985;142(11):602–4.

Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005;115(5):897–909; quiz 910. Review.

Galli SJ, Kalesnikoff J, Grimbaldeston MA, Piliponsky AM, Williams CM, Tsai M. Mast cells as "tunable" effector and immunoregulatory cells: recent advances. *Annu Rev Immunol* 2005;23:749–86. Review.

Gelfand EW, Dakhama A. CD8+ T lymphocytes and leukotriene B4: novel interactions in the persistence and progression of asthma. *J Allergy Clin Immunol* 2006;117(3):577–82.

Gern JE, Busse WW. Relationship of viral infections to wheezing illnesses and asthma. *Nat Rev Immunol* 2002;2(2):132–8. Review.

Gern JE, Lemanske RF Jr, Busse WW. Early life origins of asthma. *J Clin Invest* 1999;104(7):837–43. Review.

Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, Wardlaw AJ, Pavord ID. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360(9347):1715–21.

Griffith KA, Sherrill DL, Siegel EM, Manolio TA, Bonekat HW, Enright PL. Predictors of loss of lung function in the elderly: the Cardiovascular Health Study. *Am J Respir Crit Care Med* 2001;163(1):61–68.

Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, Bacharier LB, Lemanske RF Jr, Strunk RC, Allen DB, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354(19):1985–97.

Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol* 2005;115(3):459–65. Review.

Holgate ST. Genetic and environmental interaction in allergy and asthma. *J Allergy Clin Immunol* 1999;104(6):1139–46. Review.

Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet* 2006;368(9537):780–93. Review.

Horwood LJ, Fergusson DM, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985;75(5):859–68.

Huss K, Adkinson NF Jr, Eggleston PA, Dawson C, Van Natta ML, Hamilton RG. House dust mite and cockroach exposure are strong risk factors for positive allergy skin test responses in the Childhood Asthma Management Program. *J Allergy Clin Immunol* 2001;107(1):48–54.

Illi S, von Mutius E, Lau S, Bergmann R, Niggemann B, Sommerfeld C, Wahn U; MAS Group. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001;322(7283):390–5.

James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, Musk AW. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005;171(2):109–14. Epub 2004.

Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF, Barnes PJ. Neutrophilic inflammation in severe persistent asthma. *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1532–9.

Kuipers H, Lambrecht BN. The interplay of dendritic cells, Th2 cells and regulatory T cells in asthma. *Curr Opin Immunol* 2004;16(6):702–8. Review.

Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339(17):1194–200.

Lange P, Scharling H, Ulrik CS, Vestbo J. Inhaled corticosteroids and decline of lung function in community residents with asthma. *Thorax* 2006;61(2):100–4.

Larche M, Robinson DS, Kay AB. The role of T lymphocytes in the pathogenesis of asthma. *J Allergy Clin Immunol* 2003;111(3):450–63; quiz 464. Review.

Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, Mathur AK, Cowley HC, Chung KF, Djukanovic R, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356(9248):2144–8.

Leff AR. Regulation of leukotrienes in the management of asthma: biology and clinical therapy. *Annu Rev Med* 2001;52:1–14. Review.

Malo JL, Lemiere C, Gautrin D, Labrecque M. Occupational asthma. *Curr Opin Pulm Med* 2004;10(1):57–61. Review.

Martinez FD. Inhaled corticosteroids and asthma prevention. *Lancet* 2006;368(9537):708–710.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133–8.

McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, Avol E, Margolis HG, Peters JM. Asthma in exercising children exposed to ozone: a cohort study. *Lancet* 2002;359(9304):386–91.

Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, Taussig LM, Wright AL, Martinez FD. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172(10):1253–8. Epub August 2005.

Ober C. Perspectives on the past decade of asthma genetics. *J Allergy Clin Immunol* 2005;116(2):274–8.

O'Byrne PM, Parameswaran K. Pharmacological management of mild or moderate persistent asthma. *Lancet* 2006;368(9537):794–803. Review.

Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, O'Byrne PM. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361(9363):1071–6.

Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 1987;70(3):171–9.

Peters-Golden M. The alveolar macrophage: the forgotten cell in asthma. *Am J Respir Cell Mol Biol* 2004;31(1):3–7. Review.

Polito AJ, Proud D. Epithelia cells as regulators of airway inflammation. *J Allergy Clin Immunol* 1998;102(5):714–8. Review.

Robinson DS. The role of the mast cell in asthma: induction of airway hyperresponsiveness by interaction with smooth muscle? *J Allergy Clin Immunol* 2004;114(1):58–65. Review.

Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997;336(19):1356–63.

Sampson AP. The role of eosinophils and neutrophils in inflammation. *Clin Exp Allergy* 2000;30 Suppl 1:22–7. Review.

Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349(15):1414–22.

Selroos O, Lofroos AB, Pietinalho A, Riska H. Asthma control and steroid doses 5 years after early or delayed introduction of inhaled corticosteroids in asthma: a real-life study. *Respir Med* 2004;98(3):254–62.

Shaheen SO, Aaby P, Hall AJ, Barker DJ, Heyes CB, Shiell AW, Goudiaby A. Measles and atopy in Guinea-Bissau. *Lancet* 1996;347(9018):1792–6.

Sherrill D, Guerra S, Bobadilla A, Barbee R. The role of concomitant respiratory diseases on the rate of decline in FEV_1 among adult asthmatics. *Eur Respir J* 2003;21(1):95–100.

Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000;161(5):1501–7.

Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990;323(8):502–7.

Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TA. Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude. Tickling the dragon's breath. *Am J Respir Crit Care Med* 1995;151(5):1388–92.

Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354(9178):541–5.

Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol* 2006;118(4):773–86; quiz 787–8. Epub September 2006. Review.

Strachan DP, Cook DG. Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children. *Thorax* 1998a;53(2):117–23. Review. Erratum in: *Thorax* 1999;54(4):366.

Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998b;53(3):204–12.

Strunk RC, Szefler SJ, Phillips BR, Zeiger RS, Chinchilli VM, Larsen G, Hodgdon K, Morgan W, Sorkness CA, Lemanske RF Jr; Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. *J Allergy Clin Immunol* 2003;112(5):883–92.

Strunk RC, Weiss ST, Yates KP, Tonascia J, Zeiger RS, Szefler SJ; for the CAMP Research Group. Mild to moderate asthma affects lung growth in children and adolescents. *J Allergy Clin Immunol* 2006;118(5):1040–7.

Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, Bauer CP, Guggenmoos-Holzmann I. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997;99(6 Pt 1):763–9.

Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;368(9537):804–13.

Wenzel SE, Szefler SJ, Leung DY, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. *Am J Respir Crit Care Med* 1997;156(3 Pt 1):737–43.

Williams TJ. The eosinophil enigma. *J Clin Invest* 2004;113(4):507–9.

Xuan W, Peat JK, Toelle BG, Marks GB, Berry G, Woolcock AJ. Lung function growth and its relation to airway hyperresponsiveness and recent wheeze. Results from a longitudinal population study. *Am J Respir Crit Care Med* 2000;161(6):1820–4.

Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). *J Allergy Clin Immunol* 1999;103(3 Pt 1):376–87.

Zimmermann N, Hershey GK, Foster PS, Rothenberg ME. Chemokines in asthma: cooperative interaction between chemokines and IL-13. *J Allergy Clin Immunol* 2003;111(2):227–42.

SECTION 3, THE FOUR COMPONENTS OF ASTHMA MANAGEMENT

Introduction

The Expert Panel Reports presenting clinical practice guidelines for the diagnosis and management of asthma have organized recommendations for asthma care around four components considered essential to effective asthma management:

- Measures of assessment and monitoring, obtained by objective tests, physical examination, patient history and patient report, to diagnose and assess the characteristics and severity of asthma and to monitor whether asthma control is achieved and maintained
- Education for a partnership in asthma care
- Control of environmental factors and comorbid conditions that affect asthma
- Pharmacologic therapy

This section updates information on each of these four components, based on the Expert Panel's review of the scientific literature. The sections that follow present specific clinical recommendations for managing asthma long term and for managing exacerbations that incorporate the four components

SECTION 3, COMPONENT 1: MEASURES OF ASTHMA ASSESSMENT AND MONITORING

Introduction

See section 1, "Overall Methods Used To Develop This Report," for literature search strategy and tally of results for the EPR—3: Full Report 2007 on this component, Measures of Asthma Assessment and Monitoring. Two Evidence Tables were prepared: 1, Predictors of Exacerbation; and 2, Usefulness of Peak Flow Measurement.

Recommendations for "Component 1: Measures of Asthma Assessment and Monitoring" are presented in five sections: "Overview of Assessing and Monitoring Severity, Control, and Responsiveness in Managing Asthma;" "Diagnosis of Asthma;" "Initial Assessment: Characterization of Asthma and Classification of Asthma Severity;" "Periodic Assessment and Monitoring of Asthma Control Essential for Asthma Management;" and "Referral to an Asthma Specialist for Consultation or Comanagement." The recommendations are based on the opinion of the Expert Panel and review of the scientific literature.

Overview of Assessing and Monitoring Asthma Severity, Control, and Responsiveness in Managing Asthma

KEY POINTS: OVERVIEW OF MEASURES OF ASTHMA ASSESSMENT AND MONITORING

- The functions of assessment and monitoring are closely linked to the concepts of severity, control, and responsiveness to treatment:
  - Severity: the intrinsic intensity of the disease process. Severity is measured most easily and directly in a patient not receiving long-term-control therapy.
  - Control: the degree to which the manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met.
  - Responsiveness: the ease with which asthma control is achieved by therapy.
- Both severity and control include the domains of current impairment and future risk:
  - Impairment: frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced
  - Risk: the likelihood of either asthma exacerbations, progressive decline in lung function (or, for children, reduced lung growth), or risk of adverse effects from medication

- The concepts of severity and control are used as follows for managing asthma:
  - During a patient's initial presentation, if the patient is not currently taking long-term control medication, asthma severity is assessed to guide clinical decisions on the appropriate medication and other therapeutic interventions.
  - Once therapy is initiated, the emphasis thereafter for clinical management is changed to the assessment of asthma control. The level of asthma control will guide decisions either to maintain or adjust therapy.
  - For population-based evaluations, clinical research, or subsequent characterization of the patient's overall severity, asthma severity can be inferred after optimal therapy is established by correlating levels of severity with the lowest level of treatment required to maintain control. For clinical management, however, the emphasis is on assessing asthma severity for initiating therapy and assessing control for monitoring and adjusting therapy.

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- The key elements of assessment and monitoring are refined to include the separate, but related, concepts of severity, control, and responsiveness to treatment. Classifying severity is emphasized for initiating therapy; assessing control is emphasized for monitoring and adjusting therapy. Asthma severity and control are defined in terms of two domains: impairment and risk.
- The distinction between the domains of impairment and risk for assessing asthma severity and control emphasizes the need to consider separately asthma's effects on quality of life and functional capacity on an ongoing basis (i.e., in the present) and the risks it presents for adverse events in the future, such as exacerbations and progressive loss of pulmonary function. These domains of asthma may respond differentially to treatment.

Diagnosing a patient as having asthma is only the first step in reducing the symptoms, functional limitations, impairment in quality of life, and risk of adverse events that are associated with the disease. The ultimate goal of treatment is to enable a patient to live with none of these manifestations of asthma, and an initial assessment of the severity of the disease allows an estimate of the type and intensity of treatment needed. Responsiveness to asthma treatment is variable; therefore, to achieve the goals of therapy, followup assessment must be made and treatment should be adjusted accordingly. Even patients who have asthma that is well controlled at the time of a clinical assessment must be monitored over time, for the processes underlying asthma can vary in intensity over time, and treatment should be adjusted accordingly.

The functions of assessment and monitoring are closely linked to the concepts of severity, control, and responsiveness to treatment:

- Severity: the intrinsic intensity of the disease process. Severity is most easily and directly measured in a patient who is not currently receiving long-term control treatment.

- Control: the degree to which the manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met.

- Responsiveness: the ease with which control is achieved by therapy.

An important point linking asthma severity, control, and responsiveness is that the goals are identical for all levels of baseline asthma severity. A patient who has severe persistent asthma compared to a patient who has mild persistent asthma, or a patient who is less responsive to therapy may require more intensive intervention to achieve well-controlled asthma; however, the goals are the same: in well-controlled asthma, the manifestations of asthma are minimized by therapeutic intervention.

Although the severity of disease is most accurately assessed in patients before initiating long-term control medication, many patients are already receiving treatment when first seen by a new health care provider. In such cases, severity can be inferred from the least amount of treatment required to maintain control. This approach presumes that the severity of asthma is closely related to its responsiveness to treatment. Although this assumption may not be true for all forms of asthma and all treatments, it does focus attention on what is important in managing patients who have asthma: achieving a satisfactory level of control.

Both asthma severity and asthma control can be broken down into two domains: impairment and risk. Impairment is an assessment of the frequency and intensity of symptoms and functional limitations that a patient is experiencing or has recently experienced. Risk is an estimate of the likelihood of either asthma exacerbations or of progressive loss of pulmonary function over time.

- An assessment of the impairment domain for determining the severity of disease (in patients on no long-term-control treatment before treatment is initiated) or the level of control (after treatment is selected) usually can be elicited by careful, directed history and lung function measurement. Standardized questionnaires like the Asthma Control Test (ACT) (Nathan et al. 2004), the Childhood Asthma Control Test (Liu et al. 2007), the Asthma Control Questionnaire (Juniper et al. 1999b), the Asthma Therapy Assessment Questionnaire (ATAQ) control index (Vollmer et al. 1999), and others have been developed to facilitate and standardize the assessment of the impairment domain of asthma control. Some patients, however, appear to perceive the severity of airflow obstruction poorly (Bijl-Hofland et al. 2000; Kikuchi et al. 1994). These patients may have unconsciously accommodated to their symptoms, or perhaps they have mistakenly attributed these symptoms to other causes, like aging, obesity, or lack of fitness, so that they do not report them readily. For these patients, some other measure, such as spirometry, may identify that the degree of airflow obstruction is poorly recognized or perceived by the patient. A trial of therapy can be initiated and lead to unexpected improvement in quality of life ("I did not realize how much better I could feel until my asthma was treated.").

- Assessment of the risk domain—that is, of adverse events in the future, especially of exacerbations and of progressive, irreversible loss of pulmonary function—is more

problematic. Some assessment of the risk of exacerbations can be inferred from the medical history. Patients who have had exacerbations requiring emergency department (ED) visits, hospitalization, or intensive care unit (ICU) admission, especially in the past year, have a great risk of exacerbations in the future (Adams et al. 2000; Eisner et al. 2001; Lieu et al. 1998). Conversely, the achievement of good control of asthma symptoms and airflow obstruction from treatment with an inhaled corticosteroid (ICS) lowers the risk for asthma exacerbations in the future (Bateman et al. 2004). It is not known, however, whether the minimum treatment to control symptoms necessarily reduces the risk of exacerbations. Some patients who have few current symptoms or impairment of quality of life may still be at grave risk of severe, even life-threatening exacerbations (Ayres et al. 2004). Finally, little is known about the prevalence of a heightened risk of progressive loss of pulmonary function among patients who have asthma or whether any current treatment can prevent it.

- The test most used for assessing the risk of future adverse events is spirometry, especially forced expiratory volume in 1 second (FEV_1) expressed as a percent of the predicted value or as a proportion of the forced vital capacity (FVC) or FEV_1/FVC. The need for a simple, easily applied, more accurate test has prompted study of "biomarkers" whose deviations from normal might correlate with the severity of risk. Many biomarkers have been proposed—airway hyperresponsiveness, blood or sputum eosinophils or eosinophilic cationic protein (ECP), fractional exhaled nitric oxide concentration (FeNO), serum immunoglobulin E (IgE), number of positive skin tests, concentration of hydrogen ion, inflammatory mediators, or various metabolites in an exhaled breath condensate (EBC). Few studies, however, have validated or "anchored" assessment of these markers by analyzing their relationship to the rate of adverse events or decline in pulmonary function over time. Further complicating the matter is that the relationship between normalization of a biomarker and normalization of risk of an adverse event may depend on the specific treatment given. What is found true for treatment with an ICS may not be true for treatment with a leuktotriene receptor antagonist (LTRA) or an inhaled long-acting $beta_2$-agonist (LABA), or vice versa.

  In the future, assessment of a combination of historical features and of biomarkers may allow accurate estimation of the risk of future adverse events, but it must be kept in mind that laboratory tests only indirectly estimate control of risk. In the end, only symptoms, exacerbations, and quality of life over time are the measures of asthma control.

- Assessment of response to therapy is important, but there is inconsistency about the definition and measurement of "response." In general, response to therapy describes the ease with which adequate control is achieved by therapy. In a randomized controlled trial (RCT) of interventions to achieve asthma control, decreased symptoms, decreased use of short-acting $beta_2$-agonist (SABA) for quick relief, improved functioning, improvement in FEV_1, reduction in exacerbations, fewer ED visits, and decreased side effects from medication were equally weighted to develop a composite score that defines a responder to therapy (Bateman et al. 2004). The investigators observed that a composite definition of a responder correlates with asthma control. In a recent editorial, Stempel and Fuhlbrigge (2005) noted that, in published clinical trials, response to therapy based on pre- or postbronchodilator FEV_1 varied widely in statistical significance, depending on the research design and number of subjects included to attain statistical power. Furthermore, when response is defined solely by FEV_1, it can be influenced by disease activity independent of the intervention. It may be significant to characterize other responses, such as decreased airway responsiveness as measured by the response to methacholine, frequency of

exacerbations, and decrease in nighttime awakening. This area of work is currently developing and will be influenced by the outcome measures chosen by researchers conducting intervention studies. Agreement is needed on what clinically significant outcomes characterize response to therapy. Agreement is also needed on the time needed to assess response accurately (Zhang et al. 2002), but this time may vary according to treatment. It will take longer to determine whether a patient has responded to a treatment whose principal benefit is reduction in the rate of exacerbations, such as an anti-IgE monoclonal antibody (Bousquet et al. 2004), than to a treatment that acts as an acute bronchodilator.

Another concept closely related to assessing and predicting response to therapy is *resistance to therapy*. Of adult patients who have asthma, approximately 5 percent have poorly controlled asthma, with frequent symptoms and exacerbations despite use of high-dose ICS (Barnes and Woolcock 1998). Little is known about why some patients who have asthma do not respond well to therapy. A high prevalence of comorbidity—such as uncontrolled gastroesophageal reflux disease (GERD), allergic rhinitis, and psychiatric illness—has been described in this population (Heaney et al. 2003). Patients who have a poor response to appropriate therapy require referral to and consultation with an asthma specialist.

Diagnosis of Asthma

KEY POINTS: DIAGNOSIS OF ASTHMA

- To establish a diagnosis of asthma, the clinician should determine that (EPR—2 1997):
  - Episodic symptoms of airflow obstruction or airway hyperresponsiveness are present.
  - Airflow obstruction is at least partially reversible.
  - Alternative diagnoses are excluded.
- Recommended methods to establish the diagnosis are (EPR—2 1997):
  - Detailed medical history.
  - Physical exam focusing on the upper respiratory tract, chest, and skin.
  - Spirometry to demonstrate obstruction and assess reversibility, including in children 5 years of age or older. Reversibility is determined either by an increase in FEV_1 of ≥12 percent from baseline or by an increase ≥10 percent of predicted FEV_1 after inhalation of a short-acting bronchodilator.
  - Additional studies as necessary to exclude alternate diagnoses.

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- Discussions have been added on the use of spirometry, especially in children, and on the criteria for reversibility.
- Information has been added on vocal cord dysfunction (VCD) and cough variant asthma as an alternative diagnosis. Reference has been added to updated information in another component on comorbid conditions that may complicate diagnosis and treatment of asthma (e.g., allergic bronchopulmonary aspergillosis (ABPA), obstructive sleep apnea (OSA), and GERD).

The Expert Panel recommends that the clinician trying to establish a diagnosis of asthma should determine that (EPR—2 1997):

- **Episodic symptoms of airflow obstruction are present.**
- **Airflow obstruction is at least partially reversible.**
- **Alternative diagnoses are excluded.**

Box 3–1 lists key indicators for considering a diagnosis of asthma. A careful medical history, physical examination, pulmonary function tests, and additional tests will provide the information needed to ensure a correct diagnosis of asthma. Each of these methods of assessment is described in this section.

Clinical judgment is needed in conducting the assessment for asthma. Patients who have asthma are heterogeneous and present signs and symptoms that vary widely from patient to patient as well as within each patient over time.

MEDICAL HISTORY

The Expert Panel recommends that a detailed medical history of the new patient who is thought to have asthma should address the items listed in figure 3–1 (EPR—2 1997). The medical history can help:

- *Identify the symptoms likely to be due to asthma.* See figure 3–2 for sample questions.
- *Support the likelihood of asthma* (e.g., patterns of symptoms, family history of asthma or allergies).

BOX 3–1. KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF ASTHMA

Consider a diagnosis of asthma and performing spirometry if any of these indicators is present.* These indicators are not diagnostic by themselves, but the presence of multiple key indicators increases the probability of a diagnosis of asthma. Spirometry is needed to establish a diagnosis of asthma.

- Wheezing—high-pitched whistling sounds when breathing out—especially in children. (Lack of wheezing and a normal chest examination do not exclude asthma.)
- History of any of the following:
  - Cough, worse particularly at night
  - Recurrent wheeze
  - Recurrent difficulty in breathing
  - Recurrent chest tightness
- Symptoms occur or worsen in the presence of:
  - Exercise
  - Viral infection
  - Animals with fur or hair
  - House-dust mites (in mattresses, pillows, upholstered furniture, carpets)
  - Mold
  - Smoke (tobacco, wood)
  - Pollen
  - Changes in weather
  - Strong emotional expression (laughing or crying hard)
  - Airborne chemicals or dusts
  - Menstrual cycles
- Symptoms occur or worsen at night, awakening the patient.

*Eczema, hay fever, or a family history of asthma or atopic diseases are often associated with asthma, but they are not key indicators.

PHYSICAL EXAMINATION

The upper respiratory tract, chest, and skin are the focus of the physical examination for asthma. Physical findings that increase the probability of asthma are listed below. The absence of these findings does not rule out asthma, because the disease is by definition variable, and signs of airflow obstruction are often absent between attacks.

- *Hyperexpansion of the thorax,* especially in children; use of accessory muscles; appearance of hunched shoulders; and chest deformity.

- *Sounds of wheezing during normal breathing, or a prolonged phase of forced exhalation* (typical of airflow obstruction). Wheezing may only be heard during forced exhalation, but it is not a reliable indicator of airflow limitation.

- *Increased nasal secretion, mucosal swelling, and/or nasal polyps.*
- *Atopic dermatitis/eczema* or any other manifestation of an allergic skin condition.

PULMONARY FUNCTION TESTING (SPIROMETRY)

The Expert Panel recommends that spirometry measurements—FEV_1, forced expiratory volume in 6 seconds (FEV_6), FVC, FEV_1/FVC—before and after the patient inhales a short-acting bronchodilator should be undertaken for patients in whom the diagnosis of asthma is being considered, including children ≥5 years of age (EPR—2 1997). These measurements help to determine whether there is airflow obstruction, its severity, and whether it is reversible over the short term (Bye et al. 1992; Li and O'Connell 1996). (See box 3–2 for further information.) Patients' perception of airflow obstruction is highly variable, and spirometry sometimes reveals obstruction much more severe than would have been estimated from the history and physical examination.

BOX 3–2. IMPORTANCE OF SPIROMETRY IN ASTHMA DIAGNOSIS

Objective assessments of pulmonary function are necessary for the diagnosis of asthma because medical history and physical examination are not reliable means of excluding other diagnoses or of characterizing the status of lung impairment. Although physicians generally seem able to identify a lung abnormality as obstructive (Russell et al. 1986), they have a poor ability to assess the degree of airflow obstruction (Nair et al. 2005; Shim and Williams 1980) or to predict whether the obstruction is reversible (Russell et al. 1986). Furthermore, pulmonary function measures often do not correlate directly with symptoms. One study reports that one-third of the children who had moderate-to-severe asthma were reclassified to a more severe asthma category when pulmonary function reports of FEV_1 were considered in addition to symptom frequency (Stout et al. 2006).

Conversely, a majority of children in another study who had mild-to-moderate asthma classified by symptoms had normal FEV_1 (Bacharier et al. 2004). These findings emphasize the importance of using multiple measures and the value of pulmonary function testing in a comprehensive assessment of asthma.

For diagnostic purposes, spirometry is generally recommended over measurements by a peak flow meter in the clinician's office because there is wide variability even in the published predicted peak expiratory flow (PEF) reference values. Reference values need to be specific to each brand of peak flow meter, and such normative brand-specific values currently are not available for most brands. Peak flow meters are designed as monitoring, not as diagnostic, tools in the office.

Spirometry typically measures the maximal volume of air forcibly exhaled from the point of maximal inhalation (FVC) and the volume of air exhaled during the first second of this maneuver (FEV_1). Spirometry is generally valuable in children ≥5 years of age, although some children cannot conduct the maneuver adequately until after age 7. Healthy young children complete exhalation of their entire vital capacity in a few seconds, but it can take older patients much longer, especially patients who have airflow obstruction, because expiratory flow is so low at low lung volumes. In these patients, sustaining a maximal expiratory effort for the time necessary for complete exhalation may be more than 12 or 15 seconds—long enough for some patients to find the maneuver uncomfortable or associated with light headedness. This accounts for the interest in measurement of the FEV_6 as a substitute for measurement of FVC in adults. In

adults, FEV_6 has been shown to be equivalent to FVC for identifying obstructive and restrictive patterns, using the American Thoracic Society (ATS) algorithm, and to be more reproducible and less physically demanding than FVC (Swanney et al. 2004). Airflow obstruction is indicated by a reduction in the values for both the FEV_1 and the FEV_1/FVC (or FEV_1/ FEV_6) relative to reference or predicted values. See figure 3–3a and 3–3b for an example of a spirometric curve for this test. Predicted values for FEV_1/FVC are based on National Health and Nutrition Examination Survey (NHANES) data, National Center for Health Statistics, Centers for Disease Control and Prevention (CDC).

Significant reversibility is indicated by ATS standards as an increase in FEV_1 of >200 mL and ≥12 percent from the baseline measure after inhalation of a short-acting bronchodilator (e.g., albuterol, 2–4 puffs of 90 mcg/puff) (ATS 1995; ATS/ERS et al. 2005; Pellegrino et al. 2005). Some studies indicate that an increase ≥10 percent of the predicted FEV_1 after inhalation of a short-acting bronchodilator may be less subject to bias than measuring percent change from baseline and may have a higher likelihood of separating patients who have asthma from those who have chronic obstructive pulmonary disease (COPD) (Appleton et al. 2005; Brand et al. 1992; Dales et al. 1988; Meslier et al. 1989). Some patients who have signs and symptoms of asthma may not demonstrate reversibility until after a 2- to 3-week trial of oral corticosteroid therapy is administered to help improve their asthma control. Furthermore, the spirometry measured after a single treatment with SABA or after a short course of oral systemic corticosteroid treatment plus acute administration of a bronchodilator may not indicate the patient's best achievable lung function; thus, followup spirometry measures are indicated as asthma control improves.

Abnormalities of lung function are categorized as restrictive and obstructive defects. A reduced ratio of FEV_1/FVC or FEV_1/FEV_6 indicates obstruction to the flow of air from the lungs, whereas a proportionately reduced FVC (or FEV_6 in adults) with a normal or increased FEV_1/FVC (or FEV_1/FEV_6) ratio suggests a restrictive pattern. The severity of abnormality of spirometric measurements is evaluated by comparison of the patient's results with reference values based on age, height, sex, and race (ATS 1995). Furthermore, chronic asthma may be associated with decreased lung function with a loss of response to bronchodilator. Although asthma is typically associated with an obstructive impairment that is reversible, neither this finding nor any other single test or measure is adequate to diagnose asthma. Many diseases are associated with this pattern of abnormality. The patient's pattern of symptoms (along with other information from the patient's medical history) and exclusion of other possible diagnoses also are needed to establish a diagnosis of asthma. In severe cases, the FVC also may be reduced due to trapping of air in the lungs.

When pulmonary function measures are obtained, measuring pulmonary function before and after bronchodilator treatment to determine reversibility is recommended. The degree of airway reversibility correlates with airway inflammation, as measured by sputum eosinophilia and FeNO (Covar et al. 2004a). In addition, those patients who have the greatest degree of reversibility in response to SABA may be at the greatest risk of developing fixed airflow obstruction and have the greatest loss of lung function (Ulrik and Backer 1999). The postbronchodilator FEV_1 measure can then be used to follow lung growth patterns over time (Covar et al. 2004b).

The Expert Panel recommends that office-based physicians who care for asthma patients should have access to spirometry, which is useful in both diagnosis and periodic monitoring. Spirometry should be performed using equipment and techniques that meet standards developed by the ATS (EPR—2 1997). Correct technique, calibration methods, and maintenance of equipment are necessary to achieve consistently accurate test results

(ATS/ERS et al. 2005). Maximal effort by the patient in performing the test is required to avoid important errors in diagnosis and management. Training courses in the performance of spirometry that are approved by the National Institute for Occupational Safety and Health are available (800–35–NIOSH).

The Expert Panel recommends that when office spirometry shows severe abnormalities, or if questions arise regarding test accuracy or interpretation, further assessment should be performed in a specialized pulmonary function laboratory (EPR—2 1997).

DIFFERENTIAL DIAGNOSIS OF ASTHMA

The Expert Panel recommends consideration of alternative diagnoses, as appropriate. Box 3–3 lists examples of possible alternative diagnoses for asthma that may be considered during the evaluation of medical history, physical examination, and pulmonary function. Additional studies are not routinely necessary but may be useful when considering alternative diagnoses (EPR—2 1997):

- *Additional pulmonary function studies* (e.g., measurement of lung volumes and evaluation of inspiratory loops) may be indicated, especially if there are questions about possible coexisting COPD, a restrictive defect, VCD, or possible central airway obstruction. A diffusing capacity test is helpful in differentiating between asthma and emphysema in patients, such as smokers and older patients, who are at risk for both illnesses.

- *Bronchoprovocation* with methacholine, histamine, cold air, or exercise challenge may be useful when asthma is suspected and spirometry is normal or near normal. For safety reasons, bronchoprovocation testing should be carried out by a trained individual in an appropriate facility and is not generally recommended if the FEV_1 is <65 percent predicted. A positive methacholine bronchoprovocation test is diagnostic for the presence of airway hyperresponsiveness, a characteristic feature of asthma that also can be present in other conditions (e.g., allergic rhinitis, cystic fibrosis, COPD, among others). Thus, although a positive test is consistent with asthma, a negative bronchoprovocation may be more helpful to rule out asthma.

- *Chest x ray* may be needed to exclude other diagnoses.

- *Allergy testing* (see component 3—Control of Environmental Factors and Comorbid Conditions That Affect Asthma).

- *Biomarkers of inflammation.* The usefulness of measurements of biomarkers of inflammation (e.g., total and differential cell count and mediator assays) in sputum, blood, urine, and exhaled air as aids to the diagnosis and assessment of asthma is currently being evaluated in clinical research trials (see “Monitoring Asthma Control With Minimally Invasive Markers and Pharmacogenetics,” in the following section on “Periodic Assessment and Monitoring of Asthma Control Essential for Asthma Management”).

Recurrent episodes of cough and wheezing are due most often to asthma in both children and adults. Underdiagnosis of asthma is a frequent problem, especially in children who wheeze when they have respiratory infections. These children are often labeled as having bronchitis, bronchiolitis, or pneumonia even though the signs and symptoms are most compatible with a diagnosis of asthma. The clinician needs, however, to be aware of other causes of airway

BOX 3–3. DIFFERENTIAL DIAGNOSTIC POSSIBILITIES FOR ASTHMA

Infants and Children

Upper airway diseases

- Allergic rhinitis and sinusitis

Obstructions involving large airways

- Foreign body in trachea or bronchus
- Vocal cord dysfunction
- Vascular rings or laryngeal webs
- Laryngotracheomalacia, tracheal stenosis, or bronchostenosis
- Enlarged lymph nodes or tumor

Obstructions involving small airways

- Viral bronchiolitis or obliterative bronchiolitis
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Heart disease

Other causes

- Recurrent cough not due to asthma
- Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux

Adults

- COPD (e.g., chronic bronchitis or emphysema)
- Congestive heart failure
- Pulmonary embolism
- Mechanical obstruction of the airways (benign and malignant tumors)
- Pulmonary infiltration with eosinophilia
- Cough secondary to drugs (e.g., angiotensin-converting enzyme (ACE) inhibitors)
- Vocal cord dysfunction

obstruction leading to wheezing (See box 3–3.). See also "Diagnosis and Prognosis of Asthma in Children" in the section "Managing Asthma Long Term in Children 0–4 Years of Age and 5–11 Years of Age," for more detailed discussion about the diagnosis of asthma in young children.

Cough variant asthma. Although chronic cough can be a sign of many health problems, it may be the principal—or only—manifestation of asthma, especially in young children. This has led to the term "cough variant asthma." Monitoring of PEF or methacholine inhalation challenge, to clarify whether there is bronchial hyperresponsiveness consistent with asthma, may be helpful in diagnosis. The diagnosis of cough variant asthma is confirmed by a positive response to asthma medication (Dicpinigaitis 2006). Treatment should follow the stepwise approach to long-term management of asthma.

Vocal cord dysfunction often mimics asthma. VCD is characterized by episodic dyspnea and wheezing caused by intermittent paradoxical vocal cord adduction during inspiration (sometimes with abnormal adduction during expiration as well). The cause of VCD is not well understood, although some patients develop VCD in response to irritant triggers, such as fumes, cold air, and exercise. Although VCD is clearly distinct from asthma, it is often confused with asthma, leading to inappropriate medication of affected individuals with anti-asthma medications. Asthma medications typically do little, if anything, to relieve symptoms if the patient has pure VCD. VCD should be considered in the differential of difficult-to-treat, atypical asthma patients. It is important to note, however, that VCD and asthma may coexist and that VCD may complicate asthma management. Elite athletes, in particular, are prone to both exercise-induced bronchospasm (EIB) and VCD, so careful workup is warranted for athletes who present with exercise-related breathlessness (Rundell and Spiering 2003). During severe VCD episodes, respiratory distress may be severe and lead to intubation. Once the trachea is intubated, the wheezing and distress abate in VCD but not in asthma.

VCD can be difficult to diagnose. Variable flattening of the inspiratory flow loop on spirometry is strongly suggestive of the diagnosis, but abnormalities of the inspiratory loop may well be absent between episodes. The diagnosis of VCD comes from indirect or direct vocal cord visualization during an episode, during which the abnormal adduction can be documented. Therapy generally consists of speech therapy and relaxation techniques (Bucca et al. 1995; Christopher et al. 1983; Newman et al. 1995).

Several conditions that may coexist with asthma can complicate diagnosis: ABPA, OSA, and GERD (See "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma.").

Initial Assessment: Characterization of Asthma and Classification of Asthma Severity

KEY POINTS: INITIAL ASSESSMENT OF ASTHMA

- Once the diagnosis has been established, information obtained from the diagnostic evaluation, and additional information, if necessary, should be used to characterize the patient's asthma in order to guide decisions for therapy (EPR—2 1997):
  - Identify precipitating factors (e.g., exposure at home, work, daycare, or school to inhalant allergens, or irritants such as tobacco smoke, or viral respiratory infections) (Evidence A)
  - Identify comorbidities that may aggravate asthma (e.g., sinusitis, rhinitis, GERD) (Evidence B)
  - Classify asthma severity, using measures in both the impairment (Evidence B) and risk domains (Evidence C)
- Measures of pulmonary function, using spirometry, are recommended for assessing asthma severity. Low FEV_1 indicates current obstruction (impairment domain) and risk for future exacerbation (risk domain) (Evidence C). For children, FEV_1/FVC appears to be a more sensitive measure of severity in the impairment domain; FEV_1 is a useful measure of risk for exacerbations (Evidence C).

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- The severity classification for asthma changed the category of mild intermittent to intermittent in order to emphasize that even patients who have intermittent asthma can have severe exacerbations. A note of emphasis has also been added that acute exacerbations can be mild, moderate, or severe in any category of persistent asthma.
- Severity classification is defined in terms of two domains—impairment and risk—to emphasize the need to consider separately asthma's effects on quality of life and functional capacity on an ongoing basis (i.e., in the present) and the risks asthma presents for adverse events in the future, such as exacerbations and progressive loss of pulmonary function. These domains of asthma may respond differentially to treatment.
- A new emphasis on using FEV_1/FVC has been added for to classifying severity in children because it may be a more sensitive measure than FEV_1.

The Expert Panel recommends that clinicians use information obtained from the diagnostic evaluation, and any additional information, if necessary, to (EPR—2 1997):

- **Identify precipitating factors**
- **Identify comorbid conditions that may aggravate asthma**
- **Assess the patient's knowledge and skills for self-management**
- **Classify asthma severity**

Once the diagnosis of asthma has been established, the next step in the initial assessment is to characterize the patient's asthma in order to guide decisions for selecting therapy. This characterization is a basic description of the patient's asthma phenotype.

As noted earlier, the usefulness of measurements of biomarkers of inflammation (e.g., total and differential cell count and mediator assays) in sputum, blood, urine, and exhaled air as aids to the diagnosis and assessment of asthma is currently being evaluated in clinical research trials (See "Monitoring Asthma Control With Minimally Invasive Markers and Pharmacogenetics," in the following section on "Periodic Assessment and Monitoring of Asthma Control Essential for Asthma Management.").

IDENTIFY PRECIPITATING FACTORS

The identification of factors that precipitate worsening of asthma—such as exposure to allergens (e.g., pets, molds, seasonal pollens), irritants (e.g., environmental tobacco smoke (ETS) and industrial pollutants (such as sulfur dioxide and ozone), or respiratory viruses (including "common cold" viruses)—can assist in educating the patient to avoid unnecessary exposures or at least to be alert to exposures that might indicate a need for increased treatment. Information obtained from the medical history (See figure 3–1.) will aid this assessment. See "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma" for additional tools to assess allergies and other relevant exposures, as well as key messages for patient education on this topic.

IDENTIFY COMORBID CONDITIONS THAT MAY AGGRAVATE ASTHMA

It is also important to identify whether the patient has chronic comorbid conditions that may complicate the presentation or the treatment of asthma, such as sinusitis, rhinitis, GERD, OSA, or ABPA (See "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma."). Identification of these comorbid conditions is helpful, because treating them adequately may improve overall control of asthma and lessen requirements for asthma medications.

ASSESS THE PATIENT'S KNOWLEDGE AND SKILLS FOR SELF-MANAGEMENT

Successful management of asthma requires that the patient or patient's caregiver have a fundamental understanding of and skills for following the therapeutic recommendations, including pharmacotherapy and measures to control factors that contribute to asthma severity. Initial assessment of the patient, therefore, should include an evaluation of the patient's self-management skills. This evaluation will guide decisions about appropriate educational training. See component 2—Education for a Partnership in Asthma Care for detailed discussion and tools for integrating assessment and education into all phases of clinical management, including the initial patient assessment.

CLASSIFY ASTHMA SEVERITY

The Expert Panel recommends that clinicians classify asthma severity by using the domains of current impairment and future risk (Evidence B—secondary analyses of clinical trials, and Evidence C—observational studies, for assessing impairment; Evidence C, for distinguishing intermittent versus persistent asthma by risk of exacerbations; Evidence D, for distinguishing different categories of persistent asthma by varying frequencies of exacerbations).

Asthma severity is the intrinsic intensity of disease. Initial assessment of patients who have confirmed asthma begins with a severity classification because the selection of type, amount, and scheduling of therapy should then correspond to the level of asthma severity. This initial assessment of asthma severity is made immediately after diagnosis, or when the patient is first encountered, generally before the patient is taking some form of long-term control medication. Assessment is made on the basis of current spirometry and the patient's recall of symptoms over the previous 2–4 weeks, because detailed recall of symptoms decreases over time. If the assessment is made during a visit in which the patient is treated for an acute exacerbation, then asking the patient to recall symptoms in the period before the onset of the current exacerbation will suffice until a followup visit can be made.

For population-based evaluations, clinical research, or subsequent characterization of the patient's overall severity, asthma severity can be inferred after optimal therapy is established by correlating levels of severity with the lowest level of treatment required to maintain control. For clinical management, however, the emphasis is to assess asthma severity prior to initiating therapy and, then, assess control for monitoring and adjusting therapy.

The severity classification of asthma shown in figures 3–4 a, b, and c uses the two domains of current impairment and future risk. The specific measures for classifying severity—symptoms, use of SABA for quick relief, exacerbations, and pulmonary function—that were presented in EPR—2 remain in the current report, although they have been organized into the new

framework of measures of impairment and risk. As noted in the "Overview" section of this component, the distinction between impairment and risk emphasizes the need to consider separately asthma's effects on quality of life and functional capacity on an ongoing basis (i.e., in the present) and the risks asthma presents for adverse events in the future, such as exacerbations and progressive loss of pulmonary function. Clinical trial data demonstrate that these "domains" of asthma may respond differentially to treatment. Data further suggest that, in estimating severity or control in either domain, different manifestations of asthma must be assessed, because they do not necessarily correlate with each other (Bacharier et al. 2004; Colice et al. 1999; Fuhlbrigge et al. 2002; Strunk et al. 2002). Thus, a composite of measures, with a distinction between domains of impairment and risk, will be useful in classifying severity.

Assessment of Impairment

Assessment of severity requires assessing the following components of current impairment:

- Symptoms
  - Nighttime awakenings
  - Need for SABA for quick relief of symptoms
  - Work/school days missed
  - Ability to engage in normal daily activities or in desired activities
  - Quality-of-life assessments
- Lung function, measured by spirometry: FEV_1, FVC (or FEV_6), FEV_1/FVC (or FEV_6 in adults). Spirometry is the preferred method for measuring lung function to classify severity. Peak flow has not been found to be a reliable variable for classifying severity (Eid et al. 2000; Llewellin et al. 2002), but it may serve as a useful tool for monitoring trends in asthma control over time (See section, "Monitoring Lung Function.").

Secondary analyses of clinical trial data and observational studies using the EPR—2 1997 or similar Global Initiative for Asthma (GINA) criteria have confirmed that the parameters for the impairment domain (symptom, activity levels, and pulmonary function) reflect increasing gradients of severity in adults (Antonicelli et al. 2004; Diette et al. 2004; EPR—2 1997; Schatz et al. 2003, 2005b).

Whether the ranges of pulmonary function for severity of asthma previously defined in guidelines (EPR—2 1997) apply well to children has been questioned in cross-sectional studies that found normal FEV_1 values (many over 90 percent predicted) in a majority of the children, 5–18 years of age, regardless of their asthma severity as classified on the basis of symptoms (Bacharier et al. 2004; Paull et al. 2005; Spahn et al. 2004). Two of those studies reported that, in contrast to FEV_1 measures, FEV_1/FVC decreased with increasing asthma severity and thus appeared to be a more sensitive measure of severity (Bacharier et al. 2004; Paull et al. 2005). On the other hand, analysis of a large, longitudinal study of children confirmed a relationship between the severity of airflow obstruction and the risk of exacerbations (Fuhlbrigge et al. 2001). Increasing risk correlated with the FEV_1 cutoffs for increasing levels of severity as defined in EPR—2 (Fuhlbrigge et al. 2006). It is emphasized that these studies also found that even children who had normal values of lung function experienced exacerbations. In addition, children who have low lung function are at greatest risk of developing fixed airflow obstruction over time (Rasmussen et al. 2002). Cumulatively, these studies underscore the importance of measuring several variables in the assessment of asthma. Making treatment decisions for children should be based on frequency and severity of past exacerbations and symptoms, with

pulmonary function measures as an additional guide. FEV_1 appears to be a useful measure indicating risk for exacerbations; FEV_1/FVC appears to be a more sensitive measure of severity in the impairment domain. The Expert Panel has updated the pulmonary function measures for assessing asthma severity and control in children by adding suggested ranges for FEV_1/FVC.

Assessment of Risk

A closely related and second dimension of severity is the concept of risk of adverse events, including exacerbations and risk of death. Assessment of the risk of future adverse events requires careful medical history, observation, and clinician judgment. Documentation of warning signs and adverse events will be necessary when a patient is felt to be at increased risk. Patients who are deemed at increased risk of adverse outcomes will need close monitoring and frequent assessment by their clinicians.

- Exacerbations of asthma are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness—or some combination of these symptoms. Exacerbations are characterized by decreases in expiratory airflow that can be documented and quantified by simple measurement of lung function (spirometry or PEF). Exacerbations of asthma can vary widely among individuals and within individuals, from very rare to frequent. Although the classification of severity focuses on the frequency of exacerbations, it is important to note that the severity of disease does not necessarily correlate with the intensity of exacerbations, which can vary from mild to very severe and life-threatening. Patients at any level of severity, even intermittent asthma, can have severe exacerbations. For example, a person who has intermittent asthma can have a severe exacerbation during a viral illness or when exposed to allergens to which he or she is sensitized or to noxious fumes and irritants. Accordingly, the Expert Panel has modified the designation of “mild intermittent asthma” in the previous guidelines (EPR—2 1997; EPR—Update 2002) to become “intermittent asthma” to emphasize that patients at any level of severity—including intermittent—can have severe exacerbations. The duration of exacerbations may vary from a few hours to a few days. These unpredictable variations in exacerbations can present treatment dilemmas for the clinician who strives to prevent future exacerbations and considers when to initiate chronic anti-inflammatory therapy.

  The frequency of exacerbations requiring intervention with oral systemic corticosteroids has been correlated in observational studies with the designation of persistent, rather than intermittent, asthma (Fuhlbrigge et al. 2001, 2006). Determination of whether the level of severity is mild, moderate, or severe will depend on consideration of both the frequency and the intensity of the exacerbations. No data are available to correspond specific numbers with each severity category. In general, the more frequent and the more intense the exacerbations (e.g., requiring urgent, unscheduled clinical care, hospitalization, or ICU admission), the greater the degree of underlying disease severity.

- Predictors that have been reported to be associated with increased risk of exacerbations (See Evidence Table 1, Predictors of Exacerbations.) or death include:

  — Severe airflow obstruction, as detected by spirometry (Adams et al. 2000; Connolly et al. 1998; Fuhlbrigge et al. 2001, 2006; Kitch et al. 2004).

  — Persistent severe airflow obstruction (Kitch et al. 2004).

- Two or more ED visits or hospitalizations for asthma in the past year; any history of intubation or ICU admission, especially if in the past 5 years (Belessis et al. 2004; Cowie et al. 2001).
- Patients report that they feel in danger or frightened by their asthma (Janson-Bjerklie et al. 1993; Ng 2000).
- Certain demographic or patient characteristics: female, nonwhite (Diette et al. 2002), nonuse of ICS therapy, and current smoking (Eisner et al. 2001).
- Psychosocial factors: depression (Eisner et al. 2005; Goodwin et al. 2004), increased stress (Goodwin et al. 2004), socioeconomic factors (Griswold et al. 2005).
- Attitudes and beliefs about taking medications (Adams et al. 2000; Apter and Szefler 2004).

For population-based management, risk stratification is used to identify patients at increased risk of morbidity and health care resource use. Several validated psychometric instruments have been shown to predict future risk of hospitalization and ED visits (Schatz et al. 2005a).

Periodic Assessment and Monitoring of Asthma Control Essential for Asthma Management

KEY POINTS: PERIODIC ASSESSMENT OF ASTHMA CONTROL

- The goals of therapy are to achieve asthma control by (Evidence A):
  - Reducing impairment:
    - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion)
    - Require infrequent use (≤2 days a week) of inhaled SABA for quick relief of symptoms
    - Maintain (near) “normal” pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients’ and families’ expectations of and satisfaction with asthma care

— Reducing risk:

  - ♦ Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations
  - ♦ Prevent progressive loss of lung function; for children, prevent reduced lung growth
  - ♦ Provide optimal pharmacotherapy with minimal or no adverse effects

- Periodic assessments (at 1- to 6-month intervals) and ongoing monitoring of asthma control are recommended to determine if the goals of therapy are being met and if adjustments in therapy are needed (Evidence B, extrapolation from clinical trials; and Evidence C, observational studies). Measurements of the following are recommended:

  — Signs and symptoms of asthma

  — Pulmonary function

  — Quality of life/functional status

  — History of asthma exacerbations

  — Pharmacotherapy (checking for adherence to therapy and potential side effects from medication)

  — Patient–provider communication and patient satisfaction

- Clinician assessment and patient self-assessment are the primary methods for monitoring asthma. Population-based assessment is used by health organizations, such as managed care organizations and disease management programs (EPR—2 1997).

- The following frequencies for spirometry tests are recommended: (1) at the time of initial assessment (Evidence C), (2) after treatment is initiated and symptoms and PEF have stabilized, (3) during periods of progressive or prolonged loss of asthma control, and (4) at least every 1–2 years (Evidence D).

- Use of minimally invasive markers (“biomarkers”) to monitor asthma control and guide treatment decisions for therapy is of increasing interest. Some markers, such as spirometry measures, are currently and widely used in clinical care; others, such as sputum eosinophils and FeNO, may also be useful, but they require further evaluation in both children and adults before they can be recommended as clinical tools for routine asthma management (Evidence D).

- Provide to all patients a written asthma action plan based on signs and symptoms and/or PEF; written action plans are particularly recommended for patients who have moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B).

- Whether peak flow monitoring, symptom monitoring (available data show similar benefits for each), or a combination of approaches is used, self-monitoring is important to the effective self-management of asthma (Evidence A).

- Patients should be taught to recognize symptom patterns indicating inadequate asthma control and the need for additional therapy (Evidence A).

- Consider peak flow monitoring for patients who have moderate or severe persistent asthma, patients who have a history of severe exacerbations (Evidence B), and patients who poorly perceive airflow obstruction and worsening asthma (Evidence D). Long-term daily peak flow monitoring can be helpful to (Evidence B):

  — Detect early changes in asthma control that require adjustment in treatment.
  — Evaluate responses to changes in treatment.
  — Provide a quantitative measure of impairment.

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- Periodic assessment of asthma *control* is emphasized.

- This update (EPR—3: Full Report 2007) makes a stronger distinction than previous guidelines between classifying asthma severity and assessing asthma control. Interpretation of previous asthma guidelines raised questions about applying the severity classifications once treatment is established and also resulted in placing more emphasis on severity than on ongoing monitoring of whether therapeutic goals were met. This update (EPR—3: Full Report 2007) clarifies the issue:

  — For initiating treatment, asthma severity should be classified, and the initial treatment should correspond to the appropriate severity category.

  — Once treatment is established, the emphasis is on assessing asthma control to determine if the goals for therapy have been met and if adjustments in therapy (step up or step down) would be appropriate.

- Assessment of asthma control includes the two domains of impairment and risk.

- Peak flow monitoring: The recommendation to assess diurnal variation was deleted. New text was added regarding the patients most likely to benefit from routine peak flow monitoring. Emphasis was added that evidence suggests equal benefits to either peak flow or symptom-based monitoring; the important issue continues to be having a monitoring plan in place.

- Parameters for lung function, specifically FEV_1/FVC, were added as measures of asthma control for children.

- Minimally invasive markers and pharmacogenetic approaches for monitoring asthma. New text was added. These approaches have gained increasing attention in clinical research, and some applications may be useful in the near future for the clinical management of asthma. The concepts are introduced here, although most require further evaluation before they can be recommended as tools for routine asthma management.

GOALS OF THERAPY: ASTHMA CONTROL

The purpose of periodic assessment and ongoing monitoring is to determine whether the goals of asthma therapy are being achieved and asthma is controlled. When asthma is not controlled, it is associated with significant asthma burden (Fuhlbrigge et al. 2002), decreased quality of life (Schatz et al. 2005b), and increased health care utilization (Schatz et al. 2005a; Vollmer et al. 2002). The level of asthma control (well controlled, not well controlled, or poorly controlled) is the degree to which both dimensions of the manifestations of asthma—impairment and risk—are minimized by therapeutic intervention. The level of control at the time of followup assessment will determine clinical actions—that is, whether to maintain or adjust therapy. In previous guidelines (EPR—2 1997; GINA 2002), parameters for control were selected on the basis of research that used individual outcomes for evaluating the effectiveness of asthma treatments. The composite list of goals reflected the Panel's opinions of a complete list of relevant outcomes that could define asthma control. A recent large international trial demonstrated that significant reductions in the rate of severe exacerbations and improvements in quality of life were achieved by aiming at achieving guideline-defined asthma control and by adjusting therapy to achieve it. At the end of 1 year, 30 percent of the patients achieved total control (i.e., the absence of any sign or symptom of asthma), and 60 percent had achieved well-controlled asthma (Bateman et al. 2004).

Interpretation of previous asthma guidelines, in which severity classifications before treatment corresponded to recommended steps of treatment, has raised questions about applying severity classifications once treatment is established and what elements of asthma should be used to monitor asthma during clinical followup (Graham 2006; Wolfenden et al. 2003). This update (EPR—3: Full Report 2007) clarifies the issue. For initiating treatment, asthma severity should be classified, and the initial treatment should correspond to the appropriate category of severity. Once treatment is established, the emphasis is on assessing asthma control to determine if the goals for therapy have been met and if adjustments in therapy (step up or step down) would be appropriate.

The Expert Panel recommends that asthma control be defined as follows (Evidence A):

Asthma Control

- Reduce impairment
  - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion)
  - Require infrequent use (≤2 days a week) of SABA for quick relief of symptoms
  - Maintain (near) "normal" pulmonary function
  - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
  - Meet patients' and families' expectations of and satisfaction with asthma care

- Reduce risk
  - Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations
  - Prevent progressive loss of lung function; for children, prevent reduced lung growth
  - Provide optimal pharmacotherapy with minimal or no adverse effects

See figures 3–5a, b, and c for classification of asthma control in three different age groups. Specific discussion of measures for assessment are in the following section. In general:

- Assessment of impairment is in the form of questions, such as those presented in figure 3–6 and within figure 3–7. The focus of these questions is to assess the degree of asthma control in the present. The key elements include current pulmonary function and patient's recall of symptoms, physical activity, quality of life, and need for SABA for quick relief of symptoms over the previous 2–4 weeks.

- Assessing the risk of exacerbations is through questions regarding the use of medications, particularly oral corticosteroids, or urgent care visits. Low FEV_1 is associated with increased risk for severe exacerbations (Fuhlbrigge et al. 2001).

- Assessment of the risk of progressive loss function, or, for children, the risk of reduced lung growth (measured by prolonged failure to attain predicted lung function values for age) requires longitudinal assessment of lung function, preferably using spirometry.

- Assessment of the risk of side effects from medication does not directly correspond to the varying levels of asthma control. For example, a patient might have well-controlled asthma with high doses of ICS and chronic oral corticosteroids but is likely to experience some adverse effects from this intense therapy. The risk of side effects can vary in intensity from none to very troublesome and worrisome; see component 4—Medications for discussion of potential adverse effects associated with different asthma medications. Although not directly correlated to control, the risk or evidence of side effects should be included in the overall assessment of the risk domain of asthma control.

- Future work on assessment of asthma control tools will define the relative value of including specific biological markers and test how well the tool predicts the risk of exacerbations.

MEASURES FOR PERIODIC ASSESSMENT AND MONITORING OF ASTHMA CONTROL

The Expert Panel recommends that ongoing monitoring of asthma control be performed to determine whether all the goals of therapy are met—that is, reducing both impairment and risk (Evidence B); see figures 3–5 a, b, and c for assessing asthma control for different age groups.

The Expert Panel recommends that the frequency of visits to a clinician for review of asthma control is a matter of clinical judgment; in general, patients who have intermittent or mild persistent asthma that has been under control for at least 3 months should be seen by a clinician about every 6 months, and patients who have uncontrolled and/or severe persistent asthma and those who need additional supervision to help them follow their treatment plan need to be seen more often (EPR—2 1997).

The assessment measures for control monitor six areas described in this section and are recommended based on the opinion of the Expert Panel and review of the scientific literature. A seventh area, monitoring asthma control with minimally invasive markers, is of increasing interest, but many of these markers require further evaluation before they can be recommended widely for routine asthma care.

- Monitoring signs and symptoms of asthma
- Monitoring pulmonary function
  - Spirometry
  - Peak flow monitoring
- Monitoring quality of life
- Monitoring history of asthma exacerbations
- Monitoring pharmacotherapy for adherence and for potential side effects
- Monitoring patient–provider communication and patient satisfaction
- Monitoring asthma control with minimally invasive markers and pharmacogenetics (requires further evaluation)

Monitoring Signs and Symptoms of Asthma

The Expert Panel recommends that every patient who has asthma should be taught to recognize symptom patterns that indicate inadequate asthma control (Evidence A) (See also "Component 2: Education for a Partnership in Asthma Care."). Either symptom and/or PEF monitoring should be used as a means to determine the need for intervention, including additional medication, in the context of a written asthma action plan.

The Expert Panel recommends that symptoms and clinical signs of asthma should be assessed at each health care visit through physical examination and appropriate questions (EPR—2 1997). This is important for optimal asthma care.

The Expert Panel recommends that the detailed symptoms history should be based on a short (2–4 weeks) recall period (EPR—2 1997). Patients' detailed recall of symptoms decreases over time; therefore, the clinician may choose to assess over a 2-week, 3-week, or 4-week recall period. Symptom assessment for periods longer than 4 weeks should reflect more global symptom assessment, such as inquiring whether the patient's asthma has been better or worse since the last visit and inquiring whether the patient has encountered any particular difficulties during specific seasons or events. Figure 3–7 provides an example of a set of questions that can be used to characterize both global (long-term recall) and recent (short-term recall) asthma symptoms.

The Expert Panel recommends that assessment of the patient's symptom history should include at least four key symptom expressions (Evidence B, extrapolation from clinical trials; and Evidence C, from observational studies):

- Daytime asthma symptoms (including wheezing, cough, chest tightness, or shortness of breath)
- Nocturnal awakening as a result of asthma symptoms
- Frequency of use of SABA for relief of symptoms
- Inability or difficulty performing normal activities (including exercise) because of asthma symptoms

Monitoring Pulmonary Function

The Expert Panel recommends that, in addition to assessing symptoms, it is also important to assess pulmonary function periodically (Evidence B, extrapolation from clinical trials; and Evidence C, from observational studies). The main methods are spirometry and peak flow monitoring.

Low FEV_1 is associated with increased risk of severe asthma exacerbations (Fuhlbrigge et al. 2001). Regular monitoring of pulmonary function is particularly important for asthma patients who do not perceive their symptoms until airflow obstruction is severe. There is no readily available method of detecting the "poor perceivers." The literature reports that patients who had a near-fatal asthma exacerbation, as well as older patients, are more likely to have poor perception of airflow obstruction (Connolly et al. 1992; Kikuchi et al. 1994).

Spirometry

The Expert Panel recommends the following frequencies for spirometry measurements: (1) at the time of initial assessment (Evidence C); (2) after treatment is initiated and symptoms and PEF have stabilized, to document attainment of (near) "normal" airway function; (3) during a period of progressive or prolonged loss of asthma control; and (4) at least every 1–2 years to assess the maintenance of airway function (Evidence B, extrapolation from clinical trials). Spirometry may be indicated more often than every 1–2 years, depending on the clinical severity and response to management (Evidence D). These spirometry measures should be followed over the patient's lifetime to detect potential for decline and rate of decline of pulmonary function over time (Evidence C).

As noted previously, adjusting therapy according to the level of asthma control improves the patient's quality of life and reduces morbidity due to asthma (Bateman et al. 2004). Measures of control in this and related studies, as well as in numerous clinical trials that examine drug efficacy, include measures of lung function obtained by spirometry. Lung function declines in adults as they grow older, and adults who have asthma have greater declines, on average, than adults who do not have asthma and do not smoke. For children, lung function increases as they grow older, until maximal lung function is achieved, which occurs for most individuals by 20 years of age. Children who have asthma may have reductions in lung growth compared to children who do not have asthma. The postbronchodilator FEV_1 measure can be used to follow lung growth patterns over time (Covar et al. 2004a). Observations of reduced lung growth may reflect a progressive worsening of asthma control that should be treated accordingly.

Spirometry with measurement of the FEV_1 is also useful:

- As a periodic (e.g., yearly) check on the accuracy of the peak flow meter (Miles et al. 1995) for patients who are monitoring PEF.

- When more precision is desired in measuring lung function (e.g., when evaluating response to bronchodilator or nonspecific airway responsiveness or when assessing response to a "step down" in pharmacotherapy).

- When PEF results are unreliable (e.g., in some very young or elderly patients, when neuromuscular or orthopedic problems are present, or technical artifact is suspected (see below)) and the physician needs the quality checks that are available only with spirometry (Hankinson and Wagner 1993).

Peak Flow Monitoring

The Expert Panel recommends the following:

- **If peak flow monitoring is performed, the written asthma action plan should use the patient's personal best peak flow as the reference value (EPR—Update 2002).**

- **Consider long-term daily peak flow monitoring for:**

  — **Patients who have moderate or severe persistent asthma (Evidence B).**
  — **Patients who have a history of severe exacerbations (Evidence B).**
  — **Patients who poorly perceive airflow obstruction and worsening asthma (Evidence D).**
  — **Patients who prefer this monitoring method (Evidence D).**

- **Long-term daily peak flow monitoring can be helpful to (EPR—Update 2002):**

  — **Detect early changes in disease states that require treatment.**
  — **Evaluate responses to changes in therapy.**
  — **Afford a quantitative measure of impairment.**

- **Peak flow monitoring during exacerbations will help determine the severity of the exacerbations and guide therapeutic decisions in the home, school, clinicians' office, or ED (See "Component 2: Education for a Partnership in Asthma Care" and section 5, "Managing Exacerbations of Asthma.").**

- **Consider home peak flow monitoring during exacerbations of asthma for:**

  — **Patients who have a history of severe exacerbations (Evidence B).**
  — **Patients who have moderate or severe persistent asthma (Evidence B).**
  — **Patients who have difficulty perceiving signs of worsening asthma (Evidence D).**

PEF measurements, using either handheld mechanical or electronic metered devices, provide a means to obtain simple, quantitative, and reproducible assessments of the existence and severity of airflow obstruction. *It must be stressed that peak flow meters function best as tools for ongoing* ***monitoring,*** *not* ***diagnosis****.* Because the measurement of PEF is dependent on effort and technique, patients need instructions, demonstrations, and frequent reviews of

technique. See "Component 2: Education for a Partnership in Asthma Care" for detailed instructions on using peak flow meters. The accuracy of peak flow monitoring devices may decrease over time (Irvin et al. 1997); therefore, measurements that are at odds with the clinical status of the patient may be related to technical and not physiologic factors, and consideration should be given to reviewing technique with the patient or replacing the device the patient is currently using. The patient's measured personal best peak flow is the most appropriate reference value for the patient's action plan.

In clinical trials, peak flow values have been used as major outcome measures to monitor both asthma control and treatment responses, short (Lazarus et al. 2001) and long term (Boushey et al. 2005). In the context of both impairment and risk domains for asthma severity reviewed previously, it should be noted that peak flow values may not correlate with other asthma outcome measures such as treatment failure (Leone et al. 2001) or asthma exacerbations (Lazarus et al. 2001). Although peak flow monitoring to guide chronic asthma management has been reported to be valuable in studies more reflective of clinical practice, the results are not consistent enough for this tool to be recommended uniformly for all asthma patients (Jain et al. 1998) (See Evidence Table 2, Usefulness of Peak Flow Measurement, and EPR—Update 2002.). Thus, the relative usefulness of peak flow measurements as monitoring tools can be individualized, based on the patient's age (decreased utility in preschool children and the elderly), socioeconomic status (minority and poor children show greatest benefit) (Yoos et al. 2002), asthma pattern (of questionable utility to monitor individuals who have histories of rapid onset of severe airflow obstruction), asthma severity (Llewellin et al. 2002), ability to perceive signs and symptoms of early worsening of asthma (Jain et al. 1998), and the clinician's and patient's opinions as to their contribution in achieving and maintaining acceptable asthma control.

Peak Flow Versus Symptom-Based Monitoring Action Plan

A systematic review of the evidence in 2002 concluded that, although studies available at that time were limited, studies did not clearly show that a peak flow monitoring-based action plan was better than a symptom monitoring-based plan in improving outcomes but that it did show similar benefits.

Evidence generated since the 2002 review does not change these recommendations.

The Expert Panel recommends the following:

- **Either peak flow monitoring or symptom monitoring, if taught and followed correctly, may be equally effective (Evidence B).**

- **Whether peak flow monitoring, symptom monitoring, or a combination of approaches is used, self-monitoring is important to the effective self-management of asthma (Evidence A).** The nature and intensity of self-monitoring should be individualized, based on such factors as asthma severity, the patient's ability to perceive airflow obstruction, availability of peak flow meters, and patient preferences. Patient preferences for objective measures or certain patient circumstances, such as inability either to perceive or to report signs and symptoms of worsening asthma, warrant the use of peak flow monitoring and justify the associated time, energy, and costs to the clinician and patient (Evidence D).

- **Provide to all patients a written asthma action plan that includes daily treatment and recognizing and handing worsening asthma, including self-adjustment of medications in response to acute symptoms or changes in PEF measures. Written action plans are particularly recommended for patients who have moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B).** Either peak flow or symptom self-monitoring appears to increase patients' awareness of the disease status and control, thereby helping patients "tune in" to their disease; and action plans enhance clinician–patient communication. Thus, the nature of the plan, whether it is based on symptoms or based on peak flow, is not the important issue; rather, it is having a plan in place versus not having one at all. For additional discussion of written asthma action plans, see component 2—Education for Partnership in Asthma Care and section 4, "Managing Asthma Long Term in Children, School Issues."

Monitoring Quality of Life

The Expert Panel recommends that several key areas of quality of life and related loss of physical function should be assessed periodically for each person who has asthma (Evidence C). These include:

- Any work or school missed because of asthma
- Any reduction in usual activities (either home/work/school or recreation/exercise)
- Any disturbances in sleep due to asthma
- Any change in caregivers' activities due to a child's asthma (for caregivers of children who have asthma)

See figure 3–7 for sample questions that characterize quality-of-life concerns for persons who have asthma.

The goals of asthma treatment include improving quality of life for people who have asthma in addition to controlling symptoms, reducing the risk of exacerbations, and preventing asthma-related death. It is important, therefore, to examine how the disease expression and control are affecting the patient's quality of life. Several dimensions of quality of life may be important to track; these include physical function, role function, and mental health function. Clinical asthma status parameters correlate only moderately with quality-of-life measures. Correlations between symptoms and quality of life are often in the low-to-moderate range, while correlations with pulmonary function measures are quite weak. These observations suggest that perceptions and experiences of patients must be assessed directly and not imputed from measures of clinical status. Quality of life appears to be a distinct component of asthma health status, along with nighttime symptoms, daytime symptoms, and SABA use (Juniper et al. 2004).

In general, the impact of asthma is greater on the physical functioning component of life quality than on mental functioning (Adams et al. 2006; Graham et al. 2000; Stahl et al. 2003). However, when loss of physical functioning in valued life activities occurs, a higher correlation with quality of life is found among adults who have asthma. Valued life activities are those that individuals find most meaningful or pleasurable, and loss of these has been found to have a significant association with an increase in clinical asthma severity, patients' perception of asthma severity, and decrease in general physical function (Katz et al. 2004). Similarly, among adolescents who have asthma, quality of life was found to correlate with shortness of breath during exercise (Hallstrand et al. 2003). In contrast, in younger children (mean age of

9.3 ± 2.2 years), quality of life was more associated with the level of anxiety (Annett et al. 2001). Significant reduction in quality of life is also apparent when people who have asthma also have comorbid chronic conditions, such as diabetes, arthritis, heart disease, stroke, cancer, and osteoporosis (Adams et al. 2006).

The predictors of quality of life among people who have asthma may be related to levels of asthma severity. Lung function, however, was not found to be an independent predictor of quality of life at any level of severity, whereas shortness of breath was found to predict quality of life at all levels of asthma severity (Moy et al. 2001; Wijnhoven et al. 2001). Asthma symptom frequency has been found to be the most significant determinant of the subjective experience of asthma and perception of quality of life (Schatz et al. 2005a). Another important reason to monitor health-related quality of life is that it predicts health care utilization among patients who have asthma (Eisner et al. 2002; Magid et al. 2004) and for this reason may be a useful method of identifying patients who are at risk of exacerbation. Patients' reports of impaired quality of life to their primary care providers (PCPs) also were found to result in increased interventions, especially patient education and counseling, as well as medication changes (Jacobs et al. 2001).

Quality of life, perceptions of asthma control, and depression are psychosocial factors worth assessing over time, because they may affect directly the ability to engage in self-management of asthma and affect indirectly asthma morbidity and mortality outcomes. Both asthma-specific and generic quality-of-life measures are associated with patients' perceived control of asthma (Katz et al. 2002). The coping resources and specific coping style used by patients who have respiratory disease have been associated with quality of life. Among patients who have asthma, a more emotional or avoidant coping style, low self-efficacy, and low mastery feelings were found to be independently associated with poor quality of life (Hesselink et al. 2004).

Many instruments have been developed and tested to assess quality of life among persons who have asthma in all age groups. Both asthma-specific and generic quality-of-life instruments have been tested and validated (See box 3–4.). Specific measures are more useful for assessing an individual's response to treatment and are more sensitive than generic measures in detecting the impact of changes in asthma severity or control (Graham et al. 2000). Generic measures are more useful in assessing the broad impact of asthma on the quality of life and functioning in a population of people (Graham et al. 2000; Noonan et al. 1995) and for comparing populations across diagnoses of chronic illness (Graham et al. 2000; Mancuso et al. 2001).

BOX 3–4. INSTRUMENTS FOR ASSESSING ASTHMA-SPECIFIC AND GENERIC QUALITY OF LIFE

Asthma-Specific Quality of Life

- Mini Asthma Quality of Life Questionnaire (Juniper et al. 1999a)
- Asthma Quality of Life Questionnaire (Katz et al. 1999; Marks et al. 1993)
- ITG Asthma Short Form (Bayliss et al. 2000)
- Asthma Quality of Life for Children (Juniper et al. 1996)

Generic Quality of Life

- SF-36 (Bousquet et al. 1994)
- SF-12 (Ware et al. 1996)

Most of these instruments, however, are more suited for use in research studies than in clinical settings. Certain concerns preclude the Expert Panel's recommendation of the general adoption of these instruments at this time for routine encounters. These concerns include lack of experience with the use of the instruments in clinical practice and the time involved in administering the surveys. A few questionnaires have been shortened (Juniper et al. 1996) or tested by alternate methods of administration, such as telephone surveys (Pinnock et al. 2005).

Still, the importance of this concept to people who have asthma warrants that clinicians assess and monitor the effect of asthma on quality of life. See figure 3–7 for sample questions that may be used in the clinical setting for characterizing quality-of-life concerns for persons who have asthma.

Monitoring History of Asthma Exacerbations

The Expert Panel recommends that, during periodic assessments, clinicians should question the patient and evaluate any records of patient self-monitoring (figure 3–7) to detect exacerbations, both those that are self-treated and those treated by other health care providers (Evidence C). Exacerbations of asthma are episodes of marked increases in symptoms and reductions in lung function that interfere with the ability to perform usual activities unless quick relief therapy, such as SABA and additional corticosteroid treatment, is used. (See section 5 on "Managing Exacerbations of Asthma," for the classification of severity of exacerbations.) The most common cause of severe exacerbations is infection with a respiratory virus, especially rhinovirus, but exacerbations may be brought on by exposures to allergens or irritants, air pollutants, certain medications, and, possibly, emotional stress. Exacerbations also can be triggered by withdrawal of ICS or other long-term-control therapy. (See "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma" for a review of literature on causes of exacerbations.)

It is important to evaluate the frequency, rate of onset, severity, and causes of exacerbations. A history of previous exacerbations, especially in the past year, is the strongest predictor of future severe exacerbations leading to ED visits and hospitalizations (Adams et al. 2000; Eisner et al. 2001; Ford et al. 2001; Lieu et al. 1998). The patient should be asked about precipitating exposures and other factors. Specific inquiry into unscheduled visits to health care providers, telephone calls for assistance, and use of urgent or emergency care facilities is helpful. Severity of the exacerbation can be estimated by the increased need for oral corticosteroids. Finally, any hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation. To facilitate continuity of care, the clinician then can request summaries of all care received.

Monitoring Pharmacotherapy for Adherence and Potential Side Effects

The Expert Panel recommends monitoring the following factors at each visit: patient's adherence to the regimen, inhaler technique, and side effects of medications (Evidence C). See sample questions in figure 3–7 for assessing the patient's adherence to, concerns about, or adverse experiences with the drug regimen. See component 2—Education for a Partnership in Asthma Care for further discussion of patient's adherence to treatment.

Monitoring Patient–Provider Communication and Patient Satisfaction

The Expert Panel recommends that health care providers should routinely assess the effectiveness of patient–clinician communication (Evidence D). (See figure 3–7 for sample

questions.) Open and unrestricted communication among the clinician, the patient, and the patient's family is essential to ensure successful self-management by the patient who has asthma. A patient's negative attitude toward medication and/or reluctance toward self-management are risk factors for severe exacerbations (Adams et al. 2000). Every effort should be made to encourage open discussion of concerns and expectation of therapy. See "Component 2: Education for a Partnership in Asthma Care" for specific strategies to enhance communication and patient adherence to the treatment plan.

The Expert Panel recommends that two aspects of patient satisfaction should be monitored: satisfaction with asthma control and satisfaction with the quality of care (Evidence D). Patients' satisfaction with their asthma care and resolution of fears and concerns are important goals and will increase adherence to the treatment plan (Haynes et al. 1979; Meichenbaum and Turk 1987). See figures 3–2, 3–7, and 3–8 for examples of questions to use in monitoring patient satisfaction.

Monitoring Asthma Control With Minimally Invasive Markers and Pharmacogenetics

The Expert Panel recommends some minimally invasive markers for monitoring asthma control—such as spirometry and airway hyperresponsiveness—that are appropriately used, currently and widely, in asthma care (Evidence B). Other markers, such as sputum eosinophils and FeNO, are increasingly used in clinical research and will require further evaluation in adults and children before they can be recommended as a clinical tool for routine asthma management (Evidence D).

The interest in minimally invasive markers of asthma control arises from concerns over the possible dissociation between the severity of symptoms and impairments in function in the present, and the severity of the risk of exacerbations or progressive loss of pulmonary function in the future. For example, in a patient who reported daily symptoms, twice weekly nocturnal awakenings from asthma, shortness of breath on climbing stairs, and two exacerbations requiring ED treatment in the previous 12 months when first seen, does the resolution of all symptoms while taking treatment with a low dose of an ICS necessarily mean that his/her risk of exacerbations in the future is now acceptably low? A similar question might be asked of a patient treated with a high dose of an ICS and a LABA. If symptoms are completely controlled, can treatment be tapered without jeopardizing the patient's protection against future exacerbations? Must high-dose therapy for asthma be continued in a patient whose symptoms and function are well controlled but whose spirometry reveals a severely reduced but stable airflow obstruction (e.g., FEV_1 = 55 percent predicted)? Thus, although direct questioning is the best approach for assessing impairment, measurements of "biomarkers" are being examined as a way of assessing risk and thereby guiding adjustments in treatment.

The goal is to find a marker for asthma akin to hemoglobin A1C for diabetes (Its elevation is an index of the control of diabetes, and its reduction by therapy is known to reduce the risks of cardiovascular and renal complications.). To be practical, the marker should be measurable with minimal discomfort and risk to the patient and at minimal cost.

Spirometry: Perhaps the oldest marker of asthma impairment and risk is maximal expiratory flow, most commonly measured as FEV_1 and expressed as a percentage of predicted. Two large, retrospective cohort studies have shown that a reduction in FEV_1 at an annual visit is associated with increases in the risk of an attack of wheezing and shortness of breath over the next 12 or 36 months for pediatric and adult cohorts, respectively, and that the risk is greatest for those who have values consistent with "severe asthma," as described by the guidelines

(<60 percent predicted); the risk is next greatest for those who have an FEV_1 qualifying as "moderate asthma" (60–79 percent predicted); and the risk is least for those who have an FEV_1 for "mild asthma" (80–100 percent predicted) (Fuhlbrigge et al. 2001; Fuhlbrigge et al. 2006; Kitch et al. 2004). The validity is less well established of using a reduction in FEV_1 as a marker of increased risk of progressive loss of pulmonary function in patients.

Airway responsiveness is measured by delivering serially increasing doses of a provocative agent, like methacholine, and calculating the "provocative dose" causing a 20 percent fall in FEV_1 ("PC20"). Making this measurement is time consuming, expensive, and so far has been disappointing in predicting exacerbations in patients weaned from ICS treatment (Deykin et al. 2005). More promising, but still under investigation, is measurement of the PD15 to mannitol (Leuppi et al. 2005), possibly because it provokes bronchoconstriction indirectly, through the activation of mast cells in the bronchial mucosa. A system for delivering progressively increasing doses from simple inhaler devices has been developed (Leuppi et al. 2002), but at the time of this writing, the system has been approved for use only in Australia.

Sputum eosinophils: Two approaches to measuring the intensity of eosinophilic inflammation deserve mention. One is to analyze the cells and mediators in the sputum induced by inhalation of hypertonic saline aerosol (Djukanovic et al. 2002). The other is to measure the concentration of gases or volatile substances in exhaled air.

Analysis of induced sputum has attracted much attention, and analysis of the number or proportion of eosinophils in the sample holds up well in distinguishing patients who have or do not have asthma in repeatability, in association with other markers of asthma severity, and in predicting responsiveness to starting or withdrawing ICS treatment (Deykin et al. 2005). Its principal drawbacks are the difficulties in standardizing the methods for obtaining, preparing, and analyzing the samples, even across specialized centers, and the demands on the time of highly trained technical staff for obtaining and processing the samples. Still, a controlled prospective study has shown that adjusting ICS treatment to control sputum eosinophilia—as opposed to controlling symptoms, SABA use, nocturnal awakenings, and pulmonary function—significantly reduced both the rate of exacerbations and the cumulative dose of ICS (Green et al. 2002).

Fractional exhaled nitric oxide: Increases in FeNO are thought to reflect the intensity of eosinophilic inflammation of the bronchial mucosa. Like sputum eosinophil counts, measurement of FeNO distinguishes patients who do or do not have asthma, is repeatable, is associated with other markers of asthma severity, and, in some but not all studies, predicts responsiveness to starting or withdrawing ICS or oral corticosteroid treatment (Kharitonov et al. 1997; Pijnenburg et al. 2005; Taylor 2006). A device for measuring FeNO has been approved by the U.S. Food and Drug Administration (FDA); and a prospective, controlled study has shown that when ICS treatment was adjusted to control FeNO, as opposed to controlling the standard indices of asthma, the cumulative dose of ICS was reduced, with no worsening of the frequency of asthma exacerbations (Smith et al. 2005).

Other methods include measurement of compounds, like hydrogen ion (pH), isoprostanes, leukotriene metabolites, and products of nitrosylation in EBC (Hunt 2002). The condensate is collected by passing exhaled air through a cold tube for 10–20 minutes. Several studies have shown differences in the concentrations of various compounds in the EBC of healthy persons and those who have asthma, but work remains to be done to establish the range of normal values, repeatability, association with other markers of asthma severity, and responsiveness to treatment.

A recent study in children suggests that low pulmonary function and high indicators of markers of allergic airway inflammation—such as FeNO, blood eosinophil count, and IgE—predict greater response to ICS than to LTRAs in children (Szefler et al. 2005). Several studies indicate that monitoring biomarkers—such as measures of hyperresponsiveness, sputum eosinophils, and FeNO—can be used to guide treatment decisions (Green et al. 2002; Smith et al. 2005; Sont et al. 1999). Each of these studies has shown a reduction in asthma exacerbations with the biomarker-based treatment approach, as compared to treatment based on symptoms and pulmonary function, although the trend toward decreased exacerbations did not reach statistical significance in one of the studies (Smith et al. 2005). In addition, FeNO and sputum eosinophilis may be used in diagnosing asthma, as their sensitivity and specificity approach that of methacholine challenges, and both have sensitivities greater than SABA reversibility (Dupont et al. 2003; Smith et al. 2004).

Once these tools are refined for application to the clinical setting, they could be useful in guiding treatment selection to achieve and monitor asthma control quickly. It is important that tools for using biomarkers to diagnose or monitor asthma be tested in both children and adults, because the presentation of the disease may differ between age groups.

Pharmacogenetics in Managing Asthma

Pharmacogenetics is the study of the genetic causes of between-person variation in drug treatment response. To date, three genes have been identified that influence response to specific asthma medications: LTRA (Alox 5) (Drazen 1999; Lima et al. 2006), SABA (B2AR) (Israel et al. 2000, 2004; Silverman et al. 2003; Taylor et al. 2000), and ICS (CRHR1) (Tantisira et al. 2004). It is not clear that the functional variants responsible for these associations have been identified. The ADRB2 gene has been studied the most. Multiple studies have shown that individuals homozygous for Arg/Arg at position 16 of the protein have about a 3 percent reduction in peak flow when compared to Gly/Gly homozygotes. Because individuals having Arg/Arg homozygotes account for only 16 percent of the Caucasian population in the United States, this is a small amount of variability in the clinical phenotype in a small percentage of the population and thus is of questionable clinical significance. Studies of the influence of the homozygous Arg-16 genetic variant on response to LABA are inconclusive. Some studies show reduced lung function and increased symptoms (Wechsler et al. 2006); others show no adverse effects (Bleecker et al. 2006; Taylor et al. 2000) (see component 4—Medications). None of these genotypes, in isolation, explains a sufficient amount of variation in the drug-response phenotype to warrant clinical testing at this time. It is likely, however, that prediction of response to asthma treatment will be a clinical reality in the near future.

METHODS FOR PERIODIC ASSESSMENT AND MONITORING OF ASTHMA CONTROL

Each of the key measures used in the periodic assessment of asthma (i.e., signs and symptoms, pulmonary function, quality of life, history of exacerbations, pharmacotherapy, and patient–provider communication and patient satisfaction) can be obtained by several methods. The principal methods include the clinician's assessment and the patient's (and/or parent's or caregiver's) self-assessment. In addition, population-based assessment of asthma care is being developed in the managed care field.

Clinician Assessment

The Expert Panel recommends that patients who have intermittent or mild or moderate persistent asthma (i.e., requiring steps 1, 2, 3, or 4 treatment) that has been under control for at least 3 months should be seen by a clinician about every 6 months. Patients who have uncontrolled and/or severe persistent asthma (i.e., requiring steps 5 or 6 treatment) and those who need additional supervision to help them follow their treatment plan should be seen more often (EPR—2 1997).

The frequency of visits to a clinician for review of asthma control is a matter of clinical judgment. Clinical assessment of asthma should be obtained through medical history and physical examination with appropriate pulmonary function testing. Optimal followup assessment of medical history may be achieved best via a consistent set of questions (figure 3–7).

Patient Self-Assessment

The Expert Panel recommends that clinicians should encourage patients to use self-assessment tools to determine from the perspective of the patient and/or the patient's family whether the asthma is well controlled (EPR—2 1997). The two general methods are (1) a daily diary and (2) a periodic self-assessment form to be filled out by the patient and/or family member, usually at the time of the followup visits to the clinician. Patients are less likely to see completion of diaries and forms as a burden if they receive feedback from the clinician that allows them to see value in self-monitoring.

- The daily diary should include the key factors to be monitored at home: symptoms and/or peak flow, medication use, and restricted activity (See "Component 2: Education for a Partnership in Asthma Care."). Monitoring with a daily diary will be most useful to patients whose asthma is not yet under control and who are trying new treatments. It is also useful for those who need help in identifying environmental or occupational exposures that make their asthma worse.

- The self-assessment questionnaires that can be completed at office visits are intended to capture the patient's and family's impression of asthma control, self-management skills, and overall satisfaction with care. Several multidimensional instruments have been developed to assess control. Four of those that have been validated in more than one study for their psychometric quality are listed in figure 3–8. Two that have given permission are reproduced in that figure. Each of these four validated tools includes the impairment domain by measuring the dimension of symptoms, activity limitations, and need for quick relief medication, but not all include the physiological dimension of lung function. Only one includes a biological marker. Most of the questionnaires do not assess the risk domain of asthma control. Figure 3–9 is a sample self-assessment tool that incorporates both impairment and risk domains; however, this instrument has not had standardized assessment for validity and reliability.

Population-Based Assessment

Asthma care is of increasing interest in various health care settings. Important regulatory organizations for the health care industry (e.g., the National Committee on Quality Assurance) have included the care of persons who have asthma as a key indicator of the quality of managed care. In this context, periodic population-based assessment of asthma care has begun to emerge as an issue for patients and their clinical care providers. This type of

assessment often uses population experience, such as hospitalization or ED visit rates, to examine care within different clinical settings and among different providers. Complex, standardized population surveys (including lengthy health-status instruments) are being tested experimentally in the managed care setting.

Referral to an Asthma Specialist for Consultation or Comanagement

The Expert Panel recommends referral for consultation or care to a specialist in asthma care (usually, a fellowship-trained allergist or pulmonologist; occasionally, other physicians who have expertise in asthma management, developed through additional training and experience) when (Evidence D):

- Patient has had a life-threatening asthma exacerbation.
- Patient is not meeting the goals of asthma therapy after 3–6 months of treatment. An earlier referral or consultation is appropriate if the physician concludes that the patient is unresponsive to therapy.
- Signs and symptoms are atypical, or there are problems in differential diagnosis.
- Other conditions complicate asthma or its diagnosis (e.g., sinusitis, nasal polyps, aspergillosis, severe rhinitis, VCD, GERD, COPD).
- Additional diagnostic testing is indicated (e.g., allergy skin testing, rhinoscopy, complete pulmonary function studies, provocative challenge, bronchoscopy).
- Patient requires additional education and guidance on complications of therapy, problems with adherence, or allergen avoidance.
- Patient is being considered for immunotherapy.
- Patient requires step 4 care or higher (step 3 for children 0–4 years of age). Consider referral if patient requires step 3 care (step 2 for children 0–4 years of age).
- Patient has required more than two bursts of oral corticosteroids in 1 year or has an exacerbation requiring hospitalization.
- Patient requires confirmation of a history that suggests that an occupational or environmental inhalant or ingested substance is provoking or contributing to asthma. Depending on the complexities of diagnosis, treatment, or the intervention required in the work environment, it may be appropriate in some cases for the specialist to manage the patient over a period of time or to comanage with the PCP.

In addition, patients who have significant psychiatric, psychosocial, or family problems that interfere with their asthma therapy may need referral to an appropriate mental health professional for counseling or treatment. These problems have been shown to interfere with a patient's ability to adhere to treatment (Strunk et al. 1985, 1987).

FIGURE 3–1. SUGGESTED ITEMS FOR MEDICAL HISTORY*

A detailed medical history of the new patient who is known or thought to have asthma should address the following items:

1. **Symptoms**
   - Cough
   - Wheezing
   - Shortness of breath
   - Chest tightness
   - Sputum production
2. **Pattern of symptoms**
   - Perennial, seasonal, or both
   - Continual, episodic, or both
   - Onset, duration, frequency (number of days or nights, per week or month)
   - Diurnal variations, especially nocturnal and on awakening in early morning
3. **Precipitating and/or aggravating factors**
   - Viral respiratory infections
   - Environmental allergens, indoor (e.g., mold, house-dust mite, cockroach, animal dander or secretory products) and outdoor (e.g., pollen)
   - Characteristics of home including age, location, cooling and heating system, wood-burning stove, humidifier, carpeting over concrete, presence of molds or mildew, characteristics of rooms where patient spends time (e.g., bedroom and living room with attention to bedding, floor covering, stuffed furniture)
   - Smoking (patient and others in home or daycare)
   - Exercise
   - Occupational chemicals or allergens
   - Environmental change (e.g., moving to new home; going on vacation; and/or alterations in workplace, work processes, or materials used)
   - Irritants (e.g., tobacco smoke, strong odors, air pollutants, occupational chemicals, dusts and particulates, vapors, gases, and aerosols)
   - Emotions (e.g., fear, anger, frustration, hard crying or laughing)
   - Stress (e.g., fear, anger, frustration)
   - Drugs (e.g., aspirin; and other nonsteroidal anti-inflammatory drugs, beta-blockers including eye drops, others)
   - Food, food additives, and preservatives (e.g., sulfites)
   - Changes in weather, exposure to cold air
   - Endocrine factors (e.g., menses, pregnancy, thyroid disease)
   - Comorbid conditions (e.g. sinusitis, rhinitis, GERD)
4. **Development of disease and treatment**
   - Age of onset and diagnosis
   - History of early-life injury to airways (e.g., bronchopulmonary dysplasia, pneumonia, parental smoking)
   - Progression of disease (better or worse)
   - Present management and response, including plans for managing exacerbations
   - Frequency of using SABA
   - Need for oral corticosteroids and frequency of use
5. **Family history**
   - History of asthma, allergy, sinusitis, rhinitis, eczema, or nasal polyps in close relatives
6. **Social history**
   - Daycare, workplace, and school characteristics that may interfere with adherence
   - Social factors that interfere with adherence, such as substance abuse
   - Social support/social networks
   - Level of education completed
   - Employment
7. **History of exacerbations**
   - Usual prodromal signs and symptoms
   - Rapidity of onset
   - Duration
   - Frequency
   - Severity (need for urgent care, hospitalization, ICU admission)
   - Life-threatening exacerbations (e.g., intubation, intensive care unit admission)
   - Number and severity of exacerbations in the past year.
   - Usual patterns and management (what works?)
8. **Impact of asthma on patient and family**
   - Episodes of unscheduled care (ED, urgent care, hospitalization)
   - Number of days missed from school/work
   - Limitation of activity, especially sports and strenuous work
   - History of nocturnal awakening
   - Effect on growth, development, behavior, school or work performance, and lifestyle
   - Impact on family routines, activities, or dynamics
   - Economic impact
9. **Assessment of patient's and family's perceptions of disease**
   - Patient's, parents', and spouse's or partner's knowledge of asthma and belief in the chronicity of asthma and in the efficacy of treatment
   - Patient's perception and beliefs regarding use and long-term effects of medications
   - Ability of patient and parents, spouse, or partner to cope with disease
   - Level of family support and patient's and parents', spouse's, or partner's capacity to recognize severity of an exacerbation
   - Economic resources
   - Sociocultural beliefs

*This list does not represent a standardized assessment or diagnostic instrument. The validity and reliability of this list have not been assessed.

FIGURE 3–2. SAMPLE QUESTIONS* FOR THE DIAGNOSIS AND INITIAL ASSESSMENT OF ASTHMA

A "yes" answer to any question suggests that an asthma diagnosis is likely.

In the past 12 months…

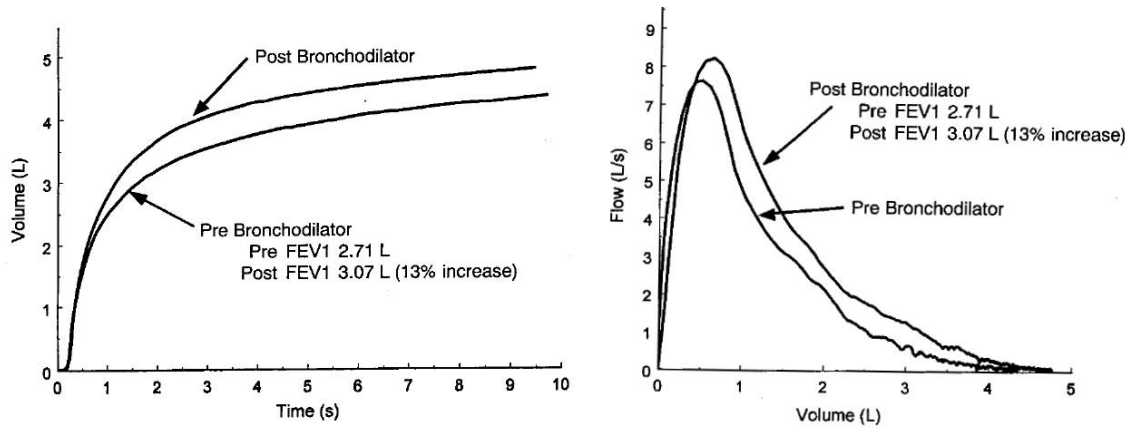
- Have you had a sudden severe episode or recurrent episodes of coughing, wheezing (high-pitched whistling sounds when breathing out), chest tightness, or shortness of breath?
- Have you had colds that "go to the chest" or take more than 10 days to get over?
- Have you had coughing, wheezing, or shortness of breath during a particular season or time of the year?
- Have you had coughing, wheezing, or shortness of breath in certain places or when exposed to certain things (e.g., animals, tobacco smoke, perfumes)?
- Have you used any medications that help you breathe better? How often?
- Are your symptoms relieved when the medications are used?

In the past 4 weeks, have you had coughing, wheezing, or shortness of breath…

- At night that has awakened you?
- Upon awakening?
- After running, moderate exercise, or other physical activity?

*These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed.

FIGURE 3–3a. SAMPLE SPIROMETRY VOLUME TIME AND FLOW VOLUME CURVES



Key: FEV_1, forced expiratory volume in 1 second

FIGURE 3–3b. REPORT OF SPIROMETRY FINDINGS PRE- AND POSTBRONCHODILATOR

Prebronchodilator

Study: bronch Age: 59	ID: Height: 175 cm	Test date: 8/7/06 Sex: M	Time: 9:38 a.m. System: 7 20 17
Trial	**FVC**	**FEV_1**	**FEV_1/ FVC (%)**
1	4.34	2.68	61.8%
2	4.44	2.62	58.9%
3	4.55	2.71	59.6%
Best Values	4.56	2.71	59.4%
Predicted Values*	4.23	3.40	80.5%
Percent Predicted	107.8%	79.7%	73.8%

Interpretations:

FEV_1 and FEV_1/FVC are below normal range. The reduced rate at which air is exhaled indicates obstruction to airflow.

*Predicted values from Knudson et al. (1983)

Postbronchodilator

Study: bronch Age: 59	ID: Height: 175 cm	Test date: 8/7/06 Sex: M	Time: 9:58 a.m. System: 7 20 17
Trial	**FVC**	**FEV_1**	**FEV_1/ FVC (%)**
1	4.73	2.94	62.2%
2	4.76	3.07	64.5%
3	4.78	3.04	63.5%
Best Values	4.78	3.07	64.3%
Reference Values	4.56	2.71	
Difference (L)	0.22	0.36	
Difference (%)	4.8%	13.4%	

Interpretations:

Significant increases in FEV_1, with bronchodilator (≥12% increase after bronchodilator indicates a significant change).

Key: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

FIGURE 3–4a. CLASSIFYING ASTHMA SEVERITY IN CHILDREN 0–4 YEARS OF AGE

- **Classifying severity in children who are not currently taking long-term control medication.**

Components of Severity		Classification of Asthma Severity (Children 0–4 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral steroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. →			
		Exacerbations of any severity may occur in patients in any severity category			

- **Level of severity is determined by both impairment and risk. Assess impairment domain by caregiver's recall of previous 2–4 weeks. Assign severity to the most severe category in which any feature occurs.**
- **At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.**

- **Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control.***

Lowest level of treatment required to maintain control (See figure 4–1a for treatment steps.)	Classification of Asthma Severity			
	Intermittent	Persistent		
		Mild	Moderate	Severe
	Step 1	Step 2	Step 3 or 4	Step 5 or 6

Key: EIB, exercise-induced bronchospasm

*Notes:

- **For population-based evaluations, clinical research, or characterization of a patient's overall asthma severity after control is achieved. For clinical management, the focus is on monitoring the level of control (See figure 3–5a.), not the level of severity, once treatment is established.**
- **See figure 3–5a for definition of asthma control.**

FIGURE 3–4b. CLASSIFYING ASTHMA SEVERITY IN CHILDREN 5–11 YEARS OF AGE

- **Classifying severity in children who are not currently taking long-term control medication.**

Components of Severity		Classification of Asthma Severity (Children 5–11 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2 in 1 year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

- **Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of the previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.**
- **At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.**

- **Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control.***

Lowest level of treatment required to maintain control (See figure 4–1b for treatment steps.)	Classification of Asthma Severity			
	Intermittent	Persistent		
		Mild	Moderate	Severe
	Step 1	Step 2	Step 3 or 4	Step 5 or 6

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in second; FVC, forced vital capacity; ICU, intensive care unit

***Notes:**

- **For population-based evaluations, clinical research, or characterization of a patient's overall asthma severity after control is achieved. For clinical management, the focus is on monitoring the level of control (See figure 3–5b.), not the level of severity, once treatment is established.**
- **See figure 3–5b for definition of asthma control.**

FIGURE 3–4c. CLASSIFYING ASTHMA SEVERITY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

- **Classifying severity for patients who are not currently taking long-term control medications.**

Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

- **Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.**
- **At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.**

- **Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control.***

Lowest level of treatment required to maintain control (See figure 4–5 for treatment steps.)	Classification of Asthma Severity			
	Intermittent	Persistent		
		Mild	Moderate	Severe
	Step 1	Step 2	Step 3 or 4	Step 5 or 6

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

***Notes:**

- **For population-based evaluations, clinical research, or characterization of a patient's overall asthma severity after control is achieved. For clinical management, the focus is on monitoring the level of control (See figure 3–5c.), not the level of severity, once treatment is established.**
- **See figure 3–5c for definition of asthma control.**

FIGURE 3–5a. ASSESSING ASTHMA CONTROL IN CHILDREN 0–4 YEARS OF AGE

Components of Control		Classification of Asthma Control (Children 0–4 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	1x/month	>1x/month	>1x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	2–3/year	>3/year
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

Key: EIB, exercise-induced bronchospasm; ICU, intensive care unit

Notes:

- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 3–5b. ASSESSING ASTHMA CONTROL IN CHILDREN 5–11 YEARS OF AGE

Components of Control		Classification of Asthma Control (Children 5–11 years of age)		
		Well Controlled	**Not Well Controlled**	**Very Poorly Controlled**
Impairment	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function ▪ FEV_1 or peak flow ▪ FEV_1/FVC	 >80% predicted/ personal best >80%	 60–80% predicted/ personal best 75–80%	 <60% predicted/ personal best <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long-term followup.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes:

- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

FIGURE 3–5c. ASSESSING ASTHMA CONTROL IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Components of Control		Classification of Asthma Control (Youths ≥12 years of age and adults)		
		Well-Controlled	Not Well-Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakening	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated Questionnaires ATAQ ACQ ACT	 0 ≤0.75* ≥20	 1–2 ≥1.5 16–19	 3–4 N/A ≤15
Risk	Exacerbations	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second. See figure 3–8 for full name and source of ATAQ, ACQ, ACT.

Notes:

- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

FIGURE 3–6. SAMPLE QUESTIONS FOR ASSESSING AND MONITORING ASTHMA CONTROL

Monitoring Asthma Control

Ask the patient:

- Has your asthma awakened you at night or early morning?
- Have you needed more quick-relief bronchodilator medication (inhaled short-acting beta$_2$-agonist) than usual?
- Have you needed any urgent medical care for your asthma, such as unscheduled visits to your doctor, an urgent care clinic, or the emergency department?
- Are you participating in your usual and desired activities?
- If you are measuring your peak flow, has it been below your personal best?

Actions to consider:

- Assess whether the medications are being taken as prescribed.
- Assess whether the medications are being inhaled with correct technique.
- Assess lung function with spirometry and compare to previous measurement.
- Adjust medications, as needed; either step up if control is inadequate or step down if control is maximized, to achieve the best control with the lowest dose of medication.

Source: Adapted and reprinted from "Global Initiative for Asthma: Pocket Guide for Asthma Management and Prevention." NIH Publication No. 96-3659B. Bethesda, MD: Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. 1995

FIGURE 3–7. COMPONENTS OF THE CLINICIAN'S FOLLOWUP ASSESSMENT: SAMPLE ROUTINE CLINICAL ASSESSMENT QUESTIONS*

Monitoring Signs and Symptoms

(Global assessment) "Has your asthma been better or worse since your last visit?"
"Has your asthma worsened during specific seasons or events?"
(Recent assessment) "In the past 2 weeks, how many days have you:

- Had problems with coughing, wheezing, shortness of breath, or chest tightness during the day?"
- Awakened at night from sleep because of coughing or other asthma symptoms?"
- Awakened in the morning with asthma symptoms that did not improve within 15 minutes of inhaling a short-acting beta$_2$-agonist?"
- Had symptoms while exercising or playing?"
- Been unable to perform a usual activity, including exercise, because of asthma?"

Monitoring Pulmonary Function

Lung Function

"What is the highest and lowest your peak flow has been since your last visit?"
"Has your peak flow dropped below ___ L/min (80 percent of personal best) since your last visit?"
"What did you do when this occurred?"

Peak Flow Monitoring Technique

"Please show me how you measure your peak flow."
"When do you usually measure your peak flow?"

Monitoring Quality of Life/Functional Status

"Since your last visit, how many days has your asthma caused you to:

- Miss work or school?"
- Reduce your activities?"
- (For caregivers) Change your activity because of your child's asthma?"

"Since your last visit, have you had any unscheduled or emergency department visits or hospital stays?"

Monitoring Exacerbation History

"Since your last visit, have you had any episodes/times when your asthma symptoms were a lot worse than usual?"
If yes, "What do you think caused the symptoms to get worse?"
If yes, "What did you do to control the symptoms?"
"Have there been any changes in your home or work environment (e.g., new smokers or pets)?"

Monitoring Pharmacotherapy

Medications

"What medications are you taking?"
"How do you feel about taking medication?"
"How often do you take each medication?"
"How much do you take each time?"
"Have you missed or stopped taking any regular doses of your medications for any reason?"
"Have you had trouble filling your prescriptions (e.g., for financial reasons, not on formulary)?"
"How many puffs of your inhaled short-acting beta$_2$-agonist (quick-relief medicine) do you use per day?"
"How many [name inhaled short-acting beta$_2$-agonist] inhalers [or pumps] have you been through in the past month?"
"Have you tried any other medicines or remedies?"

Side Effects

"Has your asthma medicine caused you any problems?"

- Shakiness, nervousness, bad taste, sore throat, cough, upset stomach, hoarseness, skin changes (e.g., bruising)

Inhaler Technique

"Please show me how you use your inhaler."

Monitoring Patient–Provider Communication and Patient Satisfaction

"What questions have you had about your asthma daily self-management plan and action plan?"
"What problems have you had following your daily self-management plan? Your action plan?"
"How do you feel about making your own decisions about therapy?"
"Has anything prevented you from getting the treatment you need for your asthma from me or anyone else?"
"Have the costs of your asthma treatment interfered with your ability to get asthma care?"
"How satisfied are you with your asthma care?"
"How can we improve your asthma care?"
"Let's review some important information:

- When should you increase your medications? Which medication(s)?"
- When should you call me [your doctor or nurse practitioner]? Do you know the after-hours phone number?"
- If you can't reach me, what emergency department would you go to?"

*These questions are examples and do not represent a standardized assessment instrument. The validity and reliability of these questions have not been assessed.

FIGURE 3–8. VALIDATED INSTRUMENTS FOR ASSESSMENT AND MONITORING OF ASTHMA

- Asthma Control Questionnaire (Juniper et al. 1999b)
- Asthma Therapy Assessment Questionnaire (Vollmer et al. 1999) (See below.)
- Asthma Control Test (Nathan et al. 2004) (See below.)
- Asthma Control score (Boulet et al. 2002)

ASTHMA THERAPY ASSESSMENT QUESTIONNAIRE© (ATAQ)

1. In the past 4 weeks did you miss any work, school, or normal daily activities because of your asthma? (1 point for YES)

2. In the past 4 weeks, did you wake up at night because of your asthma? (1 point for YES)

3. Do you believe your asthma was well controlled in the past 4 weeks? (1 point for NO)

4. Do you use an inhaler for quick relief from asthma symptoms? If yes, what is the highest number of puffs in 1 day you took of this inhaler? (1 point for more than 12)

Total points = 0–4, with more points indicating more control problems

Source: Adapted and reprinted with permission from Merck and Co., Inc. Copyright © 1997, 1998, 1999 Merck and Co., Inc. All Rights Reserved.

ASTHMA CONTROL TEST™

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an X in the one box that best describes your answer.

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐1	☐2	☐3	☐4	☐5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐1	☐2	☐3	☐4	☐5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, Maxair®, or Primatene Mist®)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
☐1	☐2	☐3	☐4	☐5

5. How would you rate your asthma control during the past 4 weeks?

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐1	☐2	☐3	☐4	☐5

For information on the interpretation and scoring of the Asthma Control Test™ (ACT™), visit www.qualitymetric.com/act.

Source: Reprinted with permission from QualityMetric Incorporated, Asthma Control Test™ Copyright ©, QualityMetric Incorporated 2002, 2004. All Rights Reserved.

CAUTION: The sample questionnaires in figure 3–8 assess only the impairment domain of asthma control and NOT the risk domain. Measure of risk, such as exacerbations, urgent care, hospitalizations, and declines in lung function, are important elements of assessing the level of asthma control.

FIGURE 3–9. SAMPLE* PATIENT SELF-ASSESSMENT SHEET FOR FOLLOWUP VISITS

Name: _____ **Date:** _____

Your Asthma Control

How many days in the past week have you had chest tightness, cough, shortness of breath, or wheezing (whistling in your chest)?	_____ 0 _____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7
How many nights in the past week have you had chest tightness, cough, shortness of breath, or wheezing (whistling in your chest)?	_____ 0 _____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7
Do you perform peak flow readings at home?	_____ yes _____ no
If yes, did you bring your peak flow chart?	_____ yes _____ no
How many days in the past week has asthma restricted your physical activity?	_____ 0 _____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7
Have you had any asthma attacks since your last visit?	_____ yes _____ no
Have you had any unscheduled visits to a doctor, including to the emergency department, since your last visit?	_____ yes _____ no
How well controlled is your asthma, in your opinion?	____very well controlled ____somewhat controlled ____not well controlled
	_____ Average number of puffs per day

Taking your medicine

What problems have you had taking your medicine or following your asthma action plan?

Please ask the doctor or nurse to review how you take your medicine.

Your questions

What questions or concerns would you like to discuss with the doctor?

How satisfied are you with your asthma care?	____very satisfied ____somewhat satisfied ____not satisfied

*These questions are examples and do not represent a standardized assessment instrument. Other examples of asthma control questions: Asthma Control Questionnaire (Juniper); Asthma Therapy Assessment Questionnaire (Volmer); Asthma Control Test (Nathan); Asthma Control Score (Boulet)

REFERENCES

Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax* 2000;55(7):566–73.

Adams RJ, Wilson DH, Taylor AW, Daly A, Tursan d'Espaignet E, Dal GE, Ruffin RE. Coexistent chronic conditions and asthma quality of life: a population-based study. *Chest* 2006;129(2):285–91.

American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152(3):1107–36.

American Thoracic Society and European Respiratory Society Task Force, Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten C, Gustafsson P, et al. Standardization of lung function testing. *Eur Respir J* 2005;26:948–68.

Annett RD, Bender BG, Lapidus J, Duhamel TR, Lincoln A. Predicting children's quality of life in an asthma clinical trial: what do children's reports tell us? *J Pediatr* 2001;139(6):854–61.

Antonicelli L, Bucca C, Neri M, De Benedetto F, Sabbatani P, Bonifazi F, Eichler HG, Zhang Q, Yin DD. Asthma severity and medical resource utilisation. *Eur Respir J* 2004;23(5):723–9.

Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE. Spirometric criteria for asthma: adding further evidence to the debate. *J Allergy Clin Immunol* 2005;116(5):976–82.

Apter AJ, Szefler SJ. Advances in adult and pediatric asthma. *J Allergy Clin Immunol* 2004;113(3):407–14.

Ayres JG, Jyothish D, Ninan T. Brittle asthma. *Paediatr Respir Rev* 2004;5(1):40–4. Review.

Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF Jr, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 2004;170(4):426–32.

Barnes PJ, Woolcock AJ. Difficult asthma. *Eur Respir J* 1998;12(5):1209–18.

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004;170(8):836–44.

Bayliss MS, Espindle DM, Buchner D, Blaiss MS, Ware JE. A new tool for monitoring asthma outcomes: the ITG Asthma Short Form. *Qual Life Res* 2000;9(4):451–66.

Belessis Y, Dixon S, Thomsen A, Duffy B, Rawlinson W, Henry R, Morton J. Risk factors for an intensive care unit admission in children with asthma. *Pediatr Pulmonol* 2004;37(3):201–9.

Bijl-Hofland ID, Cloosterman SG, Van Schayck CP, Elshout FJ, Akkermans RP, Folgering HT. Perception of respiratory sensation assessed by means of histamine challenge and threshold loading tests. *Chest* 2000;117(4):954–9.

Bleecker ER, Yancey SW, Baitinger LA, Edwards LD, Klotsman M, Anderson WH, Dorinsky PM. Salmeterol response is not affected by beta$_2$-adrenergic receptor genotype in subjects with persistent asthma. *J Allergy Clin Immunol* 2006;118(4):809–16.

Boulet LP, Boulet V, Milot J. How should we quantify asthma control? A proposal. *Chest* 2002;122(6):2217–23.

Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, Chinchilli VM, Craig TJ, DiMango EA, Deykin A, et al.; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352(15):1519–28.

Bousquet J, Knani J, Dhivert H, Richard A, Chicoye A, Ware JE Jr, Michel FB. Quality of life in asthma. I. Internal consistency and validity of the SF-36 questionnaire. *Am J Respir Crit Care Med* 1994;149(2 Pt 1):371–5.

Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 2004;125(4):1378–86.

Brand PL, Quanjer PH, Postma DS, Kerstjens HA, Koeter GH, Dekhuijzen PN, Sluiter HJ. Interpretation of bronchodilator response in patients with obstructive airways disease. The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. *Thorax* 1992;47(6):429–36.

Bucca C, Rolla G, Brussino L, De Rose V, Bugiani M. Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction? *Lancet* 1995;346(8978):791–5.

Bye MR, Kerstein D, Barsh E. The importance of spirometry in the assessment of childhood asthma. *Am J Dis Child* 1992;146(8):977–8.

Christopher KL, Wood RP, Eckert RC, Blager FB, Raney RA, Souhrada JF. Vocal-cord dysfunction presenting as asthma. *N Engl J Med* 1983;308(26):1566–70.

Colice GL, Burgt JV, Song J, Stampone P, Thompson PJ. Categorizing asthma severity. *Am J Respir Crit Care Med* 1999;160(6):1962–7.

Connolly CK, Mamun M, Alcock SM, Prescott RJ. The Darlington and Northallerton Prospective Asthma Study: best function predicts mortality during the first 10 years. *Respir Med* 1998;92(11):1274–80.

Connolly MJ, Crowley JJ, Charan NB, Nielson CP, Vestal RE. Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. *Thorax* 1992;47(6):410–3.

Covar RA, Spahn JD, Martin RJ, Silkoff PE, Sundstrom DA, Murphy J, Szefler SJ. Safety and application of induced sputum analysis in childhood asthma. *J Allergy Clin Immunol* 2004a;114(3):575–82.

Covar RA, Spahn JD, Murphy JR, Szefler SJ; Childhood Asthma Management Program Research Group. Progression of asthma measured by lung function in the childhood asthma management program. *Am J Respir Crit Care Med* 2004b;170(3):234–41. Epub March 2004.

Cowie RL, Underwood MF, Revitt SG, Field SK. Predicting emergency department utilization in adults with asthma: a cohort study. *J Asthma* 2001;38(2):179–84.

Dales RE, Spitzer WO, Tousignant P, Schechter M, Suissa S. Clinical interpretation of airway response to a bronchodilator. Epidemiologic considerations. *Am Rev Respir Dis* 1988;138(2):317–20.

Deykin A, Lazarus SC, Fahy JV, Wechsler ME, Boushey HA, Chinchilli VM, Craig TJ, DiMango E, Kraft M, Leone F, et al.; Asthma Clinical Research Network, National Heart, Lung, and Blood Institute/NIH. Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. *J Allergy Clin Immunol* 2005;115(4):720–7.

Dicpinigaitis PV. Chronic cough due to asthma: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl):75S–79S.

Diette GB, Krishnan JA, Dominici F, Haponik E, Skinner EA, Steinwachs D, Wu AW. Asthma in older patients: factors associated with hospitalization. *Arch Intern Med* 2002;162(10):1123–32.

Diette GB, Krishnan JA, Wolfenden LL, Skinner EA, Steinwachs DM, Wu AW. Relationship of physician estimate of underlying asthma severity to asthma outcomes. *Ann Allergy Asthma Immunol* 2004;93(6):546–52.

Djukanovic R, Sterk PJ, Fahy JV, Hargreave FE. Standardised methodology of sputum induction and processing. *Eur Respir J Suppl* 2002;37:1s–2s.

Drazen JM. Asthma therapy with agents preventing leukotriene synthesis or action. *Proc Assoc Am Physicians* 1999;111(6):547–59.

Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. *Chest* 2003;123(3):751–6.

Eid N, Yandell B, Howell L, Eddy M, Sheikh S. Can peak expiratory flow predict airflow obstruction in children with asthma? *Pediatrics* 2000;105(2):354–8.

Eisner MD, Ackerson LM, Chi F, Kalkbrenner A, Buchner D, Mendoza G, Lieu T. Health-related quality of life and future health care utilization for asthma. *Ann Allergy Asthma Immunol* 2002;89(1):46–55.

Eisner MD, Katz PP, Lactao G, Iribarren C. Impact of depressive symptoms on adult asthma outcomes. *Ann Allergy Asthma Immunol* 2005;94(5):566–74.

Eisner MD, Katz PP, Yelin EH, Shiboski SC, Blanc PD. Risk factors for hospitalization among adults with asthma: the influence of sociodemographic factors and asthma severity. *Respir Res* 2001;2(1):53–60. Epub December 2000.

EPR—2. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD, U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

EPR—Update 2002. *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma. Update on Selected Topics 2002* (EPR—Update 2002). NIH Publication No. 02-5074. Bethesda, MD, U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003.

Ford JG, Meyer IH, Sternfels P, Findley SE, McLean DE, Fagan JK, Richardson L. Patterns and predictors of asthma-related emergency department use in Harlem. *Chest* 2001;120(4):1129–35.

Fuhlbrigge AL, Adams RJ, Guilbert TW, Grant E, Lozano P, Janson SL, Martinez F, Weiss KB, Weiss ST. The burden of asthma in the United States: level and distribution are dependent on interpretation of the National Asthma Education and Prevention Program guidelines. *Am J Respir Crit Care Med* 2002;166(8):1044–9.

Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, Weiss ST. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 2001;107(1):61–7.

Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics* 2006;118(2):e347–e355. Epub July 2006.

Global Initiative for Asthma Management and Prevention (GINA). *NHLBI/WHO Workshop Report.* NIH Publication No. 02-3659. Bethesda, MD: Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute, 2002.

Goodwin RD, Fergusson DM, Horwood LJ. Asthma and depressive and anxiety disorders among young persons in the community. *Psychol Med* 2004;34(8):1465–74.

Graham DM, Blaiss MS, Bayliss MS, Espindle DM, Ware JE Jr. Impact of changes in asthma severity on health-related quality of life in pediatric and adult asthma patients: results from the asthma outcomes monitoring system. *Allergy Asthma Proc* 2000;21(3):151–8.

Graham LM. Classifying asthma. *Chest* 2006;130(1 Suppl):13S–20S. Review.

Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, Wardlaw AJ, Pavord ID. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360(9347):1715–21.

Griswold SK, Nordstrom CR, Clark S, Gaeta TJ, Price ML, Camargo CA Jr. Asthma exacerbations in North American adults: who are the "frequent fliers" in the emergency department? *Chest* 2005;127(5):1579–86.

Hallstrand TS, Curtis JR, Aitken ML, Sullivan SD. Quality of life in adolescents with mild asthma. *Pediatr Pulmonol* 2003;36(6):536–43.

Hankinson JL, Wagner GR. Medical screening using periodic spirometry for detection of chronic lung disease. *Occup Med* 1993;8(2):353–61.

Haynes RB, Taylor DW, Sackett DL, eds. Compliance in Health Care. Baltimore: Johns Hopkins University Press, 1979.

Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, Gamble J. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax* 2003;58(7):561–6.

Hesselink AE, Penninx BW, Schlosser MA, Wijnhoven HA, van der Windt DA, Kriegsman DM, van Eijk JT. The role of coping resources and coping style in quality of life of patients with asthma or COPD. *Qual Life Res* 2004;13(2):509–18.

Hunt J. Exhaled breath condensate: an evolving tool for noninvasive evaluation of lung disease. *J Allergy Clin Immunol* 2002;110(1):28–34.

Irvin CG, Martin RJ, Chinchilli VM, Kunselman SJ, Cherniack RM. Quality control of peak flow meters for multicenter clinical trials. The Asthma Clinical Research Network (ACRN). *Am J Respir Crit Care Med* 1997;156(2 Pt 1):396–402.

Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, Deykin A, Fagan JK, Fahy JV, Fish J, et al.; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004;364(9444):1505–12.

Israel E, Drazen JM, Liggett SB, Boushey HA, Cherniack RM, Chinchilli VM, Cooper DM, Fahy JV, Fish JE, Ford JG, et al. The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med* 2000;162(1):75–80.

Jacobs JE, van de Lisdonk EH, Smeele I, Van Weel C, Grol RP. Management of patients with asthma and COPD: monitoring quality of life and the relationship to subsequent GP interventions. *Fam Pract* 2001;18(6):574–80.

Jain P, Kavuru MS, Emerman CL, Ahmad M. Utility of peak expiratory flow monitoring. *Chest* 1998;114(3):861–76.

Janson-Bjerklie S, Ferketich S, Benner P. Predicting the outcomes of living with asthma. *Res Nurs Health* 1993;16(4):241–50.

Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999a;14(1):32–8.

Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res* 1996;5(1):35–46.

Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999b;14(4):902–7.

Juniper EF, Wisniewski ME, Cox FM, Emmett AH, Nielsen KE, O'Byrne PM. Relationship between quality of life and clinical status in asthma: a factor analysis. *Eur Respir J* 2004;23(2):287–91.

Katz PP, Eisner MD, Henke J, Shiboski S, Yelin EH, Blanc PD. The Marks Asthma Quality of Life Questionnaire: further validation and examination of responsiveness to change. *J Clin Epidemiol* 1999;52(7):667–75.

Katz PP, Yelin EH, Eisner MD, Blanc PD. Perceived control of asthma and quality of life among adults with asthma. *Ann Allergy Asthma Immunol* 2002;89(3):251–8.

Katz PP, Yelin EH, Eisner MD, Earnest G, Blanc PD. Performance of valued life activities reflected asthma-specific quality of life more than general physical function. *J Clin Epidemiol* 2004;57(3):259–67.

Kharitonov S, Alving K, Barnes PJ. Exhaled and nasal nitric oxide measurements: recommendations. The European Respiratory Society Task Force. *Eur Respir J* 1997;10(7):1683–93.

Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato K, Takishima T. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Engl J Med* 1994;330(19):1329–34.

Kitch BT, Paltiel AD, Kuntz KM, Dockery DW, Schouten JP, Weiss ST, Fuhlbrigge AL. A single measure of FEV_1 is associated with risk of asthma attacks in long-term follow-up. *Chest* 2004;126(6):1875–82.

Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127(6):725–34.

Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, Kraft M, Fish JE, Peters SP, Craig T, et al.; Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Long-acting $beta_2$-agonist monotherapy vs. continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285(20):2583–93.

Leone FT, Mauger EA, Peters SP, Chinchilli VM, Fish JE, Boushey HA, Cherniack RM, Drazen JM, Fahy JV, Ford J, et al. The utility of peak flow, symptom scores, and beta-agonist use as outcome measures in asthma clinical research. *Chest* 2001;119(4):1027–33.

Leuppi JD, Brannan JD, Anderson SD. Bronchial provocation tests: the rationale for using inhaled mannitol as a test for airway hyperresponsiveness. *Swiss Med Wkly* 2002;132(13–14):151–8.

Leuppi JD, Tandjung R, Anderson SD, Stolz D, Brutsche MH, Bingisser R, Perruchoud AP, Surber C, Knoblauch A, Andersson M, et al. Prediction of treatment-response to inhaled corticosteroids by mannitol-challenge test in COPD. A proof of concept. *Pulm Pharmacol Ther* 2005;18(2):83–8.

Li JT, O'Connell EJ. Clinical evaluation of asthma. *Ann Allergy Asthma Immunol* 1996;76(1):1–13; quiz 13–5. Review.

Lieu TA, Quesenberry CP, Sorel ME, Mendoza GR, Leong AB. Computer-based models to identify high-risk children with asthma. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1173–80.

Lima JJ, Zhang S, Grant A, Shao L, Tantisira KG, Allayee H, Wang J, Sylvester J, Holbrook J, Wise R, et al. Influence of leukotriene pathway polymorphisms on response to montelukast in asthma. *Am J Respir Crit Care Med* 2006;173(4):379–85. Epub November 2005.

Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, Rosenzweig JC, Manjunath R. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007;119(4):817–25. Epub March 2007.

Llewellin P, Sawyer G, Lewis S, Cheng S, Weatherall M, Fitzharris P, Beasley R. The relationship between FEV_1 and PEF in the assessment of the severity of airways obstruction. *Respirology* 2002;7(4):333–7.

Magid DJ, Houry D, Ellis J, Lyons E, Rumsfeld JS. Health-related quality of life predicts emergency department utilization for patients with asthma. *Ann Emerg Med* 2004;43(5):551–7.

Mancuso CA, Peterson MG, Charlson ME. Comparing discriminative validity between a disease-specific and a general health scale in patients with moderate asthma. *J Clin Epidemiol* 2001;54(3):263–74.

Marks GB, Dunn SM, Woolcock AJ. An evaluation of an asthma quality of life questionnaire as a measure of change in adults with asthma. *J Clin Epidemiol* 1993;46(10):1103–11.

Meichenbaum D, Turk DC. *Facilitating Treatment Adherence: A Practitioner's Guidebook.* New York: Plenum Press, 1987.

Meslier N, Racineux JL, Six P, Lockhart A. Diagnostic value of reversibility of chronic airway obstruction to separate asthma from chronic bronchitis: a statistical approach. *Eur Respir J* 1989;2(6):497–505.

Miles JF, Bright P, Ayres JG, Cayton RM, Miller MR. The performance of Mini Wright peak flow meters after prolonged use. *Respir Med* 1995;89(9):603–5.

Moy ML, Israel E, Weiss ST, Juniper EF, Dube L, Drazen JM; NHBLI Asthma Clinical Research Network. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med* 2001;163(4):924–9.

Nair SJ, Daigle KL, DeCuir P, Lapin CD, Schramm CM. The influence of pulmonary function testing on the management of asthma in children. *J Pediatr* 2005;147(6):797–801.

Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113(1):59–65.

Newman KB, Mason UG III, Schmaling KB. Clinical features of vocal cord dysfunction. *Am J Respir Crit Care Med* 1995;152(4 Pt 1):1382–6.

Ng TP. Validity of symptom and clinical measures of asthma severity for primary outpatient assessment of adult asthma. *Br J Gen Pract* 2000;50(450):7–12.

Noonan M, Chervinsky P, Busse WW, Weisberg SC, Pinnas J, de Boisblanc BP, Boltansky H, Pearlman D, Repsher L, Kellerman D. Fluticasone propionate reduces oral prednisone use while it improves asthma control and quality of life. *Am J Respir Crit Care Med* 1995;152(5 Pt 1):1467–73.

Paull K, Covar R, Jain N, Gelfand EW, Spahn JD. Do NHLBI lung function criteria apply to children? A cross-sectional evaluation of childhood asthma at National Jewish Medical and Research Center, 1999–2002. *Pediatr Pulmonol* 2005;39(4):311–7.

Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26(5):948–68.

Pijnenburg MW, Hofhuis W, Hop WC, de Jongste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax* 2005;60(3):215–8.

Pinnock H, Juniper EF, Sheikh A. Concordance between supervised and postal administration of the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) and Asthma Control Questionnaire (ACQ) was very high. *J Clin Epidemiol* 2005;58(8):809–14.

Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP, Sears MR. Risk factors for airway remodeling in asthma manifested by a low postbronchodilator FEV_1/vital capacity ratio: a longitudinal population study from childhood to adulthood. *Am J Respir Crit Care Med* 2002;165(11):1480–8.

Rundell KW, Spiering BA. Inspiratory stridor in elite athletes. *Chest* 2003;123(2):468–74.

Russell NJ, Crichton NJ, Emerson PA, Morgan AD. Quantitative assessment of the value of spirometry. *Thorax* 1986;41(5):360–3.

Schatz M, Dombrowski MP, Wise R, Thom EA, Landon M, Mabie W, Newman RB, Hauth JC, Lindheimer M, Caritis SN, et al. Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol* 2003;112(2):283–8.

Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB, Leong A, Johnson MS, Mendoza G, Cook EF. Relationship of validated psychometric tools to subsequent medical utilization for asthma. *J Allergy Clin Immunol* 2005a;115(3):564–70.

Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB, Leong A, Johnson MS, Mendoza G, Cook EF. Relationships among quality of life, severity, and control measures in asthma: an evaluation using factor analysis. *J Allergy Clin Immunol* 2005b;115(5):1049–55.

Shim CS, Williams MH Jr. Evaluation of the severity of asthma: patients versus physicians. *Am J Med* 1980;68(1):11–3.

Silverman EK, Kwiatkowski DJ, Sylvia JS, Lazarus R, Drazen JM, Lange C, Laird NM, Weiss ST. Family-based association analysis of beta$_2$-adrenergic receptor polymorphisms in the Childhood Asthma Management Program. *J Allergy Clin Immunol* 2003;112(5):870–6.

Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352(21):2163–73. Epub May 2005.

Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med* 2004;169(4):473–78. Epub November 2003.

Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1043–51.

Spahn JD, Cherniack R, Paull K, Gelfand EW. Is forced expiratory volume in one second the best measure of severity in childhood asthma? *Am J Respir Crit Care Med* 2004;169(7):784–6. Epub January 2004.

Stahl E, Postma DS, Juniper EF, Svensson K, Mear I, Lofdahl CG. Health-related quality of life in asthma studies. Can we combine data from different countries? *Pulm Pharmacol Ther* 2003;16(1):53–9.

Stempel DA, Fuhlbrigge AL. Defining the responder in asthma therapy. *J Allergy Clin Immunol* 2005;115(3):466–9.

Stout JW, Visness CM, Enright P, Lamm C, Shapiro G, Gan VN, Adams GK III, Mitchell HE. Classification of asthma severity in children: the contribution of pulmonary function testing. *Arch Pediatr Adolesc Med* 2006;160(8):844–50.

Strunk RC. Asthma deaths in childhood: identification of patients at risk and intervention. *J Allergy Clin Immunol* 1987;80(3 Pt 2):472–7.

Strunk RC, Mrazek DA, Fuhrmann GS, LaBrecque JF. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. A case-controlled study. *JAMA* 1985;254(9):1193–8.

Strunk RC, Sternberg AL, Bacharier LB, Szefler SJ. Nocturnal awakening caused by asthma in children with mild-to-moderate asthma in the childhood asthma management program. *J Allergy Clin Immunol* 2002;110(3):395–403.

Swanney MP, Beckert LE, Frampton CM, Wallace LA, Jensen RL, Crapo RO. Validity of the American Thoracic Society and other spirometric algorithms using FVC and forced expiratory volume at 6 s for predicting a reduced total lung capacity. *Chest* 2004;126(6):1861–6.

Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, Zeiger RS, Larsen G, Spahn JD, Bacharier LB, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115(2):233–42.

Tantisira KG, Hwang ES, Raby BA, Silverman ES, Lake SL, Richter BG, Peng SL, Drazen JM, Glimcher LH, Weiss ST. TBX21: a functional variant predicts improvement in asthma with the use of inhaled corticosteroids. *Proc Natl Acad Sci U S A* 2004;101(52):18099–104.

Taylor DR. Nitric oxide as a clinical guide for asthma management. *J Allergy Clin Immunol* 2006;117(2):259–62.

Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term beta agonist use: influence of beta(2) adrenoceptor polymorphism. *Thorax* 2000;55(9):762–7.

Ulrik CS, Backer V. Nonreversible airflow obstruction in life-long nonsmokers with moderate to severe asthma. *Eur Respir J* 1999;14(4):892–6.

Vollmer WM, Markson LE, O'Connor E, Frazier EA, Berger M, Buist AS. Association of asthma control with health care utilization: a prospective evaluation. *Am J Respir Crit Care Med* 2002;165(2):195–9.

Vollmer WM, Markson LE, O'Connor E, Sanocki LL, Fitterman L, Berger M, Buist AS. Association of asthma control with health care utilization and quality of life. *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1647–52.

Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34(3):220–33.

Wechsler ME, Lehman E, Lazarus SC, Lemanske RF Jr, Boushey HA, Deykin A, Fahy JV, Sorkness CA, Chinchilli VM, Craig TJ, et al.; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Beta-adrenergic receptor polymorphisms and response to salmeterol. *Am J Respir Crit Care Med* 2006;173(5):519–26. Epub December 2005.

Wijnhoven HA, Kriegsman DM, Hesselink AE, Penninx BW, de Haan M. Determinants of different dimensions of disease severity in asthma and COPD: pulmonary function and health-related quality of life. *Chest* 2001;119(4):1034–42.

Wolfenden LL, Diette GB, Krishnan JA, Skinner EA, Steinwachs DM, Wu AW. Lower physician estimate of underlying asthma severity leads to undertreatment. *Arch Intern Med* 2003;163(2):231–6.

Yoos HL, Kitzman H, McMullen A, Henderson C, Sidora K. Symptom monitoring in childhood asthma: a randomized clinical trial comparing peak expiratory flow rate with symptom monitoring. *Ann Allergy Asthma Immunol* 2002;88(3):283–91.

Zhang J, Yu C, Holgate ST, Reiss TF. Variability and lack of predictive ability of asthma end-points in clinical trials. *Eur Respir J* 2002;20(5):1102–9.

SECTION 3, COMPONENT 2: EDUCATION FOR A PARTNERSHIP IN ASTHMA CARE

KEY POINTS: EDUCATION FOR A PARTNERSHIP IN ASTHMA CARE

- Asthma self-management education is essential to provide patients with the skills necessary to control asthma and improve outcomes (Evidence A).
- Asthma self-management education should be integrated into all aspects of asthma care, and it requires repetition and reinforcement. It should:
  - Begin at the time of diagnosis and continue through followup care (Evidence B).
  - Involve all members of the health care team (Evidence B).
  - Introduce the key educational messages by the principal clinician, and negotiate agreements about the goals of treatment, specific medications, and the actions patients will take to reach the agreed-upon goals to control asthma (Evidence B).
  - Reinforce and expand key messages (e.g., the patient's level of asthma control, inhaler techniques, self-monitoring, and use of a written asthma action plan) by all members of the health care team (Evidence B).
  - Occur at all points of care where health professionals interact with patients who have asthma, including clinics, medical offices, EDs and hospitals, pharmacies, homes, and community sites (e.g., schools, community centers) (Evidence A or B, depending on point of care).
    - Strong evidence supports self-management education in the clinic setting (Evidence A).
    - Observational studies and limited clinical trials support consideration of focused, targeted patient education in the ED setting (e.g., teaching inhaler technique and providing an ED asthma discharge plan with instructions for discharge medications and for increasing medication or seeking medical care if asthma should worsen). Studies demonstrate the benefits of education in the hospital setting (Evidence B).
    - Studies of pharmacy-based education directed toward understanding medications and teaching inhaler and self-monitoring skills show the potential of using community pharmacies as a point of care for self-management education. Studies report difficulties in implementation, but they also demonstrate benefits in improving asthma self-management skills and asthma outcomes (Evidence B).
    - Studies demonstrate the benefits of programs provided in the patient's home for multifaceted allergen control, although further evaluation of cost-effectiveness and feasibility for widespread implementation will be helpful (Evidence A).

- ♦ Some, but not all, school-based programs have demonstrated success in reducing symptoms and urgent health care use and in improving school attendance and performance. Proven school-based programs should be considered for implementation because of their potential to reach large numbers of children who have asthma and provide an "asthma-friendly" learning environment for students who have asthma (Evidence B).

- ♦ Emerging evidence suggests the potential for using computer and Internet programs incorporated into asthma care (Evidence B).

■ Provide all patients with a written asthma action plan that includes two aspects: (1) daily management and (2) how to recognize and handle worsening asthma. Written action plans are particularly recommended for patients who have moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B).

■ Regular review, by an informed clinician, of the status of the patient's asthma control is an essential part of asthma self-management education (Evidence B). Teach and reinforce at *every* opportunity (EPR—2 1997):

— Basic facts about asthma

— What defines well-controlled asthma and the patient's current level of control

— Roles of medications

— Skills: e.g., inhaler technique, use of a valved holding chamber (VHC) or spacer, and self-monitoring

— When and how to handle signs and symptoms of worsening asthma

When and where to seek care

— Environmental exposure control measures

■ Develop an active partnership with the patient and family by (EPR—2 1997):

— Establishing open communications.

— Identifying and addressing patient and family concerns about asthma and asthma treatment.

— Identifying patient/parent/child treatment preferences regarding treatment and barriers to its implementation.

— Developing treatment goals together with patient and family.

— Encouraging active self-assessment and self-management of asthma.

- Encourage adherence by:
  - Choosing a treatment regimen that achieves outcomes and addresses preferences that are important to the patient/caregiver (Evidence B).
  - Reviewing the success of the treatment plan with the patient/caregiver at each visit and making adjustments as needed (Evidence B).
- Tailor the asthma self-management teaching approach to the needs of each patient. Maintain sensitivity to cultural beliefs and ethnocultural practices (Evidence C).
- Encourage development and evaluation of community-based interventions that provide opportunities to reach a wide population of patients and their families, particularly those patients at high risk of asthma morbidity and mortality (Evidence D).
- Asthma self-management education that is provided by trained health professionals should be considered for policies and reimbursements as an integral part of effective asthma care; the education improves patient outcomes (Evidence A) and can be cost-effective in improving patient outcomes (Evidence B).

KEY POINTS: PROVIDER EDUCATION

- Implement multidimensional, interactive clinician education in asthma care including, for example, case discussions involving active participation by the learners (Evidence B).
- Consider participation in programs to enhance skills in communicating with patients (Evidence B).
- Encourage development and use of clinical pathways for management of acute asthma (Evidence B).
- Develop, implement, and evaluate system-based interventions to support clinical decisionmaking and to support quality care for asthma (Evidence B).

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

Patient Education:

- Emphasis on the many potential points of care and sites available in which to provide asthma education, including review of new evidence regarding the efficacy of asthma self-management education outside the usual office setting.
- Greater emphasis on the two aspects of the written asthma action plan—(1) daily management, and (2) how to recognize and handle worsening asthma. Use of the terminology “written asthma action plan” encompasses both aspects. This change addresses confusion over the previous guidelines’ use of different terms. One term is now used for the written asthma action plan, although in some studies cited, investigators may have used a variation of this term.
- New sections on the impact of cultural and ethnic factors and health literacy that affect delivery of asthma self-management education.

Provider Education:

- New section with review of system-based interventions to improve the quality of asthma care, to support clinical decisionmaking, and to enhance clinical information systems
- Review of tested programs that use effective strategies to provide clinician education in asthma care, e.g., multidimensional approaches, interactive formats, and practice-based case studies

Introduction

See section 1, "Overall Methods Used To Develop This Report," for literature search strategy and tally of results for EPR—3: Full Report 2007 on this component, Education for a Partnership in Asthma Care. Six Evidence Tables were prepared: 3, Asthma Self-Management Education for Adults; 4, Asthma Self-Management Education for Children; 5, Asthma Self-Management Education in Community Settings; 6, Cost-Effectiveness of Asthma Self-Management Education; 7, Methods for Improving Clinical Behaviors: Implementing Guidelines; 8, Methods for Improving Systems Support.

Education for a Partnership in Asthma Care requires education for the patient or caregiver about asthma self-management as well as education for clinicians to enhance skills in teaching patients self-management and provide support to implement guidelines-recommended practices. In this component, recommendations are presented on asthma self-management education at multiple points of care, tools for asthma self-management, and provider education.

Evidence is now abundant that asthma self-management education is effective in improving outcomes of chronic asthma. Specific training in self-management skills is necessary to produce behavior that modifies the outcomes of chronic illnesses such as asthma. Expert care, with regular review by health professionals, is necessary but not sufficient to improve outcomes. Patients must actively participate in their own care, which means consciously using strategies and taking actions to minimize exposure to factors that make asthma harder to control and adjusting treatments to improve disease control.

The ultimate goal of both expert care and patient self-management is to reduce the impact of asthma on related morbidity, functional ability, and quality of life. The benefits of educating people who have asthma in the self-management skills of self-assessment, use of medications, and actions to prevent or control exacerbations, include reduction in urgent care visits and hospitalizations, reduction of asthma-related health care costs, and improvement in health status (Bartholomew et al. 2000; Cicutto et al. 2005; Cordina et al. 2001; Cowie et al. 1997; Gibson et al. 2000; Guevara et al. 2003; Krieger et al. 2005; Krishna et al. 2003; Madge et al. 1997; MeGhan [sic] et al. 2003; Morgan et al. 2004; Powell and Gibson 2003; Teach et al. 2006; Wesseldine et al. 1999). Other benefits of value from self-management education are reduction in symptoms, less limitation of activity, improvement in quality of life and perceived control of asthma, and improved medication adherence (Bonner et al. 2002; Christiansen et al. 1997; Clark et al. 2004; Evans et al. 1999a; Janson et al. 2003; McLean et al. 2003; Perneger et al. 2002; Saini et al. 2004; Thoonen et al. 2003). Cost-analysis studies have shown that asthma education can be delivered in a cost-effective manner and that morbidity is reduced as a result, especially in high-risk subjects (Gallefoss and Bakke 2001; Kattan et al. 1997; Powell and Gibson 2003; Schermer et al. 2002; Sullivan et al. 2002).

Although not all controlled trials of asthma self-management education have shown positive results, it is notable that controlled studies have demonstrated benefit from patient education programs delivered in a wide range of points of care, including clinics, EDs, hospitals, pharmacies, doctors' offices, schools, and community settings. These results have been achieved through face-to-face educational strategies and the use of new electronic technologies. Referenced studies are from multiple countries. Some outcomes may be dependent on the context of care and may not be completely generalizable.

Asthma Self-Management Education at Multiple Points of Care

The Expert Panel recommends that patients be educated at multiple points of care where health professionals and health educators may interact with patients who have asthma (Evidence A or B, depending on point of care). For people who have asthma, many points of care exist outside traditional clinic, office, or hospital settings. An emerging body of evidence suggests that educating people at these points of care creates opportunities to provide an essential link between the patient and the primary clinician, forming a network of support for the patient and clinician outside the clinician's office. In this way, a network of asthma education capability is built that ensures no person who has asthma is left without knowledge or skills.

Although it is beyond the scope of this document to address the issues of asthma education of persons who are not family members and are not health care professionals, those individuals who come into contact with persons with asthma on a regular basis (e.g., teachers, coaches, daycare workers, employers, etc.) should receive some basic education about asthma. Education of these individuals about asthma may help reduce asthma morbidity and mortality and may contribute to earlier diagnosis of this disease. Teachers and coaches should know how to recognize worsening asthma, administer quick-relief medications, and know how and when to call for emergency services.

CLINIC/OFFICE-BASED EDUCATION

Adults—Teach Asthma Self-Management Skills To Promote Asthma Control

The Expert Panel recommends that:

- **Clinicians provide to patients asthma self-management education that includes the following essential items: asthma information and training in asthma management skills (Evidence A), self-monitoring (either symptom– or peak flow–based) (Evidence A), written asthma action plan (Evidence B), and regular assessment by a consistent clinician (Evidence B).** (See Evidence Table 3: Asthma Self-Management Education for Adults.)

- **Clinicians involve patients in decisions about the type of self-monitoring of asthma control that they will do (Evidence B)**

- **Clinicians provide all patients with a written asthma action plan that includes instructions for (1) daily management, and (2) recognizing and handling worsening asthma, including self-adjustment of medications in response to acute symptoms or changes in PEF measures. Written asthma action plans are particularly recommended for patients who have moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B).**

- **Clinicians involve adult patients in the treatment decisionmaking within the context of a therapeutic partnership (Evidence B).**

- **Health professionals and others trained in asthma self-management education be used to implement and teach asthma self-management programs (Evidence B).**

- **Because poor attendance at multiple sessions may be a problem in some populations, consider introducing key messages and essential skills of self-management in the first session and adjusting subsequent sessions to the needs of the patients in the groups (Evidence D). Research comparing lengthy versus condensed or shorter sessions is encouraged.** (See Evidence Table 3, Asthma Self-Management for Adults.)

Written Asthma Action Plans, Clinician Review, and Self-Monitoring

In a large, scientific review of 36 RCTs involving 6,090 adults who had asthma, asthma self-management—accompanied by regular review of medications and asthma control by a medical practitioner—improved health outcomes significantly more than usual care (Gibson et al. 2003). All interventions included education, while 15 tested "optimal self-management" that included self-monitoring of symptoms and/or peak flow, regular review by a clinician, and a written asthma action plan. These intervention trials were conducted in primary care, specialty care, hospital inpatient, or community settings. The results of the statistical analysis overall, including meta-analysis where possible, showed self-management education significantly reduced hospitalizations, unscheduled acute visits, and missed work days, as well as improving quality of life. Subgroup analyses compared the intensity of the intervention (optimal self-management with regular review, self-monitoring, and a written asthma action plan versus self-monitoring and regular review versus self-monitoring only versus regular review only versus written asthma action plan with either self-monitoring or regular review). Optimal self-management, including self-monitoring of symptoms and/or peak flow and a written asthma action plan, significantly reduced hospitalizations and ED visits for asthma. There was insufficient power to compare the subgroups with less intensive interventions. There was little effect on lung function: FEV_1 did not change. A statistically significant small mean increase (14.5 L/min, $p < 0.05$) in PEF occurred, however.

Self-management education that included a written asthma action plan appeared more effective than other forms of self-management education. The intensity (number of sessions) of teaching and the number of different components taught had little impact.

Regular review of progress by a concerned clinician is the basis for the patient–clinician partnership necessary to achieve asthma control. In another scientific review, the equivalence and efficacy of different options for asthma self-management were analyzed in 15 RCTs (Powell and Gibson 2003). In six studies, regular clinical review by physicians who adjusted ICS medications was compared to self-management education allowing self-adjustment of medications by using a written asthma action plan. These two methods for achieving asthma control were found to be equivalent. No significant differences in hospitalization, ED visits, unscheduled doctor's visits, or frequency of nocturnal asthma symptoms were found between patients who self-adjusted their medication and those whose medications were adjusted by their physicians. Two of three studies found no difference between clinician review and self-management in the days lost from work or school, while the third study reported a significant effect of peak-flow-based self-management on work or school absenteeism. Lung

function, as measured by FEV_1, was not significantly improved with peak-flow-based self-adjustment of medications as compared to physician adjustment of medications.

The evidence from this analysis indicates that these two methods of adjusting medications for asthma control (change by physician during office visit or patient self-management according to a written asthma action plan) are equivalent, and the choice depends on the comfort and agreement between the clinician and the patient. Patient self-monitoring is an important tool for patients to assess the level of their asthma control and to adjust treatment according to their action plan.

When self-management is the chosen method for maintaining asthma control, peak-flow-based self-management is equivalent to symptom-based self-management as long as either method also includes a written asthma action plan with instructions on how to recognize and handle worsening asthma, including self-adjustment of medications. In three studies, both methods were found to have an equal impact on ED visits, and one study found peak flow monitoring was more effective in reducing ED visits (Powell and Gibson 2003). As noted in "Component 1: Measures of Asthma Assessment," the important point is for patients to have a plan for monitoring their asthma, regardless of whether it is peak flow or symptom based. Therefore, the Expert Panel recommends that clinicians involve patients in decisions about the type of self-monitoring they will do. All patients may benefit from a written asthma action plan that includes instructions for (1) daily management, and (2) recognizing and handling worsening asthma, including self-adjustment of medications in response to acute symptoms or changes in PEF measures. Written action plans are particularly recommended for patients who have moderate or severe asthma, a history of severe exacerbations, or poorly controlled asthma. (See "Component 1: Measures of Asthma Assessment" for further discussion of tools for assessing asthma control.)

Other studies offer evidence of varying effectiveness of patient education. Those studies conducted as RCTs with positive findings confirm the results of the large scientific reviews (Janson et al. 2003; Magar et al. 2005; Marabini et al. 2002; Perneger et al. 2002; Thoonen et al. 2003). In these trials, one conducted across multiple practices in primary care settings (Thoonen et al. 2003), providing self-management education including an asthma action plan for exacerbations resulted in reduced symptoms, fewer days of restricted activity, and improvement in quality of life. Self-management education also resulted in improved self-confidence to manage asthma (Perneger et al. 2002) and improved adherence to ICS therapy (Janson et al. 2003; Magar et al. 2005) (Evidence B).

Education that provides information only, without skills training, improves knowledge but does not reduce hospitalizations, ED visits, unscheduled doctor's visits, or lost work days; nor does it improve lung function and medication use (Gibson et al. 2002). In this review, patients' reports of symptoms improved in only 2 of the 12 RCTs of information-only programs.

Patient–Provider Partnership

The value of establishing the patient–clinician partnership when teaching asthma self-management was shown in another RCT of asthma education (Marabini et al. 2002) in which investigators purposely formed partnerships with patients in the intervention group. The control group received education on medication use, role of environmental triggers, and metered-dose inhaler (MDI) technique but no partnership. The educational intervention delivered in the context of the therapeutic relationship produced improved symptom control, quality of life, and lung function measured as FEV_1 in patients in the group who had moderate or

severe asthma only. This finding suggests asthma self-management education, reinforced in the context of a therapeutic partnership between clinician and patient, may be especially valuable in patients who have moderate or severe asthma.

Another recent RCT (Wilson et al. 2005, 2006) used the context of the patient-clinician partnership to test the impact of shared decisionmaking about asthma treatment, compared to guideline-based clinician decisionmaking and usual care, in adults who had poorly controlled asthma. Clinician care managers (nurse practitioners, pharmacists, respiratory therapists) met with the patients to adjust therapy in two visits, 1 month apart, followed by three brief telephone calls (at 3, 6, and 9 months) to assess patients' progress in both intervention groups. The unique features of shared decisionmaking included identifying patients' goals and preferences regarding treatment and negotiating a treatment regimen to accommodate best each patient's goals and preferences. Establishing rapport, providing educational information, teaching inhaler technique, writing the prescription, and preparing a written asthma action plan for the patient occurred in both the guidelines and shared-decision groups. The shared-decision group had significantly greater adherence to long-term control medication compared to the guidelines group, and both interventions produced significantly better adherence to asthma control medications than usual care over 12 months of followup.

The results of these two important RCTs suggest the value of shared decisionmaking about asthma treatment in adults. Therefore, the Expert Panel concludes that clinicians should involve adult patients in the treatment decisionmaking within the context of a therapeutic partnership.

Health Professionals Who Teach Self-Management

A variety of health professionals deliver health education effectively. Recent studies have focused on nurse-educators. Often, specially trained nurses provide asthma education. Three RCTs and three observational studies used advanced practice nurses trained in asthma to deliver self-management education to adults in outpatient settings. In one RCT, a hospital-based nurse specialist delivered self-management education during three sessions (Levy et al. 2000). Compared to patients receiving usual care, the educated patients significantly increased use of ICS; decreased use of SABA for quick relief of symptoms; achieved higher mean and less variable PEF; and had significantly lower symptom scores, doctor visits, and urgent care visits for asthma after 6 months. The reduction in asthma morbidity in this study may have been related to the strong emphasis, during the educational sessions, placed on improving asthma self-management skills during exacerbations. In another RCT, self-management education with peak flow monitoring and a written asthma action plan, individualized to the patient's severity, was delivered in one session that was then reinforced in two subsequent visits (Janson et al. 2003). Compared to the control condition (monitoring only), self-management education significantly improved adherence to ICS medications, quality of life, and perceived control of asthma. In an attempt to reduce high hospitalization rates and health care utilization, another RCT (Urek et al. 2005) examined the effectiveness of three educational interventions in adults: "asthma school," an educational booklet, and individual verbal instruction. Asthma school, which included three 4-hour sessions of group education, produced the most significant improvement in quality of life; individual verbal instruction produced the best overall response in terms of both asthma control and quality of life.

Hopman and colleagues (2004) used nurse specialists to educate children and adults who had asthma through a standardized 2-hour asthma education program given across seven clinical centers in a large, multisite observational study. The program resulted in significant

improvements (decreases) in hospital utilization and missed activity days over 6 months. Two other observational studies of adults who had asthma, in which patients were taught and cared for by specially trained asthma nurses (Lindberg et al. 2002), showed significantly reduced symptoms and days of activity limitation as well as significantly decreased markers of airway inflammation (Janson et al. 2001). In an attempt to reduce sick days lost from work, a 4-week inpatient asthma rehabilitation program was tested in an observational study that included asthma education, pharmacological optimization, physical training, and coping skill training. The program resulted in significantly reduced sick leave over 3 years (Nathell 2005). Rehabilitation programs that require patients to live in the treatment setting are expensive and rare in the United States, but such programs may be useful for those who have severe asthma and are significantly limited by their asthma.

Respiratory therapists also provide asthma education in hospital, ED, and clinic settings and may direct clinical pathways and algorithms in hospital settings. There are no published RCTs of asthma education programs delivered by respiratory therapists. An observational trial of 60 pediatric patients who attended a special clinic focusing on inhaler technique demonstrated that MDI technique improved significantly after MDI demonstration, teaching, and reinforcement (Minai et al. 2004). Respiratory therapists also participate actively in clinical protocols or pathways that are implemented in acute care settings for management of acute exacerbations in hospitalized patients. Studies of the efficacy and value of clinical pathways is reviewed in the "Provider Education Section: Methods of Improving System Supports—Clinical Pathways."

The Expert Panel encourages using health professionals and others trained in asthma self-management education to implement and teach asthma self-management programs.

Education With Multiple Sessions

Negative studies that found little or no benefit of asthma self-management education frequently contained significant design flaws or methodological errors. Several were underpowered to detect significant differences between groups (Couturaud et al. 2002; Cowie et al. 2002; Neri et al. 2001) due to small sample size and significant attrition. (See Evidence Table 3, Asthma Self-Management for Adults.) Cowie and colleagues (2002) modified the education according to age level but found no incremental benefit from this adjustment. Many of these patients were recruited from EDs immediately after treatment for an acute exacerbation, when they were presumably more open to education, but significant attrition from or no attendance at the educational sessions scheduled outside of the medical care context occurred (Bolton et al. 1991; Ford et al. 1997). Taken together, these studies demonstrate the problems that are created when education programs are not integrated into the patient's regular medical care as well as the low participation of intervention patients in educational programs designed with multiple sessions over time. Because poor attendance at multiple sessions may be a problem in some populations, the Expert Panel's opinion is that the key messages and essential skills of self-management should be introduced in the first session and that subsequent sessions should be adjusted to the needs of the patients in the groups.

Children—Teach Asthma Self-Management Skills To Promote Asthma Control

The Expert Panel recommends that asthma self-management education be incorporated into routine care for children who have asthma (Evidence A). (See Evidence Table 4, Asthma Self-Management Education for Children.)

A meta-analysis of 32 controlled trials of educational interventions for self-management in children and adolescents, involving 3,706 patients, showed significant effects of education in improving the child's self-efficacy and lung function as well as in reducing days with restricted activity, school absences, and ED visits (Guevara et al. 2003). No effects were seen on hospitalizations (Guevara et al. 2003; Wolf et al. 2003). The authors conducted subgroup analyses to determine the effect of peak flow versus symptom-based monitoring strategies, individual versus group format, single versus multiple sessions, and moderate or severe asthma versus mild or moderate asthma, but the small number of studies in each subgroup did not provide sufficient statistical power to detect significant differences.

Several other controlled studies have also shown positive effects for self-management education in children. A multicenter RCT of education delivered by asthma counselors through group sessions, individual meetings, and telephone followup showed that education significantly reduced days with asthma symptoms (Evans et al. 1999a). An RCT of education that combined group sessions, individual meetings, and having the family accompany the patient during doctor visits both decreased frequency of symptoms and activity restriction and increased the families' ability and confidence to self-manage asthma (Bonner et al. 2002). A small RCT (N = 33) with minority families found that group education that emphasized collaborative learning and use of cultural resources increased asthma knowledge and reduced ED visits significantly compared to more didactic group education and to a no-intervention control (La Roche et al. 2006). A trial of training to improve children's technique in using a breath-activated inhalation device showed that individual training provided by nurses in a single visit improved inhalation technique and that instructions to practice at home for 2 weeks resulted in further improvements (Agertoft and Pedersen 1998). These studies provide strong evidence for the benefit of providing structured self-management education to children who have asthma as well as their families in conjunction with ambulatory care for asthma.

EMERGENCY DEPARTMENT/HOSPITAL-BASED EDUCATION

Adults

The Expert Panel recommends that:

- **At the time of discharge from the ED, clinicians offer brief and focused asthma education (Evidence D) and provide patients with an ED asthma discharge plan with instructions to the patients and family for how to use it (Evidence B).**

- **Before patients are discharged home, assess inhaler techniques for all prescribed medications and reinforce correct technique (Evidence B).**

- **At the time of discharge from the ED, patients be referred for followup asthma care appointment (either PCP or asthma specialist) within 1–4 weeks (Evidence B). If appropriate, consider referral to an asthma self-management education program (Evidence B).**

- **Before patients are discharged from a hospitalization for asthma exacerbations, give them asthma self-management education (Evidence B).**

Emergency Department Asthma Education

Visits to the ED for asthma exacerbation have been characterized as a moment of opportunity for providing asthma education, inhaler technique training, and referral for followup with the PCP; yet there are very few RCTs of asthma education in the ED for patients who have exacerbations. Previous asthma guidelines (EPR 1991; EPR—2 1997) have recommended at least some asthma education at the time of discharge from the ED for an exacerbation. One observational study conducted in the EDs of a province of Canada found that only 78 percent of patients received even brief education, and the focus was usually on medicines (46 percent) or inhaler technique (73 percent). Only 38 percent were counseled on triggers of exacerbations, and only 32 percent were referred to an asthma education program (Gervais et al. 2005).

Patients who present to the ED with acute asthma are a source for identifying self-management problems. Observational studies (Griswold et al. 2005; Radeos et al. 2001) show that many of these patients have poor knowledge of self-management and have a high frequency of ED visits (Boulet et al. 1996; Griswold et al. 2005). Moreover, many adults seem to delay seeking care for acute asthma for a variety of reasons, including fear of being treated with systemic steroids (Janson and Becker 1998). These observations suggest a role for asthma education, yet there is little evidence from RCTs of the benefit of targeted education in the ED setting. A survey of 77 asthma researchers based in EDs showed that, despite agreeing that patient education was very important, few EDs have or use asthma education programs (Emond et al. 2000).

Targeting high-risk patients for asthma education at the ED visit has been explored in two RCTs (Bolton et al. 1991; Cote et al. 2001) and in two observational studies (Kelso et al. 1995, 1996). In one RCT, limited education in the ED in inhaler technique and use of a written asthma action plan was compared to a comprehensive, structured educational program and usual care (Cote et al. 2001). ED revisits were not different among the groups in the first 6 months after the intervention, but revisits declined significantly more in the structured education group by 12 months; however, reinforcement of self-management education was provided at the 6-month point only to the structured education group. In a second RCT, Bolton and coworkers (1991) provided three asthma education sessions to patients after a visit to the ED. Despite significant attrition from attendance at sessions, followup was completed with 76 percent of the study sample, and, adjusting for baseline differences, the intervention group had fewer ED visits than controls at 12-month followup ($p = .06$). In a race-specific reanalysis of the Bolton and colleagues (1991) study data, Ford and coworkers (1997) found that African American and Caucasian patients experienced similar benefits from the program.

Teaching Inhaler Technique in the Emergency Department

Most other RCTs of education for adults in the ED setting focus on teaching inhaler technique for delivery of SABA. Numata and coworkers (2002) conducted an RCT in the ED to compare teaching MDI technique to 61 adults who had asthma and nebulizer delivery of bronchodilator to 32 adults who had COPD. Median teaching time required to teach and administer MDI-delivered bronchodilator medication was 6.5 minutes. The authors concluded that teaching use of MDI with spacer delivery of bronchodilator is feasible in the ED for treatment of acute asthma exacerbation. This study suggests that patients can learn about and use MDIs in the acute care setting and that the ED provides an opportunity to teach correct inhaler technique.

Despite being provided with MDIs and instructions for using them, a significant proportion of children continue to use nebulizers at home after discharge from the ED (Cheng et al. 2002). Use of MDIs by children may be complicated, however, by numerous errors in technique,

potentially rendering the devices ineffective. Scarfone and colleagues (2002) evaluated children's skills in using an MDI and a peak flow meter in the ED and found a significant proportion were using these devices incorrectly with a large number of errors. Dry-powder inhaler (DPI) use appears to be associated with a rate of poor inhalation technique similar to that of the use of MDIs (Melani et al. 2004). Inhaler technique may be improved with tailored educational interventions aimed at specific problems (Hesselink et al. 2004).

The Expert Panel concludes that it is important to assess inhaler techniques for all prescribed medications and reinforce correct technique before patients are discharged home.

Referral for Followup Care

ED clinicians encourage patients seen for acute exacerbation to follow up with their PCPs, and ED clinicians often encourage participation in an asthma education program. Robichaud et al. (2004) found that ED clinicians can motivate some patients to attend an asthma educational program following discharge from the ED by giving a brief educational message and facilitating followup attendance at the educational program. However, others have found that ED discharge instructions that include recommending attendance at an educational session and keeping an appointment with a PCP are not adhered to in any consistent way, and even when appointments are kept, there is no impact on long-term outcomes (Baren et al. 2001, 2006). In one RCT, however, the short-term outcome of contact with the PCP did improve (Baren et al. 2001). These studies refer specifically to referral to the PCP.

The findings may not be true for facilitated referrals to an asthma specialist. Both an observational study (Schatz et al. 2005) and an interventional study (Zeiger et al. 1991) suggest that better outcomes may result for patients referred from the ED to asthma specialists.

Although evidence from RCTs is limited regarding the optimal referral site (e.g., PCP or asthma specialist), the Expert Panel concludes that patients should be referred for a followup asthma care appointment within 1–4 weeks of discharge from the ED. The followup appointment should include patient education; if appropriate, consider referral to an asthma self-management education program. Because there are so few studies of self-management education in the ED setting, and because the several interventions to improve patient followup have not demonstrated benefit, more research is needed to understand how to make education effective at this point of care.

Hospital-Based Asthma Education

Patients who are admitted to the hospital for acute severe asthma exacerbations represent another opportunity for teaching asthma self-management. Castro and colleagues (2003) conducted an RCT to determine if an intensive asthma intervention program led by specially trained nurses could prevent readmissions of adult patients who were noted to be high users of health care. The multiple-component intervention included asthma education, a written asthma action plan, extra social support, and telephone followup calls after discharge. The combination of all of these produced a significant decrease in readmissions for asthma and in total hospitalizations compared to patients in usual care. The effect of the individual components of the intervention was not determined. Similarly, another hospital-based randomized trial of an inpatient education program (George et al. 1999) targeted to young, economically disadvantaged adults who were admitted with acute asthma showed that inpatient asthma education, assistance with discharge planning, postdischarge followup telephone calls, and scheduled followup clinic visits had an impact after discharge. Patients who received the

intervention had a higher followup rate, fewer subsequent ED visits, and fewer repeat hospitalizations.

In another RCT of asthma self-management education during hospital admission, 80 patients admitted with acute asthma received two 30-minute self-management education sessions and a written asthma action plan (Morice and Wrench 2001). The education group improved knowledge of asthma management compared to controls, but no significant differences between groups occurred in number of readmissions. Using a brief self-management intervention during hospital admission was found to reduce patients' daytime wheezing, nighttime awakenings, activity limitations, and hospital readmission (Osman et al. 2002). The session was 40–60 minutes of self-management education and included a written asthma action plan. All of these outcomes were improved compared to control patients but were more significant in patients for whom it was a first-time admission. The results of these trials suggest that asthma education at the time of hospitalization can have a significant effect in reducing repeat hospitalizations for asthma exacerbations.

Children

The Expert Panel recommends that asthma education programs that have been shown to be effective be delivered to children during or following discharge from the ED or the hospital (Evidence B). More research is needed to understand how to make education maximally effective at this point of care.

The Expert Panel recommends that:

- **At the time of discharge from the ED, clinicians offer brief and focused asthma education (Evidence D) and provide patients with an ED asthma discharge plan with instructions to the patients and family for how to use it (Evidence B).**
- **Before patients are discharged home, assess inhaler techniques for all prescribed medications and reinforce correct technique (Evidence B).**
- **At the time of discharge from the ED, patients be referred for followup asthma care appointment (either PCP or asthma specialist) within 1–4 weeks (Evidence B). If appropriate, consider referral to an asthma self-management education program (Evidence B).**
- **Before patients are discharged from a hospitalization for asthma exacerbations, give them asthma self-management education (Evidence B).**

A meta-analysis of eight controlled studies of educational interventions for children or adolescents following ED visits or hospital admissions found no significant benefit for health status or readmission and concluded that more research is needed (Haby et al. 2001). The authors of the meta-analysis noted trends toward clinically relevant, yet not statistically significant, decreases in ED visits, unscheduled visits, and hospitalizations. Haby and colleagues recommended more studies with larger sample sizes to assess adequately the effectiveness of educational interventions after use of emergency care. Two successful studies included in this meta-analysis showed very different approaches. An RCT of a nurse-led discharge program (consisting of a 20-minute patient education program and a written asthma action plan) significantly reduced unscheduled doctor visits, ED visits, and readmissions to hospital over 12 months (Wesseldine et al. 1999). In another RCT, a nurse-led training program

administered during admission with one outpatient followup visit to the nurse resulted in reduced hospital admissions in the following 14 months (Madge et al. 1997).

Five recent RCTs show mixed results for the effectiveness of education postdischarge from the ED. Walders and colleagues (2006) provided all participants with medical care by a specialist, including written asthma action plans, peak flow meters, and spacer devices. Participants who also received an intervention that included an asthma education session, a session on problem-solving based on an individualized asthma risk profile, and access to an asthma advice telephone service had significantly fewer ED visits at 12-month followup than the controls who received no education (Walders et al. 2006). Teach and coworkers (2006) scheduled a followup visit, within 2 weeks, to a specialized asthma clinic located in the ED, where followup care and education were provided. The intervention group received a written asthma action plan and referrals to ongoing primary care, plus education about asthma self-monitoring and management as well as environmental modification and trigger control. Compared with controls, the intervention group had significantly greater ICS use, fewer ED visits, and improved quality of life in the 6-month followup period (Teach et al. 2006). Sockrider and colleagues (2006) provided children and their families with tailored education, including a customized asthma action plan and an educational summary, before discharge from the ED for an acute episode of asthma. At 2-week followup, intervention families had significantly greater confidence than controls in their ability to manage asthma. At 9-month followup, among participants who had intermittent asthma, children whose families received education had significantly fewer ED visits than controls, but there was no difference between groups for children who had persistent asthma (Sockrider et al. 2006). Two other controlled trials of brief education, by telephone postdischarge from the ED (Khan et al. 2004) and by a combination of computer instruction and interaction with a nurse practitioner (Sundberg et al. 2005), did not improve patients' health status.

Two recent controlled trials to see if telephone reminders after discharge from the ED increased followup appointments with primary care showed positive findings at short-term but not long-term followup. In one study, appointment rates, quality of life, and asthma symptoms improved relative to controls at 6 months, but no difference was found at 12 months (Sin et al. 2004). In the second study, the number of appointments was higher and symptoms were lower at 2 weeks, but these differences had disappeared at 12 months (Smith et al. 2004).

In an RCT (Zorc et al. 2003), followup primary care appointments for children seen in the ED for acute asthma were scheduled by ED staff, but patients had no higher rate of attendance than when visits were simply requested. Furthermore, there was no change in return visits to the ED, missed school, or use of long-term control medications.

Based on these findings, the Expert Panel concludes that asthma education programs that have been shown to be effective should be delivered to children during or following discharge from the ED or the hospital. More research is needed to understand how to make education maximally effective at this point of care.

EDUCATIONAL INTERVENTIONS BY PHARMACISTS

The Expert Panel recommends that use of interventions provided by pharmacists be considered; such programs are feasible, and they merit further studies of effectiveness (Evidence B).

Controlled trials of asthma education delivered by pharmacists have shown mixed results (Barbanel et al. 2003; Basheti et al. 2005; Bynum et al. 2001; Cordina et al. 2001; McLean et al. 2003; Saini et al. 2004; Stergachis et al. 2002). Four of these RCTs recruited community pharmacies, provided training for their pharmacists, and evaluated the impact of pharmacist teaching on patient outcomes (Cordina et al. 2001; McLean et al. 2003; Saini et al. 2004; Stergachis et al. 2002). All of these studies involved repeated contacts with patients. One study showed reduced hospitalizations and improved inhaler technique (Cordina et al. 2001). A second study found reduced asthma severity, better lung function, less use of albuterol, and better perceived control of asthma (Saini et al. 2004). The third study showed reductions in daytime and nighttime symptoms, use of SABA, and doctor visits, as well as improvements in PEF and quality of life (McLean et al. 2003). The fourth study found no differences between intervention patients and controls on any measure (Stergachis et al. 2002). These studies noted difficulties in providing asthma education in a community pharmacy, but they demonstrated that community pharmacies may serve as effective venues for scheduled followup visits for specialized asthma care. A small study of patients randomized within a single pharmacy found significant reduction in symptoms for the intervention group (Barbanel et al. 2003). Another small study found that counseling by a pharmacist improved inhaler technique (Basheti et al. 2005). Finally, another study evaluated interactive telepharmacy video counseling, using compressed video, connecting adolescents in schools with pharmacists working from a remote site; this study found improvements in inhaler technique (Bynum et al. 2001).

The Expert Panel concludes that, despite the difficulties observed, use of interventions provided by pharmacists is feasible, may help improve self-management skills and asthma outcomes, and merits more clinical studies of pharmacists' providing education interventions.

EDUCATIONAL INTERVENTIONS IN SCHOOL SETTINGS

The Expert Panel recommends that implementation of school-based asthma education programs proven to be effective be considered to provide to as many children who have asthma as possible the opportunity to learn asthma self-management skills and to help provide an "asthma-friendly" learning environment for students who have asthma (Evidence B).

Several studies suggest that comprehensive school-based asthma education programs can improve health and quality of life in students who have persistent asthma. Five controlled trials of education in schools for children who have asthma have shown reduced symptoms for children receiving asthma education (Butz et al. 2005; Christiansen et al. 1997; Cicutto et al. 2005; Clark et al. 2004; MeGhan [sic] et al. 2003). Three of these studies have also shown reductions in the use of acute health care services (Butz et al. 2005; Cicutto et al. 2005; MeGhan [sic] et al. 2003). One program provided education for elementary school children, plus educational components for principals, custodians, and other school staff, resulting in reduced asthma morbidity, improved asthma management, and decreased school absences (Clark et al. 2004). A secondary analysis of this trial found that the program also had effects on students who had moderate or severe symptoms but no diagnosis; effects included reductions in daytime and nighttime symptoms and in days with restricted activity (Joseph et al. 2005). Two studies have shown that parents who did not attend the educational sessions had improved asthma management skills after completing learning assignments with children at home (Clark et al. 2004; Evans et al. 2001).

An innovative trial of peer education in the schools, in which older students were trained to deliver education to younger students, improved quality of life in participating students (Shah et al. 2001). Teacher-led asthma education interventions have been successful in improving asthma outcomes in secondary schools and in improving school policies. In a very large trial, teachers were trained to deliver asthma education to students who had and did not have asthma. This study revealed positive changes in students' knowledge of asthma, their perception that asthma could be controlled, and their tolerance of asthma in others (Henry et al. 2004). Five-year followup showed that this program was still being taught by 71 percent of the teachers who had been trained.

Three other RCTs of school-based education showed no significant effect on student health (Patterson et al. 2005; Velsor-Friedrich et al. 2005) or school staff efforts to communicate with community physicians about students' symptoms (Halterman et al. 2005). Another RCT tested the effectiveness of an asthma educational intervention in improving asthma knowledge, self-efficacy, and quality of life in rural families (Butz et al. 2005). Children 6–12 years of age who had persistent asthma were recruited from rural elementary schools and randomized into the control (standard asthma education) group or into an interactive educational intervention consisting of three educational workshops, an asthma coloring book, and parental educational workshops. Parent/caregiver and child asthma knowledge, self-efficacy, and quality of life were assessed at baseline and at 10 months after enrollment. Children's self-efficacy, children's asthma knowledge, and parental asthma knowledge increased significantly in the intervention group, but no significant increase in parental self-efficacy or children's or parental quality of life was found at followup.

Asthma education video gaming media were shown to be useful in improving asthma self-management knowledge and asthma quality of life for high-risk, low-income, inner-city children who have asthma (Shames et al. 2004).

Taken together, these studies suggest that asthma education delivered in schools can improve health and quality of life in students who have asthma.

COMMUNITY-BASED INTERVENTIONS

Asthma Education

It is the opinion of the Expert Panel that, although studies of community-based asthma education do not demonstrate benefits in health status, they do show that asthma education programs delivered by trained community residents are feasible, can result in behavior change and improved quality of life, and deserve further research (Evidence C). (See Evidence Table 5, Asthma Self-Management Education in Community Settings.)

Community-based asthma interventions (those delivered in various community settings) can positively affect large numbers of persons who have asthma, especially in poor, inner-city communities. A controlled trial of asthma outreach and education, delivered by trained community residents in a community center, found no difference in acute care visits between intervention and comparison communities, but the study found reduced numbers of acute care visits for those who had high levels of participation in the program (Fisher et al. 2004). Surprisingly, socially isolated residents were more likely to participate in program activities than those who were socially active. An observational study of education for caregivers of children who had asthma, delivered by trained, community peer educators, found significant increases in asthma knowledge, management behavior, and quality of life; these increases were sustained

at 3, 6, and 12 months (Bryant-Stephens and Li 2004). An asthma education program that included the interventions of group and individual education sessions taught by a nurse and a physiotherapist resulted in significantly fewer primary care visits and less absenteeism from work (Gallefoss and Bakke 2001). In an observational study, hospital inpatient asthma education combined with outpatient followup asthma education in the community for children and families improved asthma knowledge (Ochsner et al. 2002). The inclusion of a child-life specialist in community-based and family-support interventions appears to be beneficial in promoting psychological adjustment of children who have chronic health conditions, such as asthma, especially if the child has low self-esteem (Chernoff et al. 2002).

HOME-BASED INTERVENTIONS

Home-Based Asthma Education for Caregivers

The Expert Panel recommends that asthma education delivered in the homes of caregivers of young children be considered and that this area needs more research (Evidence C).

A controlled trial of a home-based asthma education intervention for caregivers of young children showed that the intervention significantly reduced the amount of reported bother from asthma symptoms and increased symptom-free days and caregiver quality of life for children 1–3 years of age (Brown et al. 2002). The age of the children who had asthma appeared to moderate the intervention effect of home-based asthma education for caregivers in relation to both asthma morbidity and caregivers' quality of life. A single-group study of home-based asthma education intervention for Latino caregivers of children who have asthma (average age, 7 years) showed reductions in bedroom allergens and increases in allergen-control devices (e.g., mattress covers) at followup (Jones et al. 2001). These studies suggest that the home may be a useful point of care for education interventions.

Home-Based Allergen-Control Interventions

The Expert Panel recommends that multifaceted allergen education and control interventions delivered in the home setting and that have been shown to be effective in reducing exposures to cockroach, rodent, and dust-mite allergen and associated asthma morbidity be considered for asthma patients sensitive to those allergens (Evidence A). Further research to evaluate the cost-effectiveness and the feasibility of widespread implementation of those programs will be helpful.

Avoiding allergens is often difficult (Leickly et al. 1998). The home may be a useful point of care for educational interventions to reduce household allergens and to increase the use of allergen-control devices in the home. Eight controlled trials have evaluated allergen-control interventions that combined education for families about implementing allergen-control strategies with provision of tools and supplies needed to carry them out (Carter et al. 2001; Custovic et al. 2000; Eggleston et al. 2005; Klinnert et al. 2005; Krieger et al. 2005; McConnell et al. 2005; Morgan et al. 2004; Woodcock et al. 2003). Some of these studies added professional allergen-reduction services (Carter et al. 2001; Custovic et al. 2000; Eggleston et al. 2005; Morgan et al. 2004), and several provided broader education about asthma management as well (Klinnert et al. 2005; Krieger et al. 2005). Four of the studies delivered allergen-control education through multiple home visits (Eggleston et al. 2005; Klinnert et al. 2005; Krieger et al. 2005; Morgan et al. 2004).

In general, the aim of these trials was to test multifaceted strategies to reduce the burden of allergens in the homes of asthma patients and to improve health outcomes rather than the efficacy of specific allergen-control techniques by themselves. An innovative trial of home intervention to control allergens included both a placebo control and a “no-visit” control to assess the relative effect of the intervention versus home visits to prompt allergen-control measures by families of children who have asthma (Carter et al. 2001). The intervention and placebo control (permeable mattress covers and instructions to wash bedding in cold water) groups did not differ significantly, but both groups had reduced acute care visits when compared to the no-visit control group, suggesting that the home visit itself resulted in improved asthma control. This study did not provide information about how families in the no-visit control group reduced allergens or improved asthma control.

Another trial evaluated allergen-control measures in the homes of infants who had atopic parents and no pets; measures included using impermeable bedding covers, replacing carpet with vinyl flooring in the infant’s room, and asking participants to wash bed linens in hot water. Over the 1-year followup, the intervention group had significantly less wheeze with shortness of breath, less wheeze after vigorous activity, and less medicine prescribed by PCPs for control of wheezy attacks (Custovic et al. 2000). This study suggests that prenatal intervention in high-risk infants can reduce the risk of asthma symptoms during the first year of life.

One large trial relied primarily on repeated home visits to educate the family in allergen-control techniques and to provide them with HEPA-filter vacuum cleaners and mattress covers. The intervention was tailored to the child’s allergen-sensitivity profile, and professional pest control was applied for children allergic to cockroach (Morgan et al. 2004). Over the 2-year followup period, significant reductions occurred in cat, dust-mite, and cockroach allergens in the child’s bedroom, and these were associated with reductions in daytime and nighttime symptoms, fewer school absences in both years, and reductions in ED visits in the first followup year. This study suggests that education about relevant environmental control in the home, coupled with the provision of tools for allergen control, can enable families to reduce allergen levels and asthma morbidity effectively.

A clinical RCT of home environmental intervention with inner-city children who had mild persistent asthma demonstrated that tailored, multifaceted environmental treatment and education can reduce airborne particulate matter in inner-city homes, resulting in a modest effect on asthma morbidity, with decreased asthma symptoms, but no improvement in lung function (Eggleston et al. 2005). The intervention group received home-based education, cockroach and rodent extermination, allergen-proof mattress and pillow encasings, and HEPA-filter air cleaners. Outcomes were measured by home evaluations at 6 and 12 months, clinic evaluation at 12 months, and multiple telephone interviews.

Three RCTs, assessing the effect of home-based education on allergens and control interventions, used community health workers. One RCT showed that a home-based allergen-control and education intervention (delivered by trained community health workers to families of children who had asthma), focusing on training residents to apply cockroach-control measures themselves during a five-visit period, could successfully reduce the number of cockroaches in the home and cockroach-allergen levels in the children’s bedding (McConnell et al. 2005). No measures of health outcomes were reported. A second trial provided allergen-control education, as well as resources and support for behavior change, by trained community heath workers in seven visits (Krieger et al. 2005). This study found reductions in the use of emergency health care services by children who had asthma and improvements in the quality of life of their caregivers. A third trial of allergen control and both allergen-specific

and general asthma education with children relied on 15 home visits over a period of 12 months by nurses trained in community outreach (Klinnert et al. 2005). Compared to controls, this intervention significantly reduced cockroach-allergen and children's cotinine levels but had no effect on health outcomes.

In adults, a trial of dust-mite-allergen control that relied on allergen-impermeable bed covers alone, without instructions to wash linens in hot water or any other education, found no significant differences in mattress dust, morning PEF, or percent of patients who were able to control asthma without ICSs (Woodcock et al. 2003). This study, which involved no educational component, suggests that the role of education in maintaining allergen control is important.

Several studies with strong education components were successful in reducing allergen exposures in the home and/or reducing asthma morbidity, whether education was delivered by community workers or research staff. More research is needed to increase our understanding about how the combination of home-based education interventions and the provision of tools for allergen control in high-risk asthma populations can reduce the burden of allergen exposure and affect asthma morbidity. Studies are also needed to evaluate the cost-effectiveness and feasibility of widespread implementation of all allergen-control interventions delivered in patients' homes.

Summary statement on asthma self-management education at points of care outside the health care system:

According to the review of RCTs, asthma education can be delivered at multiple points of care other than clinics, EDs, and hospitals. With the support of clinicians, effective educational interventions should be provided at points of care outside the traditional health care setting, including schools (Butz et al. 2005; Christiansen et al. 1997; Cicutto et al. 2005; Clark et al. 2004; MeGhan [sic] et al. 2003), pharmacies (Cordina et al. 2001; McLean et al. 2003; Saini et al. 2004), and homes. For example, pharmacy-based education directed toward understanding medications and teaching inhaler skills as well as home-based interventions to increase patient and family capacity to control allergen and irritant exposure (Custovic et al. 2000; Eggleston et al. 2005; Klinnert et al. 2005; Krieger et al. 2005; McConnell et al. 2005; Morgan et al. 2004) are strategies that will enhance overall asthma self-management support.

OTHER OPPORTUNITIES FOR ASTHMA EDUCATION

Education for Children Using Computer-Based Technology

The Expert Panel recommends that computer-based programs that are incorporated into asthma care be considered for adolescents and children (Evidence B).

Four controlled trials have tested the ability of interactive computer asthma-education programs to improve children's asthma self-management behavior, health outcomes, and use of emergency health services. Two studies of computer-based asthma-education programs that children completed over a series of clinic visits reported positive results including: reduced symptoms and hospitalizations, and increased clinic followup visits (Bartholomew et al. 2000); reduced symptoms and ED visits, and less use of ICSs (Krishna et al. 2003). In two other trials of computer-based education, no improvements were found in health status or use of emergency health services. One study involved three opportunities to complete the program over three clinic visits (Homer et al. 2000); the other study involved a single 20-minute opportunity to complete the program at home with guidance from a nurse (Huss et al. 2003).

Two other trials tested computer-based programs to facilitate recording symptoms, communicating with health care providers, and making decisions about treatment. A trial of a device used at home to monitor symptoms and medication use, obtain immediate programmed feedback, and communicate results to health care providers over a telephone link found reductions in days with activity limitation, reports of peak flow in yellow or red zones, and urgent telephone calls to the doctor (Guendelman et al. 2002). A trial that tested an interactive, Internet-based system, allowing specialists to monitor patient diaries of symptoms and peak flow and to adjust therapy quickly, rapidly improved patients' control of symptoms and quality of life (Rasmussen et al. 2005).

An observational study found that asking children and adolescents to videotape their asthma-management practices at home provided detailed evidence of problems with adherence and inhaler technique (Rich et al. 2000). Reviewing these videotape narratives with the patient may help clinicians improve teaching and care of patients.

Taken together, these studies suggest that new technologies, including computer and Internet-based education and communication with physicians, can improve patients' control of asthma. More research is needed in these areas.

Education on Tobacco Avoidance for Women Who Are Pregnant and Members of Households With Infants and Young Children

The Expert Panel recommends that all patients who have asthma and women who are pregnant be advised not to smoke and not to be exposed to ETS (Evidence C). Query patients about their smoking status, and consider specifically referring to smoking cessation programs adults who smoke and have young children who have asthma in the household (Evidence B).

Several studies strongly suggest that maternal smoking during pregnancy results in harmful in utero exposure of the fetus and increases the risk of the child's developing recurrent wheezing and asthma in the first 5 years of life (Agabiti et al. 1999; Gergen et al. 1998; Gilliland et al. 2001). Children exposed in utero to maternal smoking demonstrate persistent deficits in lung function measured by spirometry (Kelso et al. 1995). Children not exposed in utero but exposed postnatally to tobacco smoke in the home also have an increased risk of wheezing and asthma by age 5 (Gergen et al. 1998). Heavy postnatal tobacco smoke markedly increases the risk for persistent asthma in the child (Infante-Rivard et al. 1999). In addition, children 4–16 years of age who were exposed to pre- and postnatal tobacco smoke and had high cotinine levels were found to have increased wheezing, increased school absences, and decreased lung function (Mannino et al. 2001).

It is now well established that exposure to ETS increases the severity of asthma, increases the risk of asthma-related ED visits and hospitalizations, and decreases the quality of life in both children and adults (Eisner 2002; Mannino et al. 2002; Morkjaroenpong et al. 2002). In adult, nonsmoking persons who have asthma, recent secondhand smoke exposure (as directly measured by 7-day nicotine badge) and long-term 3-month exposure (as measured by levels of both nicotine and cotinine in hair) are associated with increased asthma severity and poorer asthma outcomes (Eisner et al. 2005). In terms of public health, these results support efforts to prohibit smoking in public places.

An important RCT (Wilson et al. 2001) used three nurse-led education sessions with parents who were smokers; the sessions incorporated behavior change strategies, asthma education, and repeated feedback of their children's urinary cotinine levels. The intervention significantly reduced medical visits for acute asthma in these tobacco-exposed, low-income, minority children.

Because of the marked impact of tobacco as an irritant for most people who have asthma plus the negative health consequences of smoking to the smoker, the smoking status of all patients should be obtained, and appropriate advice and support should be offered to all patients who smoke.

Case Management for High-Risk Patients

The Expert Panel recommends that case or care management by trained health professionals be considered for patients who have poorly controlled asthma and have recurrent visits to the ED or hospital (Evidence B).

Case or care management is the strategy of using expert guidelines to focus management of patients who have asthma and have high levels of health care service use on specific, stepwise goals to reduce morbidity and costs, as well as the risk of mortality from asthma. Three RCTs (Greineder et al. 1999; Hughes et al. 1991; Kelly et al. 2000) found that case management reduced ED visits, hospitalizations, and health care costs among children who had asthma and were high users of health care resources. In all three trials, the intervention included intensive education of patients combined with case management by nurses. One study (Greineder et al. 1999) found a 39 percent reduction in ED use in the group that received asthma education alone, but the extent to which this was attributable to the education rather than to developmental changes cannot be determined. However, case management with education resulted in a 73 percent decrease in ED visits—a reduction of 34 percentage points compared with education alone ($p = 0.0002$). Hospitalizations were reduced by 43 percent in the control group and by 84 percent in the case-management group. Total use of services outside the study group health plans was reduced 28 percent in control and 82 percent in case-management groups. All between-group differences were statistically significant. The positive effect of asthma education was significantly enhanced by followup case management, with continued contact with the nurse case manager. Care-management processes are tools to improve the efficiency and quality of primary care delivery. These tools are often used by organizations that provide care for chronic illnesses, such as asthma and diabetes, to low-income populations.

Another study (Delaronde 2002) explored using case management to increase use of ICSs among 249 persons who had asthma, were in a managed care program, were identified as receiving three or more SABA prescriptions for 3 consecutive months, but had no prescription for anti-inflammatory medications. The results of this study and another observational study with more intensive followup (Delaronde et al. 2005) showed that case management may improve medication use by patients who do not use asthma medications as prescribed. Patients who received intensive case-management intervention were four times more likely to be prescribed anti-inflammatory medications.

Taken together, the findings of these studies suggest that case (or care) management can be effective in improving asthma control in selected populations of individuals who have poorly controlled asthma.

COST-EFFECTIVENESS

The Expert Panel recommends that asthma self-management education that is provided by trained health professionals be considered for policies and reimbursements as an integral part of effective asthma care; the education improves patient outcomes (Evidence A) and can be cost-effective (Evidence B). (See Evidence Table 6, Cost-Effectiveness of Asthma Self-Management Education.)

Cost-effectiveness analyses provide evidence of the financial impact of interventions as well as their clinical benefits. The analyses relate costs to a measure of clinical effectiveness of the intervention. The cost-effectiveness ratio is the ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives. When an intervention that has a certain cost improves a significant clinical outcome and total costs are decreased, the intervention is considered cost-effective. For example, if self-management education improves overall control of asthma, with fewer days of symptoms, fewer ED visits, and fewer hospitalizations, then the intervention may result in lower overall direct medical costs. If these educated patients also have fewer missed work or school days, then indirect costs are reduced as well.

The cost-effectiveness and/or cost savings of asthma self-management education has been shown in six RCTs (Gallefoss and Bakke 2001; Kamps et al. 2004; Kauppinen et al. 1999; Schermer et al. 2002; Sullivan et al. 2002, 2005) and one observational study (Tinkelman and Wilson 2004). Sullivan and colleagues (2002) conducted a prospective cost analysis of an inner-city asthma-management program being studied in an RCT of 1,033 inner-city children who had asthma. The primary efficacy end point was the mean number of days with asthma symptoms self-reported over a 2-week period. Masters-level social workers worked with adult family members to improve asthma-management skills. Children attended two child-only group sessions for skill development. Compared with usual care, the intervention improved outcomes at average cost of $9.20 per symptom-free day. Cost savings increased as severity of a child's asthma increased. Cost-effectiveness was greater in subgroups of children who had more severe asthma because, for the modest increase in cost of the intervention, substantial reductions occurred in the total cost of medical care. Later, Sullivan and colleagues (2005) evaluated the cost-effectiveness of interventions designed to improve the quality of care delivered to children who had asthma and their outcomes. In this three-arm, cluster RCT, peer-led physician education was compared to combined peer-led education with a multilevel, nurse-led educational intervention to improve asthma care and compared to usual care. The primary clinical outcome, symptom-free days, was highest (13.3 days) for the combined intervention compared to peer-led education alone (6.5 days) and compared to usual care, but this outcome was achieved at an increased cost of asthma care (cost-effectiveness ratio of $18/symptom-free day for peer-led education and $68/symptom-free day for the combined intervention). The higher costs were attributable to the cost of implementing and maintaining the interventions.

Two other RCTs demonstrate the cost-effectiveness of self-management education (Gallefoss and Bakke 2001; Schermer et al. 2002). Both studies showed that guided self-management education improved quality of life, lung function, and compliance with ICS medication while reducing rates of physician consultation and absenteeism from work due to asthma. A key part of the intervention was teaching how to change medication during symptom episodes of asthma. Both studies showed a reduction in total direct and indirect costs while improving asthma outcomes, thus making the cost of the self-management interventions cost-effective.

In an earlier study, Kauppinen and coworkers (1999) conducted an RCT in newly diagnosed adults who had asthma, comparing the long-term cost-effectiveness of intensive patient education combined with supervision of self-management to a control group who received conventional brief education at the initial visit. After 3 years, a significant improvement in lung function and a significant reduction in sick days occurred in the self-management group. Quality-of-life scores did not differ between groups, and the difference in costs was not statistically significant, although costs were consistently lower in the self-management group.

Kamps and colleagues (2004) conducted an RCT of outpatient asthma management of children, who were 2–18 years of age and had asthma, by trained nurses compared to pediatricians. After all patients were seen for the first asthma-education visit with a nurse educator, the patients were randomly assigned to either a pediatrician or an experienced asthma nurse educator. Costs of followup care were less for the nurse than for the pediatrician due to lower salary costs. In this population of patients who had mild asthma, nurse-led outpatient management of childhood asthma was provided at a lower cost, with no difference in health care utilization, compared to medical care by pediatricians. Similar results were shown by Lindberg and coworkers (2002) in a comparative cohort study of adult patients cared for by trained asthma nurses versus physicians. The average costs of care were significantly less for the group of patients managed by nurses.

In an observational study, Tinkelman and Wilson (2004) reported a disease-management intervention that was effective in achieving cost savings in asthma care. Patients served as their own controls and showed a significant improvement, between baseline and postintervention, in costs of care.

Taken together, the analyses of costs in both randomized and observation trials demonstrate the cost-effectiveness of education in those asthma self-management programs that improve patients' skills and decrease health care utilization. (See Evidence Table 6, Cost-Effectiveness of Asthma Self-Management Education.)

Tools for Asthma Self-Management

ROLE OF WRITTEN ASTHMA ACTION PLANS FOR PATIENTS WHO HAVE ASTHMA

The Expert Panel recommends that clinicians provide to all patients who have asthma a written asthma action plan that includes instructions for (1) daily management and (2) recognizing and handling worsening asthma, including adjustment of dose of medications. Written action plans are particularly recommended for patients who have moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B). Written asthma action plans may be based on PEF measurements or symptoms or both, depending on the preference of the patient and clinician (Evidence B). A peak-flow-based plan may be particularly useful for patients who have difficulty perceiving signs of worsening asthma (Evidence D).

The Expert Panel prefers to use one term—"written asthma action plan"—to encompass instructions both for daily actions to keep asthma controlled and for actions to adjust treatment when symptoms or exacerbations occur. Using one term addresses the confusion over previous guidelines' use of several different terms for asthma management plans and emphasizes the importance of giving patients instructions for managing both the acute and long-term aspects of asthma. Therefore, this report uses one term "written asthma action plan," although in some studies investigators used a variation of this term.

Written asthma action plans provide a way to involve the patient directly in self-management by writing down the treatment plan the clinician and patient agree on together and by giving clear instructions that the patient can use at home. The asthma action plan should be reviewed and refined at the patient's followup visits. Clinicians should choose an action plan that suits their practice, patients, and style. Examples of asthma action plans are provided in figures 3–10 a, b, and c to demonstrate the range of possibilities; they can be modified as appropriate.

Written asthma action plans include two important elements:

- Daily management
  - What medicine to take daily, including the specific names of the medications
  - What actions to take to control environmental factors that worsen the patient's asthma
- How to recognize and handle worsening asthma
  - What signs, symptoms, and PEF measurements (if peak flow monitoring is used) indicate worsening asthma
  - What medications to take in response to these signs
  - What symptoms and PEF measurements indicate the need for urgent medical attention
  - Emergency telephone numbers for the physician, ED, and person or service to transport the patient rapidly for medical care
- The effectiveness of written asthma action plans has been addressed in several recent systematic reviews and in five individual studies. A recent systematic review of 36 RCTs showed that self-management education that included self-monitoring by either PEF or symptoms, coupled with regular medical review and a written asthma action plan, reduced hospitalizations, urgent care visits, ED visits, work absences, and nocturnal asthma in adults (Gibson et al. 2003). Although subgroup analyses were not able to isolate the specific contribution of written plans to these outcomes, the authors conclude that education programs that enable people to adjust their medication using a written asthma action plan appear to be more effective than other forms of asthma self-management.

In a later systematic review (Toelle and Ram 2004), three RCTs tested the effect of written plans versus no written plans and found no consistent evidence that written plans produced better patient outcomes than outcomes with no written plan. The trials were too small and the results too inconsistent to reach a firm conclusion about the contribution of written asthma action plans to asthma education.

Five individual studies (including four RCTs, and one with an additional, extended followup) and one case-control study have examined the contributions of written asthma action plans to the control of asthma (Abramson et al. 2001; Baldwin et al. 1997; Cowie et al. 1997; Jones et al. 1995; Klein et al. 2001; van der Palen et al. 2001). Two RCTs showed no effect for written asthma action plans compared to no written plans for measures of asthma morbidity or health care utilization (Baldwin et al. 1997; Jones et al. 1995). The individual benefit of including an asthma action plan for self-management of exacerbations was shown in a 2-year RCT

FIGURE 3–10a. SAMPLE ASTHMA ACTION PLAN

My Asthma Action Plan

Patient Name: _____

Medical Record #: _____

Physician's Name: _____ DOB: _____

Physician's Phone #: _____ Completed by: _____ Date: _____

Long-Term-Control Medicines	How Much To Take	How Often	Other Instructions
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	

Quick-Relief Medicines	How Much To Take	How Often	Other Instructions
		Take ONLY as needed	NOTE: If this medicine is needed frequently, call physician to consider increasing long-term-control medications.

Special instructions when I feel *good,* *not good,* and *awful.*

GREEN ZONE

I feel ***good.***

(My **peak flow** is in the **GREEN** zone.)

PREVENT asthma symptoms everyday:

- ☐ Take my long-term-control medicines (above) every day.
- ☐ Before exercise, take _____ puffs of _____
- ☐ Avoid things that make my asthma worse like: _____

YELLOW ZONE

I do ***not*** feel ***good.***

(My **peak flow** is in the **YELLOW** zone.)

My symptoms may include one or more of the following:

- Wheeze
- Tight chest
- Cough
- Shortness of breath
- Waking up at night with asthma symptoms
- Decreased ability to do usual activities
- _____

CAUTION. I should continue taking my long-term-control asthma medicines every day AND:

- ☐ Take _____

If I still do not feel good, or my peak flow is not back in the ***Green Zone*** within 1 hour, then I should:

- ☐ Increase _____
- ☐ Add _____
- ☐ Call _____

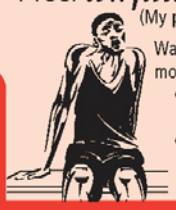
RED ZONE

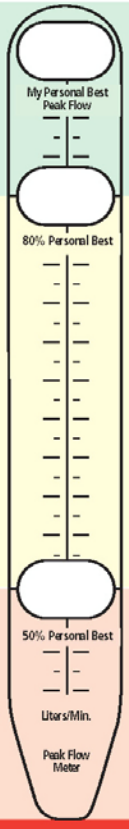
I feel ***awful.***

(My **peak flow** is in the **RED** zone.)

Warning signs may include one or more of the following:

- It's getting harder and harder to breathe
- Unable to sleep or do usual activities because of trouble breathing





MEDICAL ALERT! Get help!

- ☐ Take _____ until I get help immediately.
- ☐ Take _____
- ☐ Call _____

Danger! Get help immediately! **Call 9–1–1 if you have trouble walking or talking due to shortness of breath or lips or fingernails are gray or blue.**

Source: Adapted and reprinted with permission from the Regional Asthma Management and Prevention (RAMP) Initiative, a program of the Public Health Institute. http://www.calasthma.org/uploads/resources/actionplanpdf.pdf; San Francisco Bay Area Regional Asthma Management Plan, http://www.rampasthma.org

FIGURE 3–10b. SAMPLE ASTHMA ACTION PLAN

Child Asthma Action Plan

0–5 years of age

Patient Name: _____

Medical Record #: _____

Health Care Provider's Name: _____ DOB: _____

Health Care Provider's Phone #: _____ Completed by: _____ Date: _____

Long-Term-Control Medicines (Use Every Day To Stay Healthy)	How Much To Take	How Often	Other Instructions (such as spacers/masks, nebulizers)
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	

Quick-Relief Medicines	How Much To Take	How Often	Other Instructions
		Give ONLY as needed	NOTE: If this medicine is needed often (_____ times per week), call physician.

GREEN ZONE

Child is ***well*** and has no asthma symptoms, even during active play.

PREVENT asthma symptoms every day:

- **Give the above long-term-control medicines every day.**
- Avoid things that make the child's asthma worse:

☑ Avoid tobacco smoke; ask people to smoke outside.

☐ _____

☐ _____

YELLOW ZONE

Child is ***not well*** and has asthma symptoms that may include:

- Coughing
- Wheezing
- Runny nose or other cold symptoms
- Breathing harder or faster
- Awakening due to coughing or difficulty breathing
- Playing less than usual
- _____
- _____

Other symptoms that could indicate that your child is having trouble breathing may include: difficulty feeding (grunting sounds, poor sucking), changes in sleep patterns, cranky and tired, decreased appetite.

CAUTION. Take action by continuing to give regular asthma medicines **every day** AND:

☐ Give _____

_____ (include dose and frequency)

If the child is not in the *Green Zone* and still has symptoms after 1 hour, then:

☐ Give more _____

_____ (include dose and frequency)

☐ _____

_____ (include dose and frequency)

☐ Call _____

RED ZONE

Child ***feels awful!*** Warning signs may include:

- Child's wheeze, cough, or difficulty breathing continues or worsens, even after giving yellow zone medicines.
- Child's breathing is so hard that he/she is having trouble walking/talking/eating/playing.
- Child is drowsy or less alert than normal.

MEDICAL ALERT! Get help!

☐ Take the child to the hospital or call 9–1–1 immediately!

☐ Give more _____ (include dose and frequency) until you get help.

☐ Give _____ (include dose and frequency)

Danger! Get help immediately!

Call 9–1–1 if:

- The child's skin is sucked in around neck and ribs, or
- Lips and/or fingernails are grey or blue, or
- Child doesn't respond to you.

Adapted and reprinted with permission from the Regional Asthma Management and Prevention (RAMP) Initiative, a program of the Public Health Institute.

Source: http://www.calasthma.org/uploads/resources/actionplanpdf.pdf; San Francisco Bay Area Regional Asthma Management Plan, http://www.rampasthma.org

FIGURE 3–10c. SAMPLE ASTHMA ACTION PLAN

Asthma Action Plan

For: _____ Doctor: _____ Date: _____

Doctor's Phone Number _____ Hospital/Emergency Department Phone Number _____

GREEN ZONE

Doing Well

- No cough, wheeze, chest tightness, or shortness of breath during the day or night
- Can do usual activities

And, if a peak flow meter is used,

Peak flow: more than _____ (80 percent or more of my best peak flow)

My best peak flow is: _____

Take these long-term-control medicines each day (include an anti-inflammatory).

Medicine	How much to take	When to take it
_____	_____	_____
_____	_____	_____

Identify and avoid and control the things that make your asthma worse, like (list here):

_____

_____

_____

Before exercise, if prescribed, take: ☐ 2 or ☐ 4 puffs _____ 5 to 60 minutes before exercise

YELLOW ZONE

Asthma Is Getting Worse

- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

-Or-

Peak flow: _____ to _____ (50 to 79 percent of my best peak flow)

First

Add: quick-relief medicine—and keep taking your GREEN ZONE medicine.

_____ (short-acting beta$_2$-agonist) ☐ 2 or ☐ 4 puffs, every 20 minutes for up to 1 hour ☐ Nebulizer, once

If applicable, remove yourself from the thing that made your asthma worse.

Second

If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:

☐ Continue monitoring to be sure you stay in the green zone.

-Or-

If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:

☐ Take: _____ (short-acting beta$_2$-agonist) ☐ 2 or ☐ 4 puffs or ☐ Nebulizer

☐ Add: _____ (oral corticosteroid) mg per day For _____ (3–10) days

☐ Call the doctor, _____ (phone), ☐ before/ ☐ within _____ hours after taking the oral corticosteroid.

RED ZONE

Medical Alert!

- Very short of breath, or
- Quick-relief medicines have not helped, or
- Cannot do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow Zone

-Or-

Peak flow: less than _____ (50 percent of my best peak flow)

Take this medicine:

☐ _____ (short-acting beta$_2$-agonist) ☐ 4 or ☐ 6 puffs or ☐ Nebulizer

☐ _____ (oral corticosteroid) _____ mg

Then call your doctor NOW. Go to the hospital or call an ambulance if:

- You are still in the red zone after 15 minutes AND
- You have not reached your doctor.

DANGER SIGNS

- **Trouble walking and talking due to shortness of breath**
- **Lips or fingernails are blue**

- **Take ☐ 4 or ☐ 6 puffs of your quick-relief medicine AND**
- **Go to the hospital or call for an ambulance _____ NOW!** (phone)

Source: National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services. NIH Publication No 07-5251, October 2006.

(van der Palen et al. 2001). The self-management action plan significantly improved self-perceived asthma control, confidence (self-efficacy) for self-management, and self-treatment and self-management behavior during a hypothetical asthma exacerbation. These subjective outcomes were confirmed after 2 years of followup, but no significant effect on asthma clinical status was detected (Klein et al. 2001). Another RCT (Cowie et al. 1997) provided education for all patients during ED visits for asthma exacerbations and randomly assigned patients to three study arms: no written plan, a symptom-based written plan, and a peak flow-based written plan. Over the 6-month followup period, all groups improved their asthma control, but patients who received a peak flow-based written plan had significantly (p = 0.002) fewer urgent care visits (5 for 46 patients) compared with patients who received a symptom-based plan (45 visits for 48 patients) or no written plan (55 visits for 48 patients). A case-control study by Abramson and colleagues (2001) compared patients who died from exacerbation of asthma with controls who had severe asthma exacerbations successfully treated in the ED. After adjustment for demographic, psychosocial, and disease severity factors, having a written asthma action plan at the time of the exacerbation was significantly associated with a 70 percent reduction in the risk of death (RR = 0.29 (0.09, 0.93)).

Although the results of these studies are mixed, they suggest that the use of written plans may help patients improve control of their asthma, particularly in preventing or managing asthma exacerbations. A scientific review (Powell and Gibson 2003) examined several options for the use of written plans in asthma management. The review found no difference in outcomes when patients self-adjusted medication by using a written asthma action plan compared to when clinicians adjusted treatment. These two methods for achieving asthma control were found to be equivalent. This finding suggests that it is safe and effective for patients to use written asthma action plans for self-management of their asthma.

Adams and colleagues (2001) showed that a comprehensive program, with monthly telephone contact to discuss the asthma action plans directed by either symptoms or peak flow, was equally effective in improving outcomes. The key factor in this study was the monthly contact to provide reinforcement for the educational endeavor. Only patients who had higher levels of denial of the disease and lower self-confidence had increased numbers of ED visits for asthma flares.

ROLE OF PEAK FLOW MONITORING

The Expert Panel recommends that:

- **Written asthma action plans can be based on either symptoms or peak flow measurements (Evidence B).**
- **Long-term daily peak flow monitoring be considered for patients who have moderate or severe persistent asthma (Evidence B), poor perception of airflow obstruction or worsening asthma, unexplained response to environmental or occupational exposures, and others at the discretion of the clinician and the patient (EPR—2 1997).**

Several studies reviewed in the National Asthma Education and Prevention Program (NAEPP) “Expert Panel Report—Update 2002: Guidelines for the Diagnosis and Management of Asthma” show that peak flow and symptom-based action plans are equally effective in adults (EPR—Update 2002). The choice should be left to the discretion of the patient and the health care clinician. When peak-flow-guided action plans are chosen, the patient’s personal best peak flow must be known. Reddel and colleagues (2004) reported that personal best PEF is a

useful concept for written asthma action plans and can be determined by using the highest PEF over the previous 2 weeks. Additionally, the patient must be educated, understand how to use the action plan, and be willing to incorporate peak flow monitoring into asthma care. Use of peak flow monitoring should not replace symptom recognition but should facilitate additional discussion with the health care provider.

Peak flow monitoring for self-management of asthma may be less effective for children. In a small RCT of peak flow monitoring and diary recording in children, Kamps and coworkers (2001) found low levels of adherence over a 4-week period of monitoring peak flow twice daily. Children and their parents were not told the electronic monitor was recording date and time of measurement. Actual compliance recorded electronically was significantly lower than reported compliance in both study groups, and 50 percent of the values were either recorded incorrectly or invented. Eid and colleagues (2000) showed that PEF monitoring in children may be inaccurate compared to FEV_1, especially as the severity of airway obstruction increases. The addition of peak flow monitoring to symptom-based guided self-management was not shown to contribute to self-management decisionmaking in children 7–14 years of age in another RCT (Wensley and Silverman 2004). During acute episodes of asthma, children responded to increased symptoms by taking more ICS when PEF was greater than 70 percent of personal best. In contrast to the finding of Eid and colleagues (2000), these investigators found no evidence that FEV_1 was more sensitive than PEF in detecting airflow obstruction. In the findings of an RCT comparing symptom monitoring to PEF monitoring only when symptoms occurred, to daily and symptom-time PEF monitoring, children and their parents perceived benefit from symptom monitoring whether or not it was accompanied by peak flow measurement (McMullen et al. 2002). These investigators found no evidence of benefit from more intensive daily monitoring.

Periodic daily peak flow monitoring may be useful to evaluate responses to changes in treatment, identify the temporal relationship between environmental or occupational exposures and bronchospasm, and provide guidance for patients who have poor perception of airflow obstruction.

See “Component 1: Assessment and Monitoring” for additional discussion. See “How To Use Your Peak Flow Meter” (figure 3–11) for a sample handout for patients.

GOALS OF ASTHMA SELF-MANAGEMENT EDUCATION AND KEY EDUCATIONAL MESSAGES

Patient education is an essential component of successful asthma management. Current management approaches require patients and families to effectively carry out complex pharmacologic regimens, institute environmental control strategies, detect and self-treat most asthma exacerbations, and communicate appropriately with health care providers. Patient education is the mechanism through which patients learn to accomplish those tasks successfully. It is also a powerful tool for helping patients gain the motivation, skill, and confidence to control their asthma (Butz et al. 2005; Gibson et al. 2000; Guevara et al. 2003; Levy et al. 2000; Perneger et al. 2002). Research shows that asthma education can be cost-effective and can reduce morbidity for both adults and children, especially among high-risk patients (Gallefoss and Bakke 2001; Gibson et al. 2000, 2003; Guevara et al. 2003; Schermer et al. 2002; Sullivan et al. 2002).

This section covers strategies for enhancing the delivery of patient education and improving the likelihood that patients will follow clinical recommendations.

FIGURE 3–11. HOW TO USE YOUR PEAK FLOW METER

A peak flow meter is a device that measures how well air moves out of your lungs. During an asthma episode, the airways of the lungs usually begin to narrow slowly. The peak flow meter may tell you if there is narrowing in the airways hours—sometimes even days—before you have any asthma symptoms.

By taking your medicine(s) early (before symptoms), you may be able to stop the episode quickly and avoid a severe asthma episode. Peak flow meters are used to check your asthma the way that blood pressure cuffs are used to check high blood pressure.

The peak flow meter also can be used to help you and your doctor:

- Learn what makes your asthma worse.
- Decide if your treatment plan is working well.
- Decide when to add or stop medicine.
- Decide when to seek emergency care.

A peak flow meter is most helpful for patients who must take asthma medicine daily. Patients age 5 and older are usually able to use a peak flow meter. Ask your doctor or nurse to show you how to use a peak flow meter.

How To Use Your Peak Flow Meter

- Do the following five steps with your peak flow meter:

  1. Move the indicator to the bottom of the numbered scale.
  2. Stand up.
  3. Take a deep breath, filling your lungs completely.
  4. Place the mouthpiece in your mouth and close your lips around it. Do not put your tongue inside the hole.
  5. Blow out as hard and fast as you can in a single blow.

- Write down the number you get. But if you cough or make a mistake, don't write down the number. Do it over again.
- Repeat steps 1 through 5 two more times, and write down the best of the three blows in your asthma diary.

Find Your Personal Best Peak Flow Number

Your personal best peak flow number is the highest peak flow number you can achieve over a 2-week period when your asthma is under good control. Good control is when you feel good and do not have any asthma symptoms.

Each patient's asthma is different, and your best peak flow may be higher or lower than the peak flow of someone of your same height, weight, and sex. This means that it is important for you to find your own personal best peak flow number. Your treatment plan needs to be based on your own personal best peak flow number.

To find out your personal best peak flow number, take peak flow readings:

- At least twice a day for 2 to 3 weeks.
- When you wake up and in late afternoon or early evening.
- 15–20 minutes after you take your inhaled short-acting beta$_2$-agonist for quick relief.
- As instructed by your doctor.

FIGURE 3–11. HOW TO USE YOUR PEAK FLOW METER (CONTINUED)

The Peak Flow Zone System

Once you know your personal best peak flow number, your doctor will give you the numbers that tell you what to do. The peak flow numbers are put into zones that are set up like a traffic light. This will help you know what to do when your peak flow number changes. For example:

Green Zone (more than ___L/min [80 percent of your personal best number]) signals good control. No asthma symptoms are present. Take your medicines as usual.

Yellow Zone (between ___L/min and ___L/min [50 to less than 80 percent of your personal best number]) signals caution. If you remain in the yellow zone after several measures of peak flow, take an inhaled short-acting $beta_2$-agonist. If you continue to register peak flow readings in the yellow zone, your asthma may not be under good control. Ask your doctor if you need to change or increase your daily medicines.

Red Zone (below ___L/min [less than 50 percent of your personal best number]) signals a medical alert. You must take an inhaled short-acting $beta_2$-agonist (quick-relief medicine) right away. Call your doctor or emergency room and ask what to do, or go directly to the hospital emergency room.

Record your personal best peak flow number and peak flow zones in your asthma diary.

Use the Diary To Keep Track of Your Peak Flow

Measure your peak flow when you wake up, *before* taking medicine. Write down your peak flow number in the diary every day, or as instructed by your doctor.

Actions To Take When Peak Flow Numbers Change

- PEF goes between ___L/min and ___L/min (50 to less than 80 percent of personal best, yellow zone).

  ACTION: Take an inhaled short-acting $beta_2$-agonist (quick-relief medicine) as prescribed by your doctor.

- PEF increases 20 percent or more when measured before and after taking an inhaled short-acting $beta_2$-agonist (quick-relief medicine).

  ACTION: Talk to your doctor about adding more medicine to control your asthma better (for example, an anti-inflammatory medication).

Source: Adapted from *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute, 1997.

Establish and Maintain a Partnership

The Expert Panel recommends that a partnership between patient and clinician be established to promote effective asthma management (Evidence A).

Building a partnership requires that clinicians promote open communication and ensure that patients have a basic and accurate foundation of knowledge about asthma, understand the treatment approach, and have the self-management skills necessary to monitor the disease objectively and take medication effectively (Clark et al. 1995, 1998, 2000; Evans et al. 1997; Love et al. 2000; Marabini et al. 2002; Smith et al. 2005; Wilson et al. 2005, 2006).

The Expert Panel recommends that when nurses, pharmacists, respiratory therapists, and other health care professionals are available to provide and support patient self-management education, a team approach through multiple points of care should be used (NHLBI 1995b,c). The principal clinician, care manager, or any other health professional trained in asthma management and self-management education can introduce the key educational messages (See figure 3–12.) and negotiate agreements with patients about the goals of treatment, medications to use, and the actions the patient will take to promote asthma control (Clark et al. 1995, 1998, 2000; Marabini et al. 2002; Wilson et al. 2005, 2006). All health care professionals who encounter patients who have asthma are members of the health care team and should reinforce and expand these messages during clinic visits, ED visits, pharmacy visits, telephone calls, and in community centers and schools. National certification for asthma educators is available in the United States. Although no published data are available comparing certified to noncertified educators, certification requires a minimum number of hours of experience and passing a standardized test.

FIGURE 3–12. KEY EDUCATIONAL MESSAGES: TEACH AND REINFORCE AT EVERY OPPORTUNITY

Basic Facts About Asthma

- The contrast between airways of a person who has and a person who does not have asthma; the role of inflammation
- What happens to the airways in an asthma attack

Roles of Medications: Understanding the Difference Between:

- Long-term-control medications: prevent symptoms, often by reducing inflammation. Must be taken daily. Do not expect them to give quick relief.
- Quick-relief medications: short-acting beta$_2$-agonists relax muscles around the airway and provide prompt relief of symptoms. Do not expect them to provide long-term asthma control. Using quick-relief medication on a daily basis indicates the need for starting or increasing long-term control medications.

Patient Skills

- Taking medications correctly
  - Inhaler technique (demonstrate to patient and have the patient return the demonstration)
  - Use of devices, such as prescribed valved holding chamber (VHC), spacer, nebulizer
- Identifying and avoiding environmental exposures that worsen the patient's asthma; e.g., allergens, irritants, tobacco smoke
- Self-monitoring to:
  - Assess level of asthma control
  - Monitor symptoms and, if prescribed, peak flow
  - Recognize early signs and symptoms of worsening asthma
- Using written asthma action plan to know when and how to:
  - Take daily actions to control asthma
  - Adjust medication in response to signs of worsening asthma
  - Seek medical care as appropriate

It is the opinion of the Expert Panel that the health professional team members should consider documenting in the patient's record the key educational points (See figure 3–12.), patient concerns, and actions the patient agrees to take (Evidence C). This record will enable all members of the team to be consistent and to reinforce the educational points and the progress being made. Communication strategies that unite the network of health care professionals should be developed and strengthened. See further discussion in the section on "Communication Techniques."

TEACH ASTHMA SELF-MANAGEMENT

The Expert Panel recommends that:

- **Clinicians teach patients and families the basic facts about asthma (especially the role of inflammation), medication skills, and self-monitoring techniques (Evidence A).**

- **Provide all patients with a written asthma action plan that includes daily management and how to recognize and handle worsening asthma. Written action plans are particularly recommended for patients who have moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B).**

- **Clinicians teach patients environmental control measures (See "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma" for evidence ranking on different control measures.).**

Self-management education should include the following key points, adapted to meet the individual patient's needs:

- Figure 3–13 illustrates how education can be delivered across initial patient visits and followup visits.

- Teach basic facts about asthma so that the patient and family understand the rationale for needed actions. Give a brief verbal description of what asthma is, emphasizing the role of inflammation, and the intended role of each medication. Do not overwhelm the patient with too much information all at once, but repeat the important messages at each visit. Ask the patient to bring all medications to each appointment for review.

- Teach the patient necessary medication skills, such as correct use of the inhaler (See figure 3–14.) and VHC or spacer and knowing when and how to take quick-relief medications.

- Teach self-monitoring skills: symptom monitoring; peak flow monitoring, as appropriate; and recognizing early signs of deterioration.

- Identify current level of asthma control, goals for improvement, and teach how to self-manage worsening asthma by adjusting medications to regain asthma control.

- Teach relevant environmental control/avoidance strategies (See figure 3–15, "How To Control Things That Make Your Asthma Worse."). Teach how environmental allergens and irritants can make the patient's asthma worse at home, school, and work as well as how to recognize both immediate and delayed reactions. Teach patients strategies for removing allergens and irritants to which they are sensitive from their living spaces. If possible, refer them to evaluated, effective, home-based education programs for allergen and irritant control.

- Advise all patients not to smoke tobacco and to avoid secondhand tobacco smoke. Emphasize the importance of not smoking for women who are pregnant and for parents of small children.

FIGURE 3–13. DELIVERY OF ASTHMA EDUCATION BY CLINICIANS DURING PATIENT CARE VISITS

Assessment Questions	Information	Skills
Recommendations for Initial Visit		
Focus on: ■ Expectations of visit ■ Asthma control ■ Patients' goals of treatment ■ Medications ■ Quality of life "What worries you most about your asthma?" "What do you want to accomplish at this visit?" "What do you want to be able to do that you can't do now because of your asthma?" "What do you expect from treatment?" "What medicines have you tried?" "What other questions do you have for me today?" "Are there things in your environment that make your asthma worse?"	**Teach in simple language:** ■ What is asthma? Asthma is a chronic lung disease. The airways are very sensitive. They become inflamed and narrow; breathing becomes difficult. ■ The definition of asthma control: few daytime symptoms, no nighttime awakenings due to asthma, able to engage in normal activities, normal lung function. ■ Asthma treatments: two types of medicines are needed: — Long-term control: medications that prevent symptoms, often by reducing inflammation. — Quick relief: short-acting bronchodilator relaxes muscles around airways. ■ Bring all medications to every appointment. ■ When to seek medical advice. Provide appropriate telephone number.	**Teach or review and demonstrate:** ■ Inhaler (see figure 3–14) and spacer or valved holding chamber (VHC) use. Check performance. ■ Self-monitoring skills that are tied to a written action plan: — Recognize intensity and frequency of asthma symptoms. — Review the signs of deterioration and the need to reevaluate therapy: ♦ Waking at night or early morning with asthma ♦ Increased medication use ♦ Decreased activity tolerance ■ Use of a written asthma action plan (See figure 3–10.) that includes instructions for daily management and for recognizing and handling worsening asthma.
Recommendations for First Followup Visit (2 to 4 weeks or sooner as needed)		
Focus on: ■ Expectations of visit ■ Asthma control ■ Patients' goals of treatment ■ Medications ■ Patient treatment preferences ■ Quality of life Ask relevant questions from previous visit and also ask: "What medications are you taking?" "How and when are you taking them?" "What problems have you had using your medications?" "Please show me how you use your inhaled medications."	**Teach in simple language:** ■ Use of two types of medications. ■ Remind patient to bring all medications and the peak flow meter, if using, to every appointment for review. ■ Self-assessment of asthma control using symptoms and/or peak flow as a guide.	**Teach or review and demonstrate:** ■ Use of written asthma action plan. Review and adjust as needed. ■ Peak flow monitoring if indicated (See figure 3–11.). ■ Correct inhaler and spacer or VHC technique.

FIGURE 3–13. DELIVERY OF ASTHMA EDUCATION BY CLINICIANS DURING PATIENT CARE VISITS (CONTINUED)

Assessment Questions	Information	Skills
Recommendations for Second Followup Visit		
Focus on: ■ Expectations of visit ■ Asthma control ■ Patients' goals of treatment ■ Medications ■ Quality of life Ask relevant questions from previous visits and also ask: "Have you noticed anything in your home, work, or school that makes your asthma worse?" "Describe for me how you know when to call your doctor or go to the hospital for asthma care." "What questions do you have about the asthma action plan?" "Can we make it easier?" "Are your medications causing you any problems?" "Have you noticed anything in your environment that makes your asthma worse?" "Have you missed any of your medications?"	**Teach in simple language:** ■ Self-assessment of asthma control, using symptoms and/or peak flow as a guide. ■ Relevant environmental control/avoidance strategies (See figure 3–15.): — How to identify home, work, or school exposures that can cause or worsen asthma — How to control house-dust mites, animal exposures if applicable — How to avoid cigarette smoke (active and passive) ■ Review all medications.	**Teach or review and demonstrate:** ■ Inhaler/spacer or VHC technique. ■ Peak flow monitoring technique. ■ Use of written asthma action plan. Review and adjust as needed. ■ Confirm that patient knows what to do if asthma gets worse.
Recommendations for All Subsequent Visits		
Focus on: ■ Expectations of visit ■ Asthma control ■ Patients' goals of treatment ■ Medications ■ Quality of life Ask relevant questions from previous visits and also ask: "How have you tried to control things that make your asthma worse?" "Please show me how you use your inhaled medication."	**Teach in simple language:** ■ Review and reinforce all: — Educational messages — Environmental control strategies at home, work, or school — Medications — Self-assessment of asthma control, using symptoms and/or peak flow as a guide	**Teach or review and demonstrate:** ■ Inhaler/spacer or VHC technique. ■ Peak flow monitoring technique, if appropriate. ■ Use of written asthma action plan. Review and adjust as needed. ■ Confirm that patient knows what to do if asthma gets worse.

Sources: Adapted from Guevara et al. 2003; Janson et al. 2003; Powell and Gibson 2003; Wilson et al. 1993.

FIGURE 3–14. HOW TO USE YOUR METERED-DOSE INHALER

HOW TO USE YOUR METERED-DOSE INHALER

Using an inhaler seems simple, but most patients do not use it the right way. When you use your inhaler the wrong way, less medicine gets to your lungs.

For the next few days, read these steps aloud as you do them or ask someone to read them to you. Ask your doctor or nurse to check how well you are using your inhaler.

Use your inhaler in one of the three ways pictured below. A or B are best, but C can be used if you have trouble with A and B. Your doctor may give you other types of inhalers.

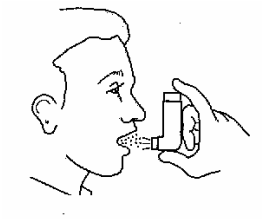
Steps for Using Your Inhaler

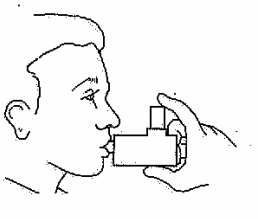
Getting ready	1. Take off the cap and shake the inhaler. 2. Breathe out all the way. 3. Hold your inhaler the way your doctor said (A, B, or C below).
Breathe in slowly	4. As you start breathing in slowly through your mouth, press down on the inhaler one time. (If you use a holding chamber, first press down on the inhaler. Within 5 seconds, begin to breathe in slowly.) 5. Keep breathing in slowly, as deeply as you can.
Hold your breath	6. Hold your breath as you count to 10 slowly, if you can. 7. For inhaled quick-relief medicine (beta$_2$-agonists), wait about 15–30 seconds between puffs. There is no need to wait between puffs for other medicines.

A. Hold inhaler 1 to 2 inches in front of your mouth (about the width of two fingers).

B. Use a spacer/holding chamber. These come in many shapes and can be useful to any patient.

C. Put the inhaler in your mouth. Do not use for steroids.





Clean your inhaler as needed, and know when to replace your inhaler. For instructions, read the package insert or talk to your doctor, other health care provider, or pharmacist.

FIGURE 3–15. HOW TO CONTROL THINGS THAT MAKE YOUR ASTHMA WORSE

You can help prevent asthma episodes by staying away from things that make your asthma worse. This guide suggests many ways to help you do this.

You need to find out what makes your asthma worse. Some things that make asthma worse for some people are not a problem for others. You do not need to do all of the things listed in this guide.

Look at the things listed in dark print below. Put a check next to the ones that you know make your asthma worse, particularly if you are allergic to the things. Then, decide with your doctor what steps you will take. Start with the things in your *bedroom* that bother your asthma. Try something simple first.

Tobacco Smoke

- If you smoke, ask your doctor for ways to help you quit. Ask family members to quit smoking, too.
- Do not allow smoking in your home, car, or around you.
- Be sure no one smokes at a child's daycare center or school.

Dust Mites

Many people who have asthma are allergic to dust mites. Dust mites are like tiny "bugs" you cannot see that live in cloth or carpet.

Things that will help the most:

- Encase your mattress in a special dust mite-proof cover.*
- Encase your pillow in a special dust mite-proof cover* or wash the pillow each week in hot water. Water must be hotter than 130 °F to kill the mites. Cooler water used with detergent and bleach can also be effective.
- Wash the sheets and blankets on your bed each week in hot water.

Other things that can help:

- Reduce indoor humidity to or below 60 percent; ideally 30–50 percent. Dehumidifiers or central air conditioners can do this.
- Try not to sleep or lie on cloth-covered cushions or furniture.
- Remove carpets from your bedroom and those laid on concrete, if you can.
- Keep stuffed toys out of the bed, or wash the toys weekly in hot water or in cooler water with detergent and bleach. Placing toys weekly in a dryer or freezer may help. Prolonged exposure to dry heat or freezing can kill mites but does not remove allergen.

***To find out where to get products mentioned in this guide, call:**

Asthma and Allergy Foundation of America (800–727–8462)

Allergy and Asthma Network/Mothers of Asthmatics, Inc. (800–878–4403)

American Academy of Allergy, Asthma, and Immunology (800–822–2762)

National Jewish Medical and Research Center (Lung Line) (800–222–5864)

American College of Allergy, Asthma, and Immunology (800–842–7777)

FIGURE 3–15. HOW TO CONTROL THINGS THAT MAKE YOUR ASTHMA WORSE (CONTINUED)

Animal Dander

Some people are allergic to the flakes of skin or dried saliva from animals.

The best thing to do:

- Keep animals with fur or hair out of your home.

If you can't keep the pet outdoors, then:

- Keep the pet out of your bedroom, and keep the bedroom door closed.
- Remove carpets and furniture covered with cloth from your home. If that is not possible, keep the pet out of the rooms where these are.

Cockroach

Many people with asthma are allergic to the dried droppings and remains of cockroaches.

- Keep all food out of your bedroom.
- Keep food and garbage in closed containers (never leave food out).
- Use poison baits, powders, gels, or paste (for example, boric acid). You can also use traps.
- If a spray is used to kill roaches, stay out of the room until the odor goes away.

Vacuum Cleaning

- Try to get someone else to vacuum for you once or twice a week, if you can. Stay out of rooms while they are being vacuumed and for a short while afterward.
- If you vacuum, use a dust mask (from a hardware store), a central cleaner with the collecting bag outside the home, or a vacuum cleaner with a HEPA filter or a double-layered bag.*

Indoor Mold

- Fix leaking faucets, pipes, or other sources of water.
- Clean moldy surfaces.
- Dehumidify basements if possible.

Pollen and Outdoor Mold

During your allergy season (when pollen or mold spore counts are high):

- Try to keep your windows closed.
- If possible, stay indoors with windows closed during the midday and afternoon, if you can. Pollen and some mold spore counts are highest at that time.
- Ask your doctor whether you need to take or increase anti-inflammatory medicine before your allergy season starts.

Smoke, Strong Odors, and Sprays

- If possible, do not use a wood-burning stove, kerosene heater, fireplace, unvented gas stove, or heater.
- Try to stay away from strong odors and sprays, such as perfume, talcum powder, hair spray, paints, new carpet, or particle board.

Exercise or Sports

- You should be able to be active without symptoms. See your doctor if you have asthma symptoms when you are active—such as when you exercise, do sports, play, or work hard.
- Ask your doctor about taking medicine before you exercise to prevent symptoms.
- Warm up for a period before you exercise.
- Check the air quality index and try not to work or play hard outside when the air pollution or pollen levels (if you are allergic to the pollen) are high.

Other Things That Can Make Asthma Worse

- Sulfites in foods: Do not drink beer or wine or eat shrimp, dried fruit, or processed potatoes if they cause asthma symptoms.
- Cold air: Cover your nose and mouth with a scarf on cold or windy days.
- Other medicines: Tell your doctor about all the medicines you may take. Include cold medicines, aspirin, and even eye drops.

JOINTLY DEVELOP TREATMENT GOALS

The Expert Panel recommends that clinicians determine the patient's personal treatment goals and preferences for treatment; review the general goals of asthma treatment; and agree on the goals of treatments (Evidence B).

Fundamental to building a partnership is that clinicians and patients jointly develop and agree on both short- and long-term treatment goals. Such agreements can encourage active participation, enhance the partnership, and improve asthma management (Clark et al. 1995, 2000; Marabini et al. 2002; Wilson et al. 2005, 2006).

- **Determine the patient's personal treatment goals and preferences for treatment.** Ask how asthma interferes with the patient's life (e.g., inability to sleep through the night, play a sport), and incorporate the responses into personal treatment goals. Involve the patient in decisionmaking about treatment.

- **Share the general goals of asthma treatment with the patient and family.** Tell patients, "Our measures of control are to have you:

  — Be free from troublesome symptoms day and night, including sleeping through the night."
  — Have the best possible lung function."
  — Be able to participate fully in any activities of your choice."
  — Not miss work or school because of asthma symptoms."
  — Need fewer or no urgent care visits or hospitalizations for asthma."
  — Use medications to control asthma with as few side effects as possible."
  — Be satisfied with your asthma care."

- **Agree on the goals of treatment.** The clinicians, the patient, and, when appropriate, the patient's family should agree on the goals of asthma management, which include both the patient's personal goals and the general goals (see list above) suggested by the clinicians. Negotiate the treatment plans to accomplish joint goals of treatment.

- **Provide a written asthma action plan that reflects the agreed upon goals for treatment.** See earlier discussion, "The Role of Written Asthma Action Plans for Patients Who Have Asthma."

ASSESS AND ENCOURAGE ADHERENCE TO RECOMMENDED THERAPY

The Expert Panel recommends that clinicians assess and encourage adherence during all asthma visits (Evidence C).

An important part of patient education is encouraging adherence. In a meta-analysis of methods to improve adherence to medical regimens, Roter and colleagues (1998) used multiple measures of compliance (health outcomes; direct indicators, such as urine and blood tracers; indirect indicators, such as pill and refill counts; subjective patient reports; and utilization, such as appointment keeping) to identify successful adherence strategies. The authors found that no single strategy or programmatic focus showed any clear advantage but that comprehensive interventions combining multiple strategies with cognitive, behavioral, and affective components were more likely to be effective than those using a single focus. Magar and coworkers (2005) showed that a multifocused strategy that tailored asthma education goals and messages to the individual patient improved outcomes. Other studies in small numbers of adults have shown that self-management education programs in asthma led to improved adherence over periods of

7 weeks to 6 months (Janson et al. 2003; Schaffer and Tian 2004). Onyirimba and colleagues (2003) found that direct clinician-to-patient discussion and feedback of adherence rates improved use of ICSs over a 10-week period.

Evidence concerning the optimal frequency for assessing and encouraging adherence among asthma patients is lacking, and no evidence from adherence studies identifies any single successful method. Evidence from studies in multiple diseases and in asthma, however, indicates that repetition is important, perhaps especially so in a variable, chronic disease such as asthma, and that consideration of the following strategies would be helpful for assessing and improving adherence within the context of clinical visits.

- Use effective techniques to promote open communication. Studies of physicians' communication styles suggest that being willing to address all questions, active listening, and using good communication techniques can improve patient adherence and/or satisfaction with care (Brown et al. 2004; Clark et al. 1998, 2000; Smith et al. 2005).

- Start each visit by asking about the patient's or parent's concerns and goals for the visit. Studies of adults and children have shown the most common concerns of patients and families include: fear and misunderstanding of effects of medications, including concerns of becoming "dependent" on asthma medications (Bender and Bender 2005; Janson and Becker 1998; Leickly et al. 1998; Muntner et al. 2001; Yawn 2003), and uncertainty of when to seek help (Bender and Bender 2005; Janson and Becker 1998). Open-ended questions, such as "What worries you most about your asthma?," may encourage patients and families to voice issues, personal beliefs, or concerns they may be apprehensive about discussing or may think are not of interest to the clinician. Most nonadherence originates in personal beliefs or concerns about asthma that have not been discussed with the clinician (Bender and Bender 2005; Janson and Becker 1998; Janz et al. 1984; Korsch et al. 1968; Yawn 2003). Until such fears and worries are identified and addressed, patients will not be able to adhere to the clinician's recommendations (Adams et al. 2003; Colland et al. 2004; Cowie et al. 2004; Gibson et al. 2002, 2005; Janson and Becker 1998; Korsch et al. 1968; Levy et al. 2000; Lindberg et al. 1999).

- Ask specifically about any concerns patients or parents have about medicines (e.g., safety, impact, convenience, and cost) (Bender and Bender 2005; Janson and Becker 1998; Leickly et al. 1998; Muntner et al. 2001; Yawn 2003).

- Assess the patient's and family's perceptions of the severity level of the disease and how well it is controlled. Beliefs that the asthma is not really severe have been shown to affect adherence adversely (Bender and Bender 2005; Muntner et al. 2001). Ask questions such as "How much danger do you believe you are in from your asthma?" Identifying patients who are overwhelmed by fear of death offers the opportunity to put their fears in perspective with the results of objective assessments and expert opinion. A written asthma action plan that directs the patient how to respond to worsening asthma (figure 3–10a, b, and c) may also be helpful in reducing anxiety and directing appropriate use of health care resources (Bender and Bender 2005; Janson-Bjerklie et al. 1992; Janz et al. 1984; Muntner et al. 2001).

- Assess the patient's and family's level of social support, and encourage family involvement. Ask "Who among your family or friends can you turn to for help if your asthma worsens?" Counsel patients to identify an asthma "partner" among their family or friends who is willing to be educated and provide support. Include at least one of these individuals in followup appointments with the patient so that he or she can hear what is expected of the patient in following the self-management and action plans (Graham et al. 1990).

- Assess levels of stress, family disruption, anxiety, and depression associated with asthma and asthma management. Although stress, anxiety, and depression do not cause asthma, they can make management more difficult (Busse et al. 1995) and can complicate an individual's attempts at self-management. Use tools to formally assess these conditions (USPSTF 2004) and, when appropriate, refer the patient to a psychologist, social worker, psychiatrist, or other licensed professional when stress seems to interfere unduly with daily asthma management. Referral to a local support group also may be useful.

- Assess ability to adhere to the written asthma action plan. Adherence to the action plan is enhanced when the plan is simplified, the number of medications and frequency of daily doses are minimized, the medication doses and frequency fit into the patient's and family's daily routine (Bender et al. 1998; Bender and Bender 2005; Clark et al. 1995; Eisen et al. 1990; Evans 1993; Haynes et al. 2005; Janson and Becker 1998; Meichenbaum and Turk 1987), and the plan considers the patient's ability to afford the medications (Bender and Bender 2005; Hindi-Alexander et al. 1987).

TAILOR EDUCATION TO THE NEEDS OF THE INDIVIDUAL PATIENT

The Expert Panel recommends that:

- **Asthma education interventions be tailored as much as possible to an individual's underlying knowledge and beliefs about the disease (Evidence C).**

- **Health care professionals who develop asthma education programs consider the needs of patients who have limited literacy (Evidence C).**

- **Clinicians consider assessing cultural or ethnic beliefs or practices that may influence self-management activities, and modify educational approaches as needed (Evidence C).**

Knowledge and Beliefs

People who have asthma have different levels of knowledge about the disease and diverse underlying asthma-related beliefs. African Americans and other minorities who have asthma often accept suboptimal levels of asthma control because they are not aware of the effect that proper asthma management can have on their quality of life. Incorrect underlying beliefs about asthma may constitute a major obstacle to adherence to daily anti-inflammatory therapy and other self-management behavior, and such beliefs thereby may contribute to poor asthma outcomes. Studies have highlighted the lack of appreciation, on the part of people who have asthma and/or their caregivers, of the importance of the use of ICSs on days when the asthma is asymptomatic. This behavior appears to be based on the belief that asthma is absent if overt asthma symptoms are absent, and therefore asthma medications are only necessary when an acute episode occurs (Halm et al. 2006; Riekert et al. 2003). Doubts about the usefulness of anti-inflammatory asthma medications and concerns about the long-term side effects of these medications also contribute to this pattern of behavior (George et al. 2003; Leickly et al. 1998; Mansour et al. 2000; Van Sickle and Wright 2001). Moreover, African Americans are significantly more likely than Caucasians to report distrust of the health care system (George et al. 2003; Halbert et al. 2006).

A recent study demonstrated how underlying beliefs about asthma may serve as an obstacle to adherence with daily anti-inflammatory therapy and other self-management behaviors in high-risk patients who have moderate or severe persistent asthma (Halm et al. 2006). This prospective, longitudinal, observational cohort study assessed disease beliefs and

self-management behaviors. In this group of low-income, high-risk, predominantly Latino and African American people, more than half of the persons who had asthma believed they have asthma only when they have symptoms. This “no symptoms, no asthma” belief was associated with one-third lower odds of adherence to ICS use when the asthma was asymptomatic. One study suggested that, if enough time is taken to explain the function and use of ICSs, adherence to therapy might be improved in African American patients who have asthma (Apter et al. 2003).

Another study demonstrated that education focusing on changing behavior, rather than providing information alone, improved quality of life. Perceived control of asthma and asthma-specific quality of life significantly improved after patients who have asthma completed a behavior modification-based asthma education program for adults. The authors concluded that assessment of perceived control of asthma may enable educators to target and tailor educational interventions for individuals who perceive a lack of control over their asthma and to monitor the effectiveness of asthma education (Olajos-Clow et al. 2005). Qualitative research is one important methodology for understanding the health beliefs and attitudes of patients and for formulating hypotheses for improving ICS adherence that can be tested in the future by using quantitative research methods (George et al. 2003).

Health Literacy

Nationally, almost one-quarter of the adult population cannot read and understand basic written material (Kirsh et al. 1993). Traditional patient education relies largely on printed materials that are often written at too high a level for patients who have a low level of literacy to read and adequately comprehend. Inadequate literacy is a barrier to asthma knowledge and self-care (Williams et al. 1998). Asthma education programs may not adequately reach those patients who suffer the greatest morbidity and mortality from asthma. Some asthma education strategies may not reach a large number of patients who have asthma and poor reading skills. Therefore, it is important that health education literature meet the readability standards (of 5th-grade level or lower) recommended by health education experts (Doak et al. 1996). Knowledge of asthma may affect health behaviors and disease outcomes. Patients need to understand proper health behaviors and acquire self-management skills. Correcting knowledge and behavior deficits through asthma instructional programs has been shown to be cost-effective (Neri et al. 1996) and to reduce physician visits and hospitalizations (Kelso et al. 1996; Patel et al. 2004).

Self-management skills and asthma knowledge are poorer among patients who have limited reading ability. In a cross-sectional survey, using multivariate analysis, a patient’s reading level was the strongest predictor of asthma knowledge score and the strongest predictor of skills in use of MDI (Williams et al. 1998). A prospective cohort study examined the relationship between inadequate health literacy and the capacity to learn and retain instructions about discharge medications and appropriate MDI technique. Before instruction, inadequate health literacy was associated with lower asthma medication knowledge and worse MDI technique; after instruction, it was demonstrated that inadequate health literacy was not associated with difficulty in learning or retaining instructions. This study demonstrated that tailored education can successfully overcome barriers related to inadequate health literacy and improve asthma self-management skills (Paasche-Orlow et al. 2005).

Overcoming the barrier of inadequate literacy may be facilitated by structuring asthma education programs for low literacy levels and by developing systematic approaches to tailor asthma education to patients. Additional studies are needed to determine whether tailored asthma education provided to vulnerable populations will result in long-term gains in asthma self-management.

Cultural/Ethnic Considerations

Cultural variables may affect patient understanding of and adherence to medical regimens (Kleinman et al. 1978; Pachter and Weller 1993). Moudgil and colleagues (2000) have suggested that using a culturally sensitive patient education approach directed toward altering attitudes and beliefs, as well as toward physical management of the disease is a more successful approach to improving asthma health outcomes. Improved understanding is needed concerning how ethnocultural practices, independent of socioeconomic variables, may influence asthma care and the use of health care services. Open-ended questions such as "In your community, what does having asthma mean?" can elicit informative responses. The culturally sensitive clinician should attempt to find ways to incorporate harmless or potentially beneficial remedies with the pharmacologic plan.

For example, a prevalent ethnocultural belief among the Latino population is that illnesses are either "hot" or "cold" (Pachter et al. 2002; Risser and Mazur 1995). Asthma is viewed as a "cold" illness amenable to "hot" treatment. Suggesting that asthma medications be taken with hot tea or hot water incorporates this belief into the therapeutic regimen and helps build the therapeutic partnership. In a study of Dominican Americans, most of the mothers of persons who had asthma used folk remedies called "zumos" instead of prescription medicines. These folk remedies were derived from their folk beliefs about health and illness. In this study, most of the mothers said that prescribed medications are overused in this country and that physicians hide therapeutic information from them (Bearison et al. 2002). It is important to be aware of potential barriers posed by ethnocultural beliefs within racial/ethnic minority communities about the practice of traditional Western medicine. When harmful home remedies are being used, clinicians should discourage their use by suggesting a culturally acceptable alternative as a replacement or recommending a safer route of administration (Pachter et al. 1995). These and other strategies may be useful in working with ethnic minorities (NHLBI 1995a).

Every effort should be made to discuss asthma care, especially the asthma action plan, in the patient's native language so that educational messages are fully understood. It is the opinion of the Expert Panel that, for some ethnic groups, the word "action" may require additional explanation to patients and their families when used in the context of a medical treatment plan. Research suggests that lack of language concordance between the clinician and the patient affects adherence and appropriate use of health care services (Manson 1988). Language is a significant barrier for Latinos seeking health care for asthma. In a study assessing risk factors for inadequate asthma therapy in children, the risk of receiving inadequate asthma therapy when Spanish was the preferred language was 1.4 times greater than if English was the preferred language (Halterman et al. 2000). In a study of Latinos attending an inner-city pediatric clinic, immigrant parents cited language as the greatest barrier to health care access for their children (Flores et al. 1998). Language barriers also may complicate the assessment of cultural differences. Often, medical interpreters are not used; when used, they sometimes lack formal training in this skill (Baker et al. 1996). If interpreters are used, they should be equally competent in both English and the patient's language as well as knowledgeable about medical terms (Woloshin et al. 1995).

MAINTAIN THE PARTNERSHIP

As part of ongoing care, the clinician should continue to build the partnership by being a sympathetic coach and by helping the patient follow the written asthma action plan and take other needed actions. Educational efforts should be continuous, because it may take up to 6 months for the effect of education to be evident (Gallefoss and Bakke 2001; Gibson et al. 2003; Toelle et al. 1993). Furthermore, it is necessary to review periodically the information and skills

covered previously, because patients' self-management behavior is likely to decline over time (Cote et al. 2001; Ries et al. 1995).

The Expert Panel recommends that clinicians demonstrate, review, evaluate, and correct inhaler technique and, if appropriate, the use of a VHC or spacer at each visit, because these skills can deteriorate rapidly (Evidence C). Written instructions are helpful (See figure 3–14.) but insufficient (Nimmo et al. 1993; Wilson et al. 1993). Research suggests that patients who use inhalers tend to make specific mistakes that need to be corrected (Hanania et al. 1994; Hesselink et al. 2004; Kesten et al. 1993; Larsen et al. 1994; Scarfone et al. 2002). Patients especially need to be reminded to inhale slowly, to activate the inhaler only *once* for each breath (Rau et al. 1996), and to use DPI devices correctly (Melani et al. 2004). Inhaler technique may be improved with educational interventions (Agertoft and Pedersen 1998; Hesselink et al. 2004).

The Expert Panel recommends that clinicians continue to promote open communication with the patient and family by addressing, as much as possible, the following elements in each followup visit (Evidence B unless otherwise noted) (See also figure 3–13.):

- **Continue asking patients early *in each visit* what concerns they have about their asthma and what they especially want addressed during the visit.**

- **Review the short-term goals agreed on in the initial visit.** Assess how well the goals are being achieved (e.g., was the patient's wish to engage in physical activity achieved?). Revise the goals as needed. Achievement of short-term goals should be discussed as indicators that the patient is moving toward long-term goals. Give positive verbal reinforcement for achievement of a goal, and recognize the patient's success in moving closer to full control of the disease (Clark et al. 1998, 2000; Evans et al. 1997).

- **Review the written asthma action plan and the steps the patient is to take. Adjust the plan as needed.** For example, give recommendations on how to use medicines if the dose or type is not working, and confirm that the patient knows what to do if his or her asthma gets worse. Identify other problems the patient has in following the agreed-on steps (e.g., disguising the bad taste of medicine). Treat these as areas that need more work, not as adherence failures (Clark et al. 1995, 1998, 2000).

- **Either encourage parents to take a copy of the child's written asthma action plan to the child's school or childcare setting, or obtain parental permission and send a copy to the school nurse or designee (Evidence C) (See figures 3–16a, b.).**

- **Continue teaching and reinforcing key educational messages (See figure 3–12.).** Provide information and teach skills over several visits so as not to overwhelm the patient with too much information at one time. Repeat important points often.

- **Give patients simple, brief, written materials that reinforce the actions recommended and skills taught (Gibson et al. 2000).** See "Asthma Education Resources" for a list of organizations that distribute patient education materials. Many of these organizations also have some Spanish-language materials.

FIGURE 3–16a. SCHOOL ASTHMA ACTION PLAN

Asthma and Allergy Foundation of America

STUDENT ASTHMA ACTION CARD

National Asthma Education and Prevention Program

Name: _____ Grade: _____ Age: _____

Homeroom Teacher: _____ Room: _____

Parent/Guardian Name: _____ Ph: (h): _____

Address: _____ Ph: (w): _____

Parent/Guardian Name: _____ Ph: (h): _____

Address: _____ Ph: (w): _____

ID Photo

Emergency Phone Contact #1 _____
Name Relationship Phone

Emergency Phone Contact #2 _____
Name Relationship Phone

Physician Treating Student for Asthma: _____ Ph: _____

Other Physician: _____ Ph: _____

EMERGENCY PLAN

Emergency action is necessary when the student has symptoms such as, _____ , _____, _____ , _____or has a peak flow reading of _____.

• Steps to take during an asthma episode:

1. Check peak flow.
2. Give medications as listed below. Student should respond to treatment in 15-20 minutes.
3. Contact parent/guardian if _____
4. Re-check peak flow.
5. Seek emergency medical care if the student has any of the following:
   - ✔ Coughs constantly
   - ✔ No improvement 15-20 minutes after initial treatment with medication and a relative cannot be reached.
   - ✔ Peak flow of _____
   - ✔ Hard time breathing with:
     - Chest and neck pulled in with breathing
     - Stooped body posture
     - Struggling or gasping
   - ✔ Trouble walking or talking
   - ✔ Stops playing and can't start activity again
   - ✔ Lips or fingernails are grey or blue

IF THIS HAPPENS, GET EMERGENCY HELP NOW!

• Emergency Asthma Medications

	Name	Amount	When to Use
1.			
2.			
3.			
4.			

See reverse for more instructions

Source: Reprint with permission from the Asthma and Allergy Foundation of America. Copyright © 2006 The Asthma and Allergy Foundation of America. For more information on asthma and allergies, visit http://www.aafa.org.

FIGURE 3–16a. SCHOOL ASTHMA ACTION PLAN (CONTINUED)

DAILY ASTHMA MANAGEMENT PLAN

- **Identify the things which start an asthma episode (Check each that applies to the student.)**

☐ Exercise
☐ Respiratory infections
☐ Change in temperature
☐ Animals
☐ Food _____
☐ Strong odors or fumes
☐ Chalk dust / dust
☐ Carpets in the room
☐ Pollens
☐ Molds
☐ Other _____

Comments _____

- **Control of School Environment**

(List any environmental control measures, pre-medications, and/or dietary restrictions that the student needs to prevent an asthma episode.) _____

- **Peak Flow Monitoring**

Personal Best Peak Flow number: _____

Monitoring Times: _____ _____ _____ _____

- **Daily Medication Plan**

	Name	Amount	When to Use
1.			
2.			
3.			
4.			

COMMENTS / SPECIAL INSTRUCTIONS

_____

FOR INHALED MEDICATIONS

☐ I have instructed _____ in the proper way to use his/her medications. It is my professional opinion that _____ should be allowed to carry and use that medication by him/herself.

☐ It is my professional opinion that _____ should not carry his/her inhaled medication by him/herself.

_____ Physician Signature _____ Date

_____ Parent/Guardian Signature _____ Date

AAFA • 1233 20th Street, N.W., Suite 402 , Washington, DC 20036 • www.aafa.org • 1-800-7-ASTHMA

02/00

Source: Reprint with permission from the Asthma and Allergy Foundation of America. Copyright © 2006 The Asthma and Allergy Foundation of America. For more information on asthma and allergies, visit http://www.aafa.org.

FIGURE 3–16b. SCHOOL ASTHMA ACTION PLAN

School Information

Asthma Action Plan for Schools and Families

Health Care Provider Information

Last Name: _____ First Name: _____

Date of Birth (mm/dd/yyyy): _____ Medical Record #: _____

School Name: _____ School Contact Phone #: _____

Parent/Guardian Name: _____ Parent/Guardian Phone #: _____

Emergency Contact: _____ **Emergency Phone #:** _____

Health Care Provider Name: _____ Health Care Provider Phone #: _____

To be completed by health care provider: **Asthma Severity:** ☐ Intermittent ☐ Mild Persistent ☐ Moderate Persistent ☐ Severe Persistent

Attention Parent/Guardian/School Personnel: ANY student with asthma (of any severity) can have a severe asthma attack.

Asthma symptoms are triggered by: ☐ Exercise ☐ Dust ☐ Animal dander ☐ Strong odors or fumes ☐ Mold ☐ _____

Green Zone **Personal Best Peak Flow (PF)** _____ Date: _____

Peak flow is between_____ (80% of personal best) and _____ (100% of personal best)

1. Take LONG-TERM-CONTROL medication(s) (at home) EVERY DAY:

Take _____ (Name of medicine) inhaler_____ (How much) puffs _____ (How often) times/day.

Take _____ (Name of medicine) inhaler _____ (How much) puffs _____ (How often) times/day.

If asthma is triggered by exercise (at school or home), take ☐ Albuterol or _____ (Name of medicine) inhaler_____ (How much) puffs at least _____ minutes before exercise. Restrictions or activity limitations: _____

Yellow Zone—Caution! **DO NOT LEAVE STUDENT ALONE!**

Peak flow is between_____ (50% of personal best) and _____ (80% of personal best).

1. Begin QUICK RELIEF medication (at school or home) right NOW:

Take ☐ Albuterol or _____ (Name of medicine) inhaler _____ (How much) puffs **OR** _____ (Name of medicine) solution _____ (How much) ml by nebulizer.

- If symptoms are better or if the peak flow is improved within ☐ 15 minutes/_____minutes, THEN repeat QUICK-RELIEF MEDICATION (as listed above in 1) every _____ (Number) hours for ____ (Number) days.
- If symptoms are **NOT** better or if the peak flow is **NOT** improved, go to Red Zone.

☐ **Attention School: Call Parent/Guardian when quick-relief medication has been administered by student and/or staff.**

2. Attention Parent/Guardian (Home Instructions):

☐ Call your child's Health Care Provider

☐ Continue to take LONG-TERM-CONTROL medication (at home) every day as written above in *Green Zone* instructions.

☐ Increase LONG-TERM-CONTROL medication:

Take _____ (Name of medicine) inhaler_____ (How much) puffs _____ (How often) times/day for _____ (Number) days.

Red Zone—Medical Alert! **Get Help! DO NOT LEAVE STUDENT ALONE! Peak flow is below**_____ (50% of personal best)

1. Take QUICK-RELIEF medication (at school or home) right NOW:

Take ☐ Albuterol or _____ (Name of medicine) inhaler _____ (How much) puffs **OR** _____ (Name of medicine) solution ____ (How much) ml by nebulizer and **REPEAT EVERY 20 MINUTES UNTIL PARAMEDICS ARRIVE!**

- **Call 9–1–1 immediately and call Parent/Guardian**

2. Attention Parent/Guardian (Home Instructions):

☐ Call your child's Health Care Provider. ☐ Continue CONTROLLER medication (at home):

Take _____ (Name of medicine) inhaler_____ (How much) puffs _____ (How often) times/day for _____ (Number) days.

☐ And ADD_____ (Name of medicine) _____ (How much) mg orally once daily for_____ (Number) days.

Authorization and Disclaimer from Parent/Guardian: I request that the school assist my child with the above asthma medications and the Asthma Action Plan in accordance with state laws and regulations. Yes ☐ No ☐

My child may carry and self-administer asthma medications and I agree to release the school district and school personnel from all claims of liability if my child suffers any adverse reactions from self-administration of asthma medications: Yes ☐ No ☐

_____ Parent/Guardian Signature _____ Date

Health Care Provider: My signature provides authorization for the above written orders. I understand that all procedures will be implemented in accordance with state laws and regulations. Student may carry and self-administer asthma medications: Yes ☐ No ☐ (This authorization is for a maximum of 1 year from signature date.)

_____ Health Care Provider Signature _____ Date

Reprint with permission from the Asthma and Allergy Foundation of America. ©2006 The Asthma and Allergy Foundation of America. For more information on asthma and allergies, visit http://www.aafa.org.

(Source: California Asthma Public Health Initiative, California Department of Public Health. http://www.cdph.ca.gov/healthinfo/discond/pages/asthma.aspx.)

ASTHMA EDUCATION RESOURCES

ALLERGY AND ASTHMA NETWORK **1–800–878–4403**
MOTHERS OF ASTHMATICS **1–703–641–9595**
2751 Prosperity Avenue, Suite 150
Fairfax, VA 22030
www.breatherville.org

AMERICAN ACADEMY OF ALLERGY, ASTHMA, AND IMMUNOLOGY **1–414–272–6071**
555 East Wells Street
Suite 1100
Milwaukee, WI 53202-3823
www.aaaai.org

AMERICAN ASSOCIATION FOR RESPIRATORY CARE **1–972–243–2272**
9125 North MacArthur Boulevard, Suite 100
Irving, TX 75063
www.aarc.org

AMERICAN COLLEGE OF ALLERGY, ASTHMA, **1–800–842–7777**
AND IMMUNOLOGY **1–847–427–1200**
85 West Algonquin Road, Suite 550
Arlington Heights, IL 60005
www.acaai.org

AMERICAN LUNG ASSOCIATION **1–800–586–4872**
61 Broadway
New York, NY 10006
www.lungusa.org

ASSOCIATION OF ASTHMA EDUCATORS **1–888–988–7747**
1215 Anthony Avenue
Columbia, SC 29201
www.asthmaeducators.org

ASTHMA AND ALLERGY FOUNDATION OF AMERICA **1–800–727–8462**
1233 20th Street, NW., Suite 402
Washington, DC 20036
www.aafa.org

CENTERS FOR DISEASE CONTROL AND PREVENTION **1–800–311–3435**
1600 Clifton Road
Atlanta, GA 30333
http://www.cdc.gov

FOOD ALLERGY & ANAPHYLAXIS NETWORK **1–800–929–4040**
11781 Lee Jackson Highway, Suite 160
Fairfax, VA 22033
www.foodallergy.org

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE **1–301–592–8573**
HEALTH INFORMATION CENTER
P.O. BOX 30105
Bethesda, MD 20824-0105
www.nhlbi.nih.gov

NATIONAL JEWISH MEDICAL AND RESEARCH CENTER **1–800–222–LUNG**
1400 Jackson Street
Denver, CO 80206
www.njc.org

U.S. ENVIRONMENTAL PROTECTION AGENCY **1–800–490-9198**
P.O. BOX 42419
Cincinnati, OH 45242-0419
www.airnow.gov

Provider Education

METHODS OF IMPROVING CLINICIAN BEHAVIORS

Implementing Guidelines—Recommended Practices

The Expert Panel recommends the use of multifaceted, clinician education programs that reinforce guidelines-based asthma care and are based on interactive learning strategies (Evidence B). (See Evidence Table 7, Methods for Improving Clinician Behaviors.)

In an attempt to improve and standardize the quality of care given to people with asthma, several studies have focused on methods of implementing guideline-based practice. This process of implementation is designed to change the behavior of clinicians. Eight RCTs and one trial's secondary analysis (Baker et al. 2003; Brown et al. 2004; Cabana et al. 2006; Clark et al. 2000; Finkelstein et al. 2005; Kattan et al. 2006; Lagerlov et al. 2000; White et al. 2004) show the variable effects of interventions designed to change clinicians' use of recommended asthma guidelines. Lagerlov and colleagues (2000) provided 199 general practitioners with two evening meetings, 1 week apart, lasting almost 3 hours each. At the first meeting, participants discussed how they diagnosed asthma and the treatment they prescribed. At the second meeting, guidelines were presented, and the group agreed on quality criteria for prescribing based on the guidelines. The educational sessions resulted in a small (6 percent) but statistically significant increase in the mean proportion of acceptably treated patients compared to controls. In peer groups of doctors, combining feedback about prescribing behavior along with guideline recommendations improved the quality of care of their patients who had asthma.

Clark and coworkers (2000) evaluated the long-term impact of an interactive seminar for pediatricians that focused on teaching and communication skills in managing asthma according to published guidelines. Two years after the intervention, physicians who attended the seminar were more likely than controls to deliver asthma education, supply patients with written directions for adjusting medications when symptoms change, and offer more guidance for modifying therapy. Children seen by physicians in the intervention group had fewer hospitalizations and ED visits. Notably, no differences were found between intervention physicians and controls in time they spent with patients at 1-year followup (Clark et al. 1998). In a reanalysis of the trial by Clark and coworkers, Brown and colleagues (2004) found the program was more effective for children in low-income families than children in families with greater income. Cabana and coworkers (2006) replicated the intervention by Clark and colleagues in a large RCT to test whether the seminar could be delivered effectively by local faculty trained by the investigators. One year postintervention, physicians who attended the seminar were more likely than physicians in the control group to ask about patients' concerns about asthma, to encourage patients to be more physically active, and set goals for successful treatment. Compared with patients in the control group, patients of physicians who attended the seminar had greater decreases in ED visits and in days with limited activity at 1-year followup (Cabana et al. 2006).

On the other hand, two trials of methods to increase use of guidelines (Baker et al. 2003; White et al. 2004) had negative results. In an RCT designed to impart techniques for teaching patients about their asthma, White and colleagues (2004) compared a standard didactic lecture for physicians to problem-based learning. Groups did not differ in knowledge gained, but problem-based learning was perceived to have more educational value than the lectures. Baker and coworkers (2003) showed that neither distribution of evidence-based guidelines alone, nor

presentation of guidelines in a prioritized format (with or without performance feedback), led to increased implementation of the guideline recommendations.

To promote use of asthma guidelines, Lozano and colleagues (2004) conducted a 2-year RCT of 422 primary care pediatric practices using two different asthma care improvement strategies. Peer leader education (training one physician per practice in asthma guidelines) was compared to peer leader education combined with nurse-driven organizational change through planned visits focused on assessment, care planning, and self-management support. Children in the planned care approach had significantly reduced symptoms and lower rates of oral steroid bursts, as well as greater adherence to controller medications. The comprehensive approach was an effective model for improving asthma care. A large, 1-year RCT (n = 937) aimed at inner-city PCPs working with 5- to 11-year-old children who had moderate or severe asthma evaluated the benefit of sending timely clinical information regarding the patient's asthma status in a single-page letter to the physicians in the intervention group. The computer-generated letter summarized the results of bimonthly telephone calls to the child's caretaker; provided information on the child's asthma symptoms, health service use, and medication use; and included a corresponding recommendation to step up or step down the child's medication. The letter served as a prompt to the clinician to change treatment. Children who were in the intervention group had significantly more scheduled preventative asthma visits, resulting in appropriate medication changes, and fewer ED visits and fewer school absences as compared with children who were controls (Kattan et al. 2006).

An observational study was conducted to see whether an organized citywide asthma-management program delivered by PCPs would increase adherence to the asthma guidelines (Cloutier et al. 2005). Among the 3,748 children enrolled in the disease-management program, prescriptions for ICS increased by providers' adherence to the guidelines, and overall hospitalization rates and ED visits decreased.

Finkelstein and coworkers (2005) randomized primary care practices to one of two care-improvement strategies—physician peer leaders alone or in combination with asthma education nurses—or to usual care. The primary outcome, prescription of at least one long-term-control medication, improved in all arms of the study, but there were no differences among groups overall except a slight increase in ambulatory visits for asthma.

Observational studies support the value of targeting physicians to participate in workshops. Rossiter and colleagues (2000) conducted a unique study in recruiting physicians to enroll in communication workshops using multimedia and adult learning techniques to improve communication skills. Hands-on workshops that included negotiating treatment plans for asthma were incorporated in the 6-hour sessions. Free continuing medical education, a discount on malpractice insurance, and free patient-education materials were used as incentives. Medicaid claims for ED care for asthma were reduced, with a marked increase in guideline-based asthma prescriptions. Doctors also got feedback reports identifying patients in need of followup because of poor asthma outcomes in terms of emergency room (ER) visits. However, only 33 percent of physicians from the community participated in the intervention.

Reasons for lack of adherence to guidelines were shown in an observational study (Cabana et al. 2001) that is enlightening on the barriers to pediatricians' adherence to asthma guidelines. Lack of time, lack of educational materials, lack of support staff, and lack of reimbursement were cited as major reasons for not adopting guidelines; notably, these are similar to reasons for patients' nonadherence. This study reinforces the need for multifaceted interventions to address characteristic barriers for each guideline component.

Taken together, these findings suggest that multifaceted clinician education programs based on interactive learning strategies (Cabana et al. 2006; Clark et al. 1998, 2000; Kattan et al. 2006; Lagerlov et al. 2000) can improve quality of care and patient outcomes. In the absence of multifaceted tailored interventions, a prioritized guideline format, with or without feedback, is unlikely to promote change in general practice care. However, it is acknowledged that practice-level interventions may have significant effects on subgroups of patients, but these effects are difficult to detect. More research is needed to understand how to increase adherence to guidelines and improved quality of care for asthma. From available evidence, multifaceted clinician education programs based on interactive learning strategies are a promising alternative to noninteractive educational sessions that provide information only.

Communication Techniques

The Expert Panel recommends that:

- **Clinicians consider participating in programs designed to enhance their skills in communicating with patients (Evidence B).**
- **Clinicians consider documenting communication and negotiated agreements between patients and clinicians during medical encounters and that the level of asthma control be documented in the medical record of a patient at every visit to facilitate communication with patients during subsequent visits (Evidence C).**
- **Communication skills-building programs include strategies to increase competence in caring for multicultural populations (Evidence D).**

The RCT reported on by Clark and colleagues (1998, 2000) and Brown and coworkers (2004) demonstrated that a physician education program could improve the communication skills of pediatricians caring for children and adolescents who have asthma and could result in improved patient outcomes. The program involved two educational sessions, each 2.5 hours long, and combined didactic sessions with interactive role playing. Bratton and coworkers (2006) have replicated this study in a population of physicians providing care to Medicaid patients. Data from providers indicate that the intervention improved providers' use of communication skills, efforts to counsel patients in self-management strategies, and provision of written asthma action plans (Bratton et al. 2006). The results among pediatricians suggest that physicians can be taught improved communication skills that enhance patient adherence as well as asthma self-management and control. Love and coworkers (2000) showed that continuity of clinicians' care can improve patient adherence and quality of life but not other outcomes. In qualitative work, Yawn (2003) reported that parents of children who have asthma were frustrated by lack of clear communication with health professionals, especially regarding changes in diagnosis, classification of asthma severity, and methods for asthma management.

In a slightly different variation of patient–health professional communication, Cabana and colleagues (2003, 2005) and Yawn (2004) have shown that the documentation of the content of medical visits for asthma, if not the actual communication that occurs at those visits, frequently lacks information that is necessary to assess either asthma severity or asthma control as well as current adherence to asthma therapy. These studies suggest a need to document patient–clinician communications that occur in the context of asthma care. Such documentation may improve the content of subsequent communication during asthma care visits.

Wondering whether asthma severity was documented in medical records and whether such documentation prompted actions, Cabana and colleagues (2003) conducted an observational review of outpatient pediatric medical records. Only 34 percent of charts showed documentation of asthma severity during the previous 2 years. Documentation of severity, when identified, was associated with use of written asthma action plans and documented asthma education. Documentation of severity appeared to be associated with markers of improved long-term management of asthma.

In a large, prospective cohort 1-year study of 1,663 children receiving Medicaid in five large, nonprofit health plans, Lieu and coworkers (2004) demonstrated that, at sites that promoted cultural competence combined with physician feedback and improved access to care, improved use of long-term control medications and better ratings of care, according to the parents, resulted.

METHODS OF IMPROVING SYSTEM SUPPORTS

Clinical Pathways

The Expert Panel recommends that clinical pathways be considered for the inpatient setting for patients who are admitted to hospital with asthma exacerbations (Evidence B).

Clinical pathways are tools, ideally based on clinical guidelines, that outline a sequence of evaluations and interventions to be carried out by clinicians for patients who have asthma. These pathways are designed to improve and maintain the quality of care while containing costs. Three studies described below reported the outcomes of implementing clinical pathways to guide patient care either in the ED or in the hospital setting.

In an RCT, Johnson and colleagues (2000) demonstrated that, for children hospitalized for asthma, a clinical pathway directed by nurses can safely and reliably wean children from acute treatments and thereby significantly decrease the length of hospitalizations, the cost associated with the hospital admission, and the overall amount of nebulized beta$_2$-agonist used.

In another RCT, directed at children 2–18 years of age presenting to the ED with acute asthma, Zorc and coworkers (2003) used a clinical pathway to improve followup with PCPs. They found, however that even when followup appointments with the PCP 3–5 days later were scheduled by the ED staff, there was no effect on ED return visits, missed school days, or use of long-term control medications in the 4 weeks after the initial ED visit. The only positive outcome identified was an increased likelihood that urban children who had asthma would keep their followup appointment with the PCP. However, only 29 percent of children in the intervention group saw their PCP within 5 days after their ED visit, as requested, compared to 23 percent in the control group. Overall, 63 percent in the intervention group saw a PCP within 4 weeks versus 44 percent in the control group. No information was provided about the reasons for missed followup visits. This study illustrates the difficulties in scheduling followup appointments after acute exacerbation as well as the problem of ensuring that patients go to PCPs as requested.

A recent observational study showed that education of general practitioners in an asthma clinical pathway for children who have persistent asthma decreased prescription rates of oral beta$_2$-agonists compared to rates prescribed by clinicians who were not educated in the pathway (Mitchell et al. 2005). Three other observational studies of pediatric patients show that implementation of an asthma clinical pathway may reduce hospital length of stay and costs

without increasing morbidity or rates of readmission (Kelly et al. 2000; McDowell et al. 1998; Wazeka et al. 2001).

These studies show mixed results for the effectiveness of clinical pathways, depending on the outcomes chosen and the setting.

Clinical Decision Supports

The Expert Panel recommends that:

- **Prompts encouraging guideline-based care be integrated into system-based interventions focused on improving the overall quality of care rather than used as a single intervention strategy (Evidence B).**

- **System-based interventions that address multiple dimensions of the organization and delivery of care and clinical decision support be considered to improve and maintain quality of care for patients who have asthma (Evidence B and C).**

(See Evidence Table 8, Methods for Improving Systems Support.)

Some investigators have studied the use of computer-based prompts to encourage the use of guidelines in asthma management. McCowan and colleagues (2001) conducted an RCT of a software decision-support system to prompt use of asthma guidelines. The system had a positive effect resulting in reduction of exacerbations in patients whose physicians used the system, but the system had no effect on reported symptoms, physicians' prescribing of long-term-control medications, or use of hospital services by patients. In another RCT (Tierney et al. 2005), care suggestions were delivered by computerized prompts to physicians and pharmacists in the intervention group. The prompts did not result in improved medication adherence, quality of life, patient satisfaction with care, ED visits, or hospitalizations. Intervention physicians had higher health care costs for asthma care of their patients, but care suggestions had no effect on the delivery or the outcomes of care. The results of these two trials suggest that, although the use of computerized prompts is intuitively appealing, there is insufficient evidence that prompts result in improved asthma care.

In a retrospective analysis of administrative claims data, Dombkowski and colleagues (2005) found that adherence to national asthma guidelines varied widely among health care plans covering 3,970 children who had persistent asthma and were enrolled in Medicaid. After low-income families who had children who had asthma enrolled in a statewide insurance plan, Szilagyi and coworkers (2006) interviewed parents at baseline and 1 year later. They found improvements in access to care and a decrease in asthma exacerbations and hospitalizations for the enrolled children. Quality of asthma care improved for most general measures. Taken together, these observational studies suggest opportunities for population-based health care plan interventions to improve access and quality of asthma care.

In one RCT, Lozano and colleagues (2004) demonstrated that multidimensional system-based interventions improved patient outcomes. Observational analysis (Patel et al. 2004) of a large database of 3,400 patients who had asthma and were in a medical group practice that initiated a multidisciplinary asthma disease-management program showed that the program worked in several, but not all, areas: documentation of diagnoses and patient education improved, and ED visits and hospitalizations were reduced. A multidimensional approach, utilizing all staff to assist in implementation of the program, was an important part of the intervention. The key to

clinicians' ownership of the program included having clinicians lead the design process, using physician champions who had both formal and informal influence, and using rewards and recognition. In a comprehensive program to restructure health care delivery for all patients who had asthma, one large organization serving children instituted a systemwide restructured plan, including a new inpatient unit, standardized treatment protocol, direct admission policies for PCPs with optional specialist consultation, and use of case managers to help families address barriers to care and facilitate adherence (Evans et al. 1999b). The restructured program resulted in significant reductions in ED visits and length of hospital stays, as well as fewer readmissions to the hospital, while maintaining high quality of care and parental satisfaction with care.

Taken together, these system-based interventions for large populations of low-income children and adults who have asthma demonstrate effectiveness in improving quality of care and reducing use of health resources. Compared to provider-dependent strategies, these systemwide interventions may be more likely to result in consistent improved health outcomes for large populations of patients who have asthma.

References

Abramson MJ, Bailey MJ, Couper FJ, Driver JS, Drummer OH, Forbes AB, McNeil JJ, Haydn WE; Victorian Asthma Mortality Study Group. Are asthma medications and management related to deaths from asthma? *Am J Respir Crit Care Med* 2001;163(1):12–8.

Adams RJ, Boath K, Homan S, Campbell DA, Ruffin RE. A randomized trial of peak-flow and symptom-based action plans in adults with moderate-to-severe asthma. *Respirology* 2001;6(4):297–304.

Adams RJ, Weiss ST, Fuhlbrigge A. How and by whom care is delivered influences anti-inflammatory use in asthma: results of a national population survey. *J Allergy Clin Immunol* 2003;112(2):445–50.

Agabiti N, Mallone S, Forastiere F, Corbo GM, Ferro S, Renzoni E, Sestini P, Rusconi F, Ciccone G, Viegi G, et al. The impact of parental smoking on asthma and wheezing. SIDRIA Collaborative Group. Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente. *Epidemiology* 1999;10(6):692–8.

Agertoft L, Pedersen S. Importance of training for correct Turbuhaler use in preschool children. *Acta Paediatr* 1998;87(8):842–7.

Apter AJ, Boston RC, George M, Norfleet AL, Tenhave T, Coyne JC, Birck K, Reisine ST, Cucchiara AJ, Feldman HI. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. *J Allergy Clin Immunol* 2003;111(6):1219–26.

Baker DW, Parker RM, Williams MV, Coates WC, Pitkin K. Use and effectiveness of interpreters in an emergency department. *JAMA* 1996;275(10):783–8.

Baker R, Fraser RC, Stone M, Lambert P, Stevenson K, Shiels C. Randomised controlled trial of the impact of guidelines, prioritized review criteria and feedback on implementation of recommendations for angina and asthma. *Br J Gen Pract* 2003;53(489):284–91.

Baldwin DR, Pathak UA, King R, Vase BC, Pantin CFA. Outcome of asthmatics attending asthma clinics utilizing self-management plans in general practice. *Asthma in General Practice* 1997;5:31–2.

Barbanel D, Eldridge S, Griffiths C. Can a self-management programme delivered by a community pharmacist improve asthma control? A randomised trial. *Thorax* 2003;58(10):851–4.

Baren JM, Boudreaux ED, Brenner BE, Cydulka RK, Rowe BH, Clark S, Camargo CA Jr. Randomized controlled trial of emergency department interventions to improve primary care follow-up for patients with acute asthma. *Chest* 2006;129(2):257–65.

Baren JM, Shofer FS, Ivey B, Reinhard S, DeGeus J, Stahmer SA, Panettieri R, Hollander JE. A randomized, controlled trial of a simple emergency department intervention to improve the rate of primary care follow-up for patients with acute asthma exacerbations. *Ann Emerg Med* 2001;38(2):115–22.

Bartholomew LK, Gold RS, Parcel GS, Czyzewski DI, Sockrider MM, Fernandez M, Shegog R, Swank P. Watch, Discover, Think, and Act: evaluation of computer-assisted instruction to improve asthma self-management in inner-city children. *Patient Educ Couns* 2000;39(2–3):269–80.

Basheti IA, Reddel HK, Armour CL, Bosnic-Anticevich SZ. Counseling about turbuhaler technique: needs assessment and effective strategies for community pharmacists. *Respir Care* 2005;50(5):617–23.

Bearison DJ, Minian N, Granowetter L. Medical management of asthma and folk medicine in a Hispanic community. *J Pediatr Psychol* 2002;27(4):385–92.

Bender B, Milgrom H, Rand C, Ackerson L. Psychological factors associated with medication nonadherence in asthmatic children. *J Asthma* 1998;35(4):347–53.

Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am* 2005;25(1):107–30.

Bolton MB, Tilley BC, Kuder J, Reeves T, Schultz LR. The cost and effectiveness of an education program for adults who have asthma. *J Gen Intern Med* 1991;6(5):401–7.

Bonner S, Zimmerman BJ, Evans D, Irigoyen M, Resnick D, Mellins RB. An individualized intervention to improve asthma management among urban Latino and African-American families. *J Asthma* 2002;39(2):167–79.

Boulet LP, Belanger M, Lajoie P. Characteristics of subjects with a high frequency of emergency visits for asthma. *Am J Emerg Med* 1996;14(7):623–8.

Bratton SL, Cabana MD, Brown RW, White DF, Wang Y, Lang SW, Clark NM. Asthma educational seminar targeting Medicaid providers. *Respir Care* 2006;51(1):49–55.

Brown JV, Bakeman R, Celano MP, Demi AS, Kobrynski L, Wilson SR. Home-based asthma education of young low-income children and their families. *J Pediatr Psychol* 2002;27(8):677–88.

Brown R, Bratton SL, Cabana MD, Kaciroti N, Clark NM. Physician asthma education program improves outcomes for children of low-income families. *Chest* 2004;126(2):369–74.

Bryant-Stephens T, Li Y. Community asthma education program for parents of urban asthmatic children. *J Natl Med Assoc* 2004;96(7):954–60.

Busse WW, Kiecolt-Glaser JK, Coe C, Martin RJ, Weiss ST, Parker SR. NHLBI Workshop summary. Stress and asthma. *Am J Respir Crit Care Med* 1995;151(1):249–52. Review.

Butz A, Pham L, Lewis L, Lewis C, Hill K, Walker J, Winkelstein M. Rural children with asthma: impact of a parent and child asthma education program. *J Asthma* 2005;42(10):813–21.

Bynum A, Hopkins D, Thomas A, Copeland N, Irwin C. The effect of telepharmacy counseling on metered-dose inhaler technique among adolescents with asthma in rural Arkansas. *Telemed J E Health* 2001;7(3):207–17.

Cabana MD, Bruckman D, Meister K, Bradley JF, Clark N. Documentation of asthma severity in pediatric outpatient clinics. *Clin Pediatr (Phila)* 2003;42(2):121–5.

Cabana MD, Rand CS, Becher OJ, Rubin HR. Reasons for pediatrician nonadherence to asthma guidelines. *Arch Pediatr Adolesc Med* 2001;155(9):1057–62.

Cabana MD, Slish KK, Evans D, Mellins RB, Brown RW, Lin X, Kaciroti N, Clark NM. Impact of physician asthma care education on patient outcomes. *Pediatrics* 2006;117(6):2149–57.

Cabana MD, Slish KK, Nan B, Lin X, Clark NM. Asking the correct questions to assess asthma symptoms. *Clin Pediatr (Phila)* 2005;44(4):319–25.

California Department of Public Health. 2004. California Asthma Public Health Initiative. Asthma Action Plan for Schools and Families. Available at: http://www.cdph.ca.gov/healthinfo/discond/pages/asthma.aspx.

Carter MC, Perzanowski MS, Raymond A, Platts-Mills TA. Home intervention in the treatment of asthma among inner-city children. *J Allergy Clin Immunol* 2001;108(5):732–7.

Castro M, Zimmermann NA, Crocker S, Bradley J, Leven C, Schechtman KB. Asthma intervention program prevents readmissions in high healthcare users. *Am J Respir Crit Care Med* 2003;168(9):1095–9. Epub June 2003.

Cheng NG, Browne GJ, Lam LT, Yeoh R, Oomens M. Spacer compliance after discharge following a mild to moderate asthma attack. *Arch Dis Child* 2002;87(4):302–5.

Chernoff RG, Ireys HT, DeVet KA, Kim YJ. A randomized, controlled trial of a community-based support program for families of children with chronic illness: pediatric outcomes. *Arch Pediatr Adolesc Med* 2002;156(6):533–9.

Christiansen SC, Martin SB, Schleicher NC, Koziol JA, Mathews KP, Zuraw BL. Evaluation of a school-based asthma education program for inner-city children. *J Allergy Clin Immunol* 1997;100(5):613–7.

Cicutto L, Murphy S, Coutts D, O'Rourke J, Lang G, Chapman C, Coates P. Breaking the access barrier: evaluating an asthma center's efforts to provide education to children with asthma in schools. *Chest* 2005;128(4):1928–35.

Clark NM, Brown R, Joseph CL, Anderson EW, Liu M, Valerio MA. Effects of a comprehensive school-based asthma program on symptoms, parent management, grades, and absenteeism. *Chest* 2004;125(5):1674–9.

Clark NM, Gong M, Schork MA, Evans D, Roloff D, Hurwitz M, Maiman L, Mellins RB. Impact of education for physicians on patient outcomes. *Pediatrics* 1998;101(5):831–6.

Clark NM, Gong M, Schork MA, Kaciroti N, Evans D, Roloff D, Hurwitz M, Maiman LA, Mellins RB. Long-term effects of asthma education for physicians on patient satisfaction and use of health services. *Eur Respir J* 2000;16(1):15–21.

Clark NM, Nothwehr F, Gong M, Evans D, Maiman LA, Hurwitz ME, Roloff D, Mellins RB. Physician-patient partnership in managing chronic illness. *Acad Med* 1995;70(11):957–9.

Cloutier MM, Hall CB, Wakefield DB, Bailit H. Use of asthma guidelines by primary care providers to reduce hospitalizations and emergency department visits in poor, minority, urban children. *J Pediatr* 2005;146(5):591–7.

Colland VT, Essen-Zandvliet LE, Lans C, Denteneer A, Westers P, Brackel HJ. Poor adherence to self-medication instructions in children with asthma and their parents. *Patient Educ Couns* 2004;55(3):416–21.

Cordina M, McElnay JC, Hughes CM. Assessment of a community pharmacy-based program for patients with asthma. *Pharmacotherapy* 2001;21(10):1196–203.

Cote J, Bowie DM, Robichaud P, Parent JG, Battisti L, Boulet LP. Evaluation of two different educational interventions for adult patients consulting with an acute asthma exacerbation. *Am J Respir Crit Care Med* 2001;163(6):1415–9.

Couturaud F, Proust A, Frachon I, Dewitte JD, Oger E, Quiot JJ, Leroyer C. Education and self-management: a one-year randomized trial in stable adult asthmatic patients. *J Asthma* 2002;39(6):493–500.

Cowie RL, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. *Chest* 1997;112(6):1534–8.

Cowie RL, Underwood MF, Field SK. Inhaled corticosteroid therapy does not control asthma. *Can Respir J* 2004;11(8):555–8.

Cowie RL, Underwood MF, Little CB, Mitchell I, Spier S, Ford GT. Asthma in adolescents: a randomized, controlled trial of an asthma program for adolescents and young adults with severe asthma. *Can Respir J* 2002;9(4):253–9.

Custovic A, Simpson BM, Simpson A, Hallam C, Craven M, Brutsche M, Woodcock A. Manchester Asthma and Allergy Study: low-allergen environment can be achieved and maintained during pregnancy and in early life. *J Allergy Clin Immunol* 2000;105(2 Pt 1):252–8.

Delaronde S. Using case management to increase antiinflammatory medication use among a managed care population with asthma. *J Asthma* 2002;39(1):55–63.

Delaronde S, Peruccio DL, Bauer BJ. Improving asthma treatment in a managed care population. *Am J Manag Care* 2005;11(6):361–8.

Doak CC, Doak LG, Root JH. *Teaching Patients With Low Literacy.* 2nd ed. Philadelphia: Lippincott, 1996.

Dombkowski KJ, Cabana MD, Cohn LM, Gebremariam A, Clark SJ. Geographic variation of asthma quality measures within and between health plans. *Am J Manag Care* 2005;11(12):765–72.

Eggleston PA, Butz A, Rand C, Curtin-Brosnan J, Kanchanaraksa S, Swartz L, Breysse P, Buckley T, Diette G, Merriman B, et al. Home environmental intervention in inner-city asthma: a randomized controlled clinical trial. *Ann Allergy Asthma Immunol* 2005;95(6):518–24.

Eid N, Yandell B, Howell L, Eddy M, Sheikh S. Can peak expiratory flow predict airflow obstruction in children with asthma? *Pediatrics* 2000;105(2):354–8.

Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990;150(9):1881–4.

Eisner MD. Environmental tobacco smoke exposure and pulmonary function among adults in NHANES III: impact on the general population and adults with current asthma. *Environ Health Perspect* 2002;110(8):765–70.

Eisner MD, Klein J, Hammond SK, Koren G, Lactao G, Iribarren C. Directly measured second hand smoke exposure and asthma health outcomes. *Thorax* 2005;60(10):814–21.

Emond SD, Reed CR, Graff LG IV, Clark S, Camargo CA Jr. Asthma education in the Emergency Department. On behalf of the MARC Investigators. *Ann Emerg Med* 2000;36(3):204–11.

EPR. Expert panel report: guidelines for the diagnosis and management of asthma (EPR 1991). NIH Publication No. 91-3642. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1991.

EPR—2. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

EPR—Update 2002. Expert panel report: guidelines for the diagnosis and management of asthma. Update on Selected Topics 2002 (EPR—Update 2002). NIH Publication No. 02-5074. Bethesda, MD, U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003.

Evans D. To help patients control asthma the clinician must be a good listener and teacher. *Thorax* 1993;48(7):685–7.

Evans D, Clark NM, Levison MJ, Levin B, Mellins RB. Can children teach their parents about asthma? *Health Educ Behav* 2001;28(4):500–11.

Evans D, Mellins R, Lobach K, Ramos-Bonoan C, Pinkett-Heller M, Wiesemann S, Klein I, Donahue C, Burke D, Levison M, et al. Improving care for minority children with asthma: professional education in public health clinics. *Pediatrics* 1997;99(2):157–64.

Evans R III, Gergen PJ, Mitchell H, Kattan M, Kercsmar C, Crain E, Anderson J, Eggleston P, Malveaux FJ, Wedner HJ. A randomized clinical trial to reduce asthma morbidity among inner-city children: results of the National Cooperative Inner-City Asthma Study. *J Pediatr* 1999a;135(3):332–8.

Evans R III, LeBailly S, Gordon KK, Sawyer A, Christoffel KK, Pearce B. Restructuring asthma care in a hospital setting to improve outcomes. *Chest* 1999b;116(4 Suppl 1):210S–6S.

Finkelstein JA, Lozano P, Fuhlbrigge AL, Carey VJ, Inui TS, Soumerai SB, Sullivan SD, Wagner EH, Weiss ST, Weiss KB; Pediatric Asthma Care Patient Outcomes Research Team. Practice-level effects of interventions to improve asthma care in primary care settings: the Pediatric Asthma Care Patient Outcomes Research Team. *Health Serv Res* 2005;40(6 Pt 1):1737–57.

Fisher EB, Strunk RC, Sussman LK, Sykes RK, Walker MS. Community organization to reduce the need for acute care for asthma among African American children in low-income neighborhoods: the Neighborhood Asthma Coalition. *Pediatrics* 2004;114(1):116–23.

Flores G, Abreu M, Olivar MA, Kastner B. Access barriers to health care for Latino children. *Arch Pediatr Adolesc Med* 1998;152(11):1119–25.

Ford ME, Havstad SL, Tilley BC, Bolton MB. Health outcomes among African American and Caucasian adults following a randomized trial of an asthma education program. *Ethn Health* 1997;2(4):329–39.

Gallefoss F, Bakke PS. Cost-effectiveness of self-management in asthmatics: a 1-yr follow-up randomized, controlled trial. *Eur Respir J* 2001;17(2):206–13.

George M, Freedman TG, Norfleet AL, Feldman HI, Apter AJ. Qualitative research-enhanced understanding of patients' beliefs: results of focus groups with low-income, urban, African American adults with asthma. *J Allergy Clin Immunol* 2003;111(5):967–73.

George MR, O'Dowd LC, Martin I, Lindell KO, Whitney F, Jones M, Ramondo T, Walsh L, Grissinger J, Hansen-Flaschen J, et al. A comprehensive educational program improves clinical outcome measures in inner-city patients with asthma. *Arch Intern Med* 1999;159(15):1710–6.

Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD. The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics* 1998;101(2):E8.

Gervais P, Larouche I, Blais L, Fillion A, Beauchesne MF. Asthma management at discharge from the emergency department: a descriptive study. *Can Respir J* 2005;12(4):219–22.

Gibson PG, Coughlan J, Wilson AJ, Abramson M, Bauman A, Hensley MJ, Walters EH. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 2000;(2):CD001117.

Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, Bauman A, Hensley MJ, Walters EH. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 2003;(1):CD001117.

Gibson PG, Powell H, Coughlan J, Wilson AJ, Hensley MJ, Abramson M, Bauman A, Walters EH. Limited (information only) patient education programs for adults with asthma. *Cochrane Database Syst Rev* 2002;(2):CD001005.

Gibson PG, Powell H, Ducharme F. Long-acting beta$_2$-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005;(4):CD005076.

Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001;163(2):429–36.

Graham NM, Woodward AJ, Ryan P, Douglas RM. Acute respiratory illness in Adelaide children. II: The relationship of maternal stress, social supports and family functioning. *Int J Epidemiol* 1990;19(4):937–44.

Greineder DK, Loane KC, Parks P. A randomized controlled trial of a pediatric asthma outreach program. *J Allergy Clin Immunol* 1999;103(3 Pt 1):436–40.

Griswold SK, Nordstrom CR, Clark S, Gaeta TJ, Price ML, Camargo CA Jr. Asthma exacerbations in North American adults: who are the "frequent fliers" in the emergency department? *Chest* 2005;127(5):1579–86.

Guendelman S, Meade K, Benson M, Chen YQ, Samuels S. Improving asthma outcomes and self-management behaviors of inner-city children: a randomized trial of the Health Buddy interactive device and an asthma diary. *Arch Pediatr Adolesc Med* 2002;156(2):114–120.

Guevara JP, Wolf FM, Grum CM, Clark NM. Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. *BMJ* 2003;326(7402):1308–9.

Haby MM, Waters E, Robertson CF, Gibson PG, Ducharme FM. Interventions for educating children who have attended the emergency room for asthma. *Cochrane Database Syst Rev* 2001;(1):CD001290.

Halbert CH, Armstrong K, Gandy OH Jr, Shaker L. Racial differences in trust in health care providers. *Arch Intern Med* 2006;166(8):896–901.

Halm EA, Mora P, Leventhal H. No symptoms, no asthma: the acute episodic disease belief is associated with poor self-management among inner-city adults with persistent asthma. *Chest* 2006;129(3):573–80.

Halterman JS, Aligne CA, Auinger P, McBride JT, Szilagyi PG. Inadequate therapy for asthma among children in the United States. *Pediatrics* 2000;105(1 Pt 3):272–6.

Halterman JS, McConnochie KM, Conn KM, Yoos HL, Callahan PM, Neely TL, Szilagyi PG. A randomized trial of primary care provider prompting to enhance preventive asthma therapy. *Arch Pediatr Adolesc Med* 2005;159(5):422–7.

Hanania NA, Wittman R, Kesten S, Chapman KR. Medical personnel's knowledge of and ability to use inhaling devices. Metered-dose inhalers, spacing chambers, and breath-actuated dry powder inhalers. *Chest* 1994;105(1):111–6.

Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. *Cochrane Database Syst Rev* 2005;(4):CD000011. Review.

Henry RL, Gibson PG, Vimpani GV, Francis JL, Hazell J. Randomized controlled trial of a teacher-led asthma education program. *Pediatr Pulmonol* 2004;38(6):434–42.

Hesselink AE, Penninx BW, van der Windt DA, van Duin BJ, de Vries P, Twisk JW, Bouter LM, van Eijk JT. Effectiveness of an education programme by a general practice assistant for asthma and COPD patients: results from a randomised controlled trial. *Patient Educ Couns* 2004;55(1):121–8.

Hindi-Alexander MC, Throm J, Middleton E Jr. Collaborative asthma self-management. Evaluation designs. *Clin Rev Allergy* 1987;5(3):249–58. Review.

Homer C, Susskind O, Alpert HR, Owusu M, Schneider L, Rappaport LA, Rubin DH. An evaluation of an innovative multimedia educational software program for asthma management: report of a randomized, controlled trial. *Pediatrics* 2000;106(1 Pt 2):210–5.

Hopman WM, Garvey N, Olajos-Clow J, White-Markham A, Lougheed MD. Outcomes of asthma education: results of a multisite evaluation. *Can Respir J* 2004;11(4):291–7.

Hughes DM, McLeod M, Garner B, Goldbloom RB. Controlled trial of a home and ambulatory program for asthmatic children. *Pediatrics* 1991;87(1):54–61.

Huss K, Winkelstein M, Nanda J, Naumann PL, Sloand ED, Huss RW. Computer game for inner-city children does not improve asthma outcomes. *J Pediatr Health Care* 2003;17(2):72–8.

Infante-Rivard C, Gautrin D, Malo JL, Suissa S. Maternal smoking and childhood asthma. *Am J Epidemiol* 1999;150(5):528–31.

Janson S, Becker G. Reasons for delay in seeking treatment for acute asthma: the patient's perspective. *J Asthma* 1998;35(5):427–35.

Janson S, Hardie G, Fahy J, Boushey H. Use of biological markers of airway inflammation to detect the efficacy of nurse-delivered asthma education. *Heart Lung* 2001;30(1):39–46.

Janson SL, Fahy JV, Covington JK, Paul SM, Gold WM, Boushey HA. Effects of individual self-management education on clinical, biological, and adherence outcomes in asthma. *Am J Med* 2003;115(8):620–6.

Janson-Bjerklie S, Ferketich S, Benner P, Becker G. Clinical markers of asthma severity and risk: importance of subjective as well as objective factors. *Heart Lung* 1992;21(3):265–72.

Janz NK, Becker MH, Hartman PE. Contingency contracting to enhance patient compliance: a review. *Patient Educ Couns* 1984;5(4):165–78.

Johnson KB, Blaisdell CJ, Walker A, Eggleston P. Effectiveness of a clinical pathway for inpatient asthma management. *Pediatrics* 2000;106(5):1006–12.

Jones JA, Wahlgren DR, Meltzer SB, Meltzer EO, Clark NM, Hovell MF. Increasing asthma knowledge and changing home environments for Latino families with asthmatic children. *Patient Educ Couns* 2001;42(1):67–79.

Jones KP, Mullee MA, Middleton M, Chapman E, Holgate ST. Peak flow based asthma self-management: a randomised controlled study in general practice. British Thoracic Society Research Committee. *Thorax* 1995;50(8):851–7.

Joseph CL, Havstad S, Anderson EW, Brown R, Johnson CC, Clark NM. Effect of asthma intervention on children with undiagnosed asthma. *J Pediatr* 2005;146(1):96–104.

Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. *Thorax* 2001;56(3):180–2.

Kamps AW, Roorda RJ, Kimpen JL, Overgoor-van de Groes AW, van Helsdingen-Peek LC, Brand PL. Impact of nurse-led outpatient management of children with asthma on healthcare resource utilisation and costs. *Eur Respir J* 2004;23(2):304–9.

Kattan M, Crain EF, Steinbach S, Visness CM, Walter M, Stout JW, Evans R III, Smartt E, Gruchalla RS, Morgan WJ, et al. A randomized clinical trial of clinician feedback to improve quality of care for inner-city children with asthma. *Pediatrics* 2006;117(6):e1095–e1103.

Kattan M, Mitchell H, Eggleston P, Gergen P, Crain E, Redline S, Weiss K, Evans R III, Kaslow R, Kercsmar C, et al. Characteristics of inner-city children with asthma: the National Cooperative Inner-City Asthma Study. *Pediatr Pulmonol* 1997;24(4):253–62.

Kauppinen R, Sintonen H, Vilkka V, Tukiainen H. Long-term (3-year) economic evaluation of intensive patient education for self-management during the first year in new asthmatics. *Respir Med* 1999;93(4):283–9.

Kelly CS, Andersen CL, Pestian JP, Wenger AD, Finch AB, Strope GL, Luckstead EF. Improved outcomes for hospitalized asthmatic children using a clinical pathway. *Ann Allergy Asthma Immunol* 2000;84(5):509–16.

Kelso TM, Abou-Shala N, Heilker GM, Arheart KL, Portner TS, Self TH. Comprehensive long-term management program for asthma: effect on outcomes in adult African-Americans. *Am J Med Sci* 1996;311(6):272–80.

Kelso TM, Self TH, Rumbak MJ, Stephens MA, Garrett W, Arheart KL. Educational and long-term therapeutic intervention in the ED: effect on outcomes in adult indigent minority asthmatics. *Am J Emerg Med* 1995;13(6):632–7.

Kesten S, Zive K, Chapman KR. Pharmacist knowledge and ability to use inhaled medication delivery systems. *Chest* 1993;104(6):1737–42.

Khan MS, O'Meara M, Stevermuer TL, Henry RL. Randomized controlled trial of asthma education after discharge from an emergency department. *J Paediatr Child Health* 2004;40(12):674–7.

Kirsh I, Juneblut A, Jenkins L, Kolstad A. Adult literacy in america: a first look at the results of the national adult literacy survey. Washington, DC: U.S. Department of Education, National Center for Education Statistics, 1993.

Klein JJ, van der Palen J, Uil SM, Zielhuis GA, Seydel ER, van Herwaarden CL. Benefit from the inclusion of self-treatment guidelines to a self-management programme for adults with asthma. *Eur Respir J* 2001;17(3):386–94.

Kleinman A, Eisenberg L, Good B. Culture, illness, and care: clinical lessons from anthropologic and cross-cultural research. *Ann Intern Med* 1978;88(2):251–8.

Klinnert MD, Liu AH, Pearson MR, Ellison MC, Budhiraja N, Robinson JL. Short-term impact of a randomized multifaceted intervention for wheezing infants in low-income families. *Arch Pediatr Adolesc Med* 2005;159(1):75–82.

Korsch BM, Gozzi EK, Francis V. Gaps in doctor-patient communication. 1. Doctor-patient interaction and patient satisfaction. *Pediatrics* 1968;42(5):855–71.

Krieger JW, Takaro TK, Song L, Weaver M. The Seattle-King County Healthy Homes Project: a randomized, controlled trial of a community health worker intervention to decrease exposure to indoor asthma triggers. *Am J Public Health* 2005;95(4):652–9.

Krishna S, Francisco BD, Balas EA, Konig P, Graff GR, Madsen RW. Internet-enabled interactive multimedia asthma education program: a randomized trial. *Pediatrics* 2003;111(3):503–10.

La Roche MJ, Koinis-Mitchell D, Gualdron L. A culturally competent asthma management intervention: a randomized controlled pilot study. *Ann Allergy Asthma Immunol* 2006;96(1):80–5.

Lagerlov P, Loeb M, Andrew M, Hjortdahl P. Improving doctors' prescribing behaviour through reflection on guidelines and prescription feedback: a randomised controlled study. *Qual Health Care* 2000;9(3):159–65.

Lahdensuo A, Haahtela T, Herrala J, Kava T, Kiviranta K, Kuusisto P, Peramaki E, Poussa T, Saarelainen S, Svahn T. Randomised comparison of guided self management and traditional treatment of asthma over one year. *BMJ* 1996;312(7033):748–52.

Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. *J Asthma* 1994;31(3):193–9.

Leickly FE, Wade SL, Crain E, Kruszon-Moran D, Wright EC, Evans R III. Self-reported adherence, management behavior, and barriers to care after an emergency department visit by inner city children with asthma. *Pediatrics* 1998;101(5):E8.

Levy ML, Robb M, Allen J, Doherty C, Bland JM, Winter RJ. A randomized controlled evaluation of specialist nurse education following accident and emergency department attendance for acute asthma. *Respir Med* 2000;94(9):900–8.

Lieu TA, Finkelstein JA, Lozano P, Capra AM, Chi FW, Jensvold N, Quesenberry CP, Farber HJ. Cultural competence policies and other predictors of asthma care quality for Medicaid-insured children. *Pediatrics* 2004;114(1):e102–e110.

Lindberg M, Ahlner J, Ekstrom T, Jonsson D, Moller M. Asthma nurse practice improves outcomes and reduces costs in primary health care. *Scand J Caring Sci* 2002;16(1):73–8.

Lindberg M, Ahlner J, Moller M, Ekstrom T. Asthma nurse practice—a resource-effective approach in asthma management. *Respir Med* 1999;93(8):584–8.

Love MM, Mainous AG III, Talbert JC, Hager GL. Continuity of care and the physician-patient relationship: the importance of continuity for adult patients with asthma. *J Fam Pract* 2000;49(11):998–1004.

Lozano P, Finkelstein JA, Carey VJ, Wagner EH, Inui TS, Fuhlbrigge AL, Soumerai SB, Sullivan SD, Weiss ST, Weiss KB. A multisite randomized trial of the effects of physician education and organizational change in chronic-asthma care: health outcomes of the Pediatric Asthma Care Patient Outcomes Research Team II Study. *Arch Pediatr Adolesc Med* 2004;158(9):875–83.

Madge P, McColl J, Paton J. Impact of a nurse-led home management training programme in children admitted to hospital with acute asthma: a randomised controlled study. *Thorax* 1997;52(3):223–8.

Magar Y, Vervloet D, Steenhouwer F, Smaga S, Mechin H, Rocca Serra JP, Marchand C, d'Ivernois JF. Assessment of a therapeutic education programme for asthma patients: "un souffle nouveau". *Patient Educ Couns* 2005;58(1):41–6.

Mannino DM, Homa DM, Redd SC. Involuntary smoking and asthma severity in children: data from the Third National Health and Nutrition Examination Survey. *Chest* 2002;122(2):409–15.

Mannino DM, Moorman JE, Kingsley B, Rose D, Repace J. Health effects related to environmental tobacco smoke exposure in children in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Pediatr Adolesc Med* 2001;155(1):36–41.

Manson A. Language concordance as a determinant of patient compliance and emergency room use in patients with asthma. *Med Care* 1988;26(12):1119–28.

Mansour ME, Lanphear BP, DeWitt TG. Barriers to asthma care in urban children: parent perspectives. *Pediatrics* 2000;106(3):512–9.

Marabini A, Brugnami G, Curradi F, Casciola G, Stopponi R, Pettinari L, Siracusa A. Short-term effectiveness of an asthma educational program: results of a randomized controlled trial. *Respir Med* 2002;96(12):993–8.

McConnell R, Milam J, Richardson J, Galvan J, Jones C, Thorne PS, Berhane K. Educational intervention to control cockroach allergen exposure in the homes of Hispanic children in Los Angeles: results of the La Casa study. *Clin Exp Allergy* 2005;35(4):426–33.

McCowan C, Neville RG, Ricketts IW, Warner FC, Hoskins G, Thomas GE. Lessons from a randomized controlled trial designed to evaluate computer decision support software to improve the management of asthma. *Med Inform Internet Med* 2001;26(3):191–201.

McDowell KM, Chatburn RL, Myers TR, O'Riordan MA, Kercsmar CM. A cost-saving algorithm for children hospitalized for status asthmaticus. *Arch Pediatr Adolesc Med* 1998;152(10):977–84.

McLean W, Gillis J, Waller R. The BC Community Pharmacy Asthma Study: a study of clinical, economic and holistic outcomes influenced by an asthma care protocol provided by specially trained community pharmacists in British Columbia. *Can Respir J* 2003;10(4):195–202.

McMullen AH, Yoos HL, Kitzman H. Peak flow meters in childhood asthma: parent report of use and perceived usefulness. *J Pediatr Health Care* 2002;16(2):67–72.

MeGhan [sic] SL, Wong E, Jhangri GS, Wells HM, Michaelchuk DR, Boechler VL, Befus AD, Hessel PA. Evaluation of an education program for elementary school children with asthma. *J Asthma* 2003;40(5):523–33.

Meichenbaum D, Turk DC. Facilitating Treatment Adherence: A Practitioner's Guidebook. New York: Plenum Press, 1987.

Melani AS, Zanchetta D, Barbato N, Sestini P, Cinti C, Canessa PA, Aiolfi S, Neri M; Associazione Italiana Pneumologi Ospedalieri Educational Group. Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. *Ann Allergy Asthma Immunol* 2004;93(5):439–46.

Minai BA, Martin JE, Cohn RC. Results of a physician and respiratory therapist collaborative effort to improve long-term metered-dose inhaler technique in a pediatric asthma clinic. *Respir Care* 2004;49(6):600–5.

Mitchell EA, Didsbury PB, Kruithof N, Robinson E, Milmine M, Barry M, Newman J. A randomized controlled trial of an asthma clinical pathway for children in general practice. *Acta Paediatr* 2005;94(2):226–33.

Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R III, Stout J, Malindzak G, Smartt E, Plaut M, et al.; Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351(11):1068–80.

Morice AH, Wrench C. The role of the asthma nurse in treatment compliance and self-management following hospital admission. *Respir Med* 2001;95(11):851–6.

Morkjaroenpong V, Rand CS, Butz AM, Huss K, Eggleston P, Malveaux FJ, Bartlett SJ. Environmental tobacco smoke exposure and nocturnal symptoms among inner-city children with asthma. *J Allergy Clin Immunol* 2002;110(1):147–53.

Moudgil H, Marshall T, Honeybourne D. Asthma education and quality of life in the community: a randomised controlled study to evaluate the impact on white European and Indian subcontinent ethnic groups from socioeconomically deprived areas in Birmingham, UK. *Thorax* 2000;55(3):177–83.

Muntner P, Sudre P, Uldry C, Rochat T, Courteheuse C, Naef AF, Perneger TV. Predictors of participation and attendance in a new asthma patient self-management education program. *Chest* 2001;120(3):778–84.

Nathell L. Effects on sick leave of an inpatient rehabilitation programme for asthmatics in a randomized trial. *Scand J Public Health* 2005;33(1):57–64.

National Asthma Education Prevention Program (NAEPP 1997). Practical guide for the diagnosis and management of asthma (NAEPP 1997). Based on the expert panel report 2: guidelines for the diagnosis and management of asthma. NIH Publication No. 97-4053. Bethesda, MD, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, 1997.

National Heart, Lung, and Blood Institute (NHLBI). Asthma management in minority children: practical insights for clinicians, researchers, and public health planners (NHLBI 1995). NIH Publication No. 95-3675. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute, 1995a.

National Heart, Lung, and Blood Institute (NHLBI). Nurses: partners in asthma care (NHLBI 1995). NIH Publication No. 95-3308. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute, 1995b.

National Heart, Lung, and Blood Institute (NHLBI). The role of the pharmacist in improving asthma care (NHLBI 1995). NIH Publication No. 95-3280. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute, 1995.

Neri M, Migliori GB, Spanevello A, Berra D, Nicolin E, Landoni CV, Ballardini L, Sommaruga M, Zanon P. Economic analysis of two structured treatment and teaching programs on asthma. *Allergy* 1996;51(5):313–9.

Neri M, Spanevello A, Ambrosetti M, Ferronato P, Cagna C, Zanon P. Short and long-term evaluation of two structured self management programmes on asthma. *Monaldi Arch Chest Dis* 2001;56(3):208–10.

Nimmo CJ, Chen DN, Martinusen SM, Ustad TL, Ostrow DN. Assessment of patient acceptance and inhalation technique of a pressurized aerosol inhaler and two breath-actuated devices. *Ann Pharmacother* 1993;27(7-8):922–7.

Numata Y, Bourbeau J, Ernst P, Duquette G, Schwartzman K. Teaching time for metered-dose inhalers in the emergency setting. *Chest* 2002;122(2):498–504.

Ochsner AK, Alexander JL, Davis A. Increasing awareness of asthma and asthma resources in communities on the southwest border. *J Am Acad Nurse Pract* 2002;14(5):225–30, 32, 34.

Olajos-Clow J, Costello E, Lougheed MD. Perceived control and quality of life in asthma: impact of asthma education. *J Asthma* 2005;42(9):751–6.

Onyirimba F, Apter A, Reisine S, Litt M, McCusker C, Connors M, ZuWallack R. Direct clinician-to-patient feedback discussion of inhaled steroid use: its effect on adherence. *Ann Allergy Asthma Immunol* 2003;90(4):411–5.

Osman LM, Calder C, Godden DJ, Friend JA, McKenzie L, Legge JS, Douglas JG. A randomised trial of self-management planning for adult patients admitted to hospital with acute asthma. *Thorax* 2002;57(10):869–74.

Paasche-Orlow MK, Riekert KA, Bilderback A, Chanmugam A, Hill P, Rand CS, Brancati FL, Krishnan JA. Tailored education may reduce health literacy disparities in asthma self-management. *Am J Respir Crit Care Med* 2005;172(8):980–6. Epub August 2005.

Pachter LM, Cloutier MM, Bernstein BA. Ethnomedical (folk) remedies for childhood asthma in a mainland Puerto Rican community. *Arch Pediatr Adolesc Med* 1995;149(9):982–8.

Pachter LM, Weller SC. Acculturation and compliance with medical therapy. *J Dev Behav Pediatr* 1993;14(3):163–8.

Pachter LM, Weller SC, Baer RD, de Alba Garcia JE, Trotter RT II, Glazer M, Klein R. Variation in asthma beliefs and practices among mainland Puerto Ricans, Mexican-Americans, Mexicans, and Guatemalans. *J Asthma* 2002;39(2):119–34.

Patel PH, Welsh C, Foggs MB. Improved asthma outcomes using a coordinated care approach in a large medical group. *Dis Manag* 2004;7(2):102–11.

Patterson EE, Brennan MP, Linskey KM, Webb DC, Shields MD, Patterson CC. A cluster randomised intervention trial of asthma clubs to improve quality of life in primary school children: the School Care and Asthma Management Project (SCAMP). *Arch Dis Child* 2005;90(8):786–91.

Perneger TV, Sudre P, Muntner P, Uldry C, Courteheuse C, Naef AF, Jacquemet S, Nicod L, Rochat T, Assal JP. Effect of patient education on self-management skills and health status in patients with asthma: a randomized trial. *Am J Med* 2002;113(1):7–14.

Powell H, Gibson PG. Options for self-management education for adults with asthma. *Cochrane Database Syst Rev* 2003;(1):CD004107.

Radeos MS, Leak LV, Lugo BP, Hanrahan JP, Clark S, Camargo CA Jr; MARC Investigators. Risk factors for lack of asthma self-management knowledge among ED patients not on inhaled steroids. *Am J Emerg Med* 2001;19(4):253–9.

Rasmussen LM, Phanareth K, Nolte H, Backer V. Internet-based monitoring of asthma: a long-term, randomized clinical study of 300 asthmatic subjects. *J Allergy Clin Immunol* 2005;115(6):1137–42.

Rau JL, Restrepo RD, Deshpande V. Inhalation of single vs multiple metered-dose bronchodilator actuations from reservoir devices. An in vitro study. *Chest* 1996;109(4):969–74.

Reddel HK, Marks GB, Jenkins CR. When can personal best peak flow be determined for asthma action plans? *Thorax* 2004;59(11):922–4.

Rich M, Lamola S, Amory C, Schneider L. Asthma in life context: Video Intervention/Prevention Assessment (VIA). *Pediatrics* 2000;105(3 Pt 1):469–77.

Riekert KA, Butz AM, Eggleston PA, Huss K, Winkelstein M, Rand CS. Caregiver-physician medication concordance and undertreatment of asthma among inner-city children. *Pediatrics* 2003;111(3):e214–e220.

Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995;122(11):823–32.

Risser AL, Mazur LJ. Use of folk remedies in a Hispanic population. *Arch Pediatr Adolesc Med* 1995;149(9):978–81.

Robichaud P, Laberge A, Allen MF, Boutin H, Rossi C, Lajoie P, Boulet LP. Evaluation of a program aimed at increasing referrals for asthma education of patients consulting at the emergency department for acute asthma. *Chest* 2004;126(5):1495–501.

Rossiter LF, Whitehurst-Cook MY, Small RE, Shasky C, Bovbjerg VE, Penberthy L, Okasha A, Green J, Ibrahim IA, Yang S, et al. The impact of disease management on outcomes and cost of care: a study of low-income asthma patients. *Inquiry* 2000;37(2):188–202.

Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Med Care* 1998;36(8):1138–61.

Saini B, Krass I, Armour C. Development, implementation, and evaluation of a community pharmacy-based asthma care model. *Ann Pharmacother* 2004;38(11):1954–60.

San Francisco Bay Area. 2006. Regional Asthma Management Plan. Available at: http://www.rampasthma.org.

Scarfone RJ, Capraro GA, Zorc JJ, Zhao H. Demonstrated use of metered-dose inhalers and peak flow meters by children and adolescents with acute asthma exacerbations. *Arch Pediatr Adolesc Med* 2002;156(4):378–83.

Schaffer SD, Tian L. Promoting adherence: effects of theory-based asthma education. *Clin Nurs Res* 2004;13(1):69–89.

Schatz M, Zeiger RS, Mosen D, Apter AJ, Vollmer WM, Stibolt TB, Leong A, Johnson MS, Mendoza G, Cook EF. Improved asthma outcomes from allergy specialist care: a population-based cross-sectional analysis. *J Allergy Clin Immunol* 2005;116(6):1307–13. Epub November 2005.

Schermer TR, Thoonen BP, Van Den Boom G, Akkermans RP, Grol RP, Folgering HT, Van Weel C, Van Schayck CP. Randomized controlled economic evaluation of asthma self-management in primary health care. *Am J Respir Crit Care Med* 2002;166(8):1062–72.

Shah S, Peat JK, Mazurski EJ, Wang H, Sindhusake D, Bruce C, Henry RL, Gibson PG. Effect of peer led programme for asthma education in adolescents: cluster randomised controlled trial. *BMJ* 2001;322(7286):583–5.

Shames RS, Sharek P, Mayer M, Robinson TN, Hoyte EG, Gonzalez-Hensley F, Bergman DA, Umetsu DT. Effectiveness of a multicomponent self-management program in at-risk, school-aged children with asthma. *Ann Allergy Asthma Immunol* 2004;92(6):611–8.

Sin DD, Bell NR, Man SF. Effects of increased primary care access on process of care and health outcomes among patients with asthma who frequent emergency departments. *Am J Med* 2004;117(7):479–83.

Smith SR, Jaffe DM, Fisher EB Jr, Trinkaus KM, Highstein G, Strunk RC. Improving follow-up for children with asthma after an acute Emergency Department visit. *J Pediatr* 2004;145(6):772–7. Erratum in: *J Pediatr* 2005;146(3):413.

Smith VA, DeVellis BM, Kalet A, Roberts JC, DeVellis RF. Encouraging patient adherence: primary care physicians' use of verbal compliance-gaining strategies in medical interviews. *Patient Educ Couns* 2005;57(1):62–76.

Sockrider MM, Abramson S, Brooks E, Caviness AC, Pilney S, Koerner C, Macias CG. Delivering tailored asthma family education in a pediatric emergency department setting: a pilot study. *Pediatrics* 2006;117(4 Pt 2):S135–S144.

Stergachis A, Gardner JS, Anderson MT, Sullivan SD. Improving pediatric asthma outcomes in the community setting: does pharmaceutical care make a difference? *J Am Pharm Assoc (Wash)* 2002;42(5):743–52.

Sullivan SD, Lee TA, Blough DK, Finkelstein JA, Lozano P, Inui TS, Fuhlbrigge AL, Carey VJ, Wagner E, Weiss KB. A multisite randomized trial of the effects of physician education and organizational change in chronic asthma care: cost-effectiveness analysis of the Pediatric Asthma Care Patient Outcomes Research Team II (PAC-PORT II). *Arch Pediatr Adolesc Med* 2005;159(5):428–34.

Sullivan SD, Weiss KB, Lynn H, Mitchell H, Kattan M, Gergen PJ, Evans R; National Cooperative Inner-City Asthma Study (NCICAS) Investigators. The cost-effectiveness of an inner-city asthma intervention for children. *J Allergy Clin Immunol* 2002;110(4):576–81.

Sundberg R, Tunsater A, Palmqvist M, Ellbjar S, Lowhagen O, Toren K. A randomized controlled study of a computerized limited education program among young adults with asthma. *Respir Med* 2005;99(3):321–8.

Szilagyi PG, Dick AW, Klein JD, Shone LP, Zwanziger J, Bajorska A, Yoos HL. Improved asthma care after enrollment in the State Children's Health Insurance Program in New York. *Pediatrics* 2006;117(2):486–96.

Teach SJ, Crain EF, Quint DM, Hylan ML, Joseph JG. Improved asthma outcomes in a high-morbidity pediatric population: results of an emergency department-based randomized clinical trial. *Arch Pediatr Adolesc Med* 2006;160(5):535–41.

Thoonen BP, Schermer TR, Van Den Boom G, Molema J, Folgering H, Akkermans RP, Grol R, Van Weel C, Van Schayck CP. Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial. *Thorax* 2003;58(1):30–6.

Tierney WM, Overhage JM, Murray MD, Harris LE, Zhou XH, Eckert GJ, Smith FE, Nienaber N, McDonald CJ, Wolinsky FD. Can computer-generated evidence-based care suggestions enhance evidence-based management of asthma and chronic obstructive pulmonary disease? A randomized, controlled trial. *Health Serv Res* 2005;40(2):477–97.

Tinkelman D, Wilson S. Asthma disease management: regression to the mean or better? *Am J Manag Care* 2004;10(12):948–54.

Toelle BG, Peat JK, Salome CM, Mellis CM, Bauman AE, Woolcock AJ. Evaluation of a community-based asthma management program in a population sample of schoolchildren. *Med J Aust* 1993;158(11):742–6.

Toelle BG, Ram FS. Written individualised management plans for asthma in children and adults. *Cochrane Database Syst Rev* 2004;(2):CD002171.

U.S. Preventive Services Task Force (USPSTF) Web site. 2004. Available at: http://www.ahcpr.gov/clinic/uspstfix.htm.

Urek MC, Tudoric N, Plavec D, Urek R, Koprivc-Milenovic T, Stojic M. Effect of educational programs on asthma control and quality of life in adult asthma patients. *Patient Educ Couns* 2005;58(1):47–54.

van der Palen J, Klein JJ, Zielhuis GA, van Herwaarden CL, Seydel ER. Behavioural effect of self-treatment guidelines in a self-management program for adults with asthma. *Patient Educ Couns* 2001;43(2):161–9.

Van Sickle D, Wright AL. Navajo perceptions of asthma and asthma medications: clinical implications. *Pediatrics* 2001;108(1):E11.

Velsor-Friedrich B, Pigott T, Srof B. A practitioner-based asthma intervention program with African American inner-city school children. *J Pediatr Health Care* 2005;19(3):163–71.

Walders N, Kercsmar C, Schluchter M, Redline S, Kirchner HL, Drotar D. An interdisciplinary intervention for undertreated pediatric asthma. *Chest* 2006;129(2):292–9.

Wazeka A, Valacer DJ, Cooper M, Caplan DW, DiMaio M. Impact of a pediatric asthma clinical pathway on hospital cost and length of stay. *Pediatr Pulmonol* 2001;32(3):211–6.

Wensley D, Silverman M. Peak flow monitoring for guided self-management in childhood asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2004;170(6):606–12.

Wesseldine LJ, McCarthy P, Silverman M. Structured discharge procedure for children admitted to hospital with acute asthma: a randomised controlled trial of nursing practice. *Arch Dis Child* 1999;80(2):110–4.

White M, Michaud G, Pachev G, Lirenman D, Kolenc A, FitzGerald JM. Randomized trial of problem-based versus didactic seminars for disseminating evidence-based guidelines on asthma management to primary care physicians. *J Contin Educ Health Prof* 2004;24(4):237–43.

Williams MV, Baker DW, Honig EG, Lee TM, Nowlan A. Inadequate literacy is a barrier to asthma knowledge and self-care. *Chest* 1998;114(4):1008–15.

Wilson SR, Buist A.S., Holup J, Brown NL, Lapidus J., Luna V., Verghese S. Shared decision-making vs. management by guidelines: Impact on medication regime. *Proc Am Thor Soc* 2005;2:abstracts issue.

Wilson SR, Scamagas P, German DF, Hughes GW, Lulla S, Coss S, Chardon L, Thomas RG, Starr-Schneidkraut N, Stancavage FB, et al. A controlled trial of two forms of self-management education for adults with asthma. *Am J Med* 1993;94(6):564–76.

Wilson SR, Strub P, Buist AS, Brown NL, Lapidus J, Luna V, Verghese S. Does involving patients in treatment decisions improve asthma controller medication adherence? *Proc Am Thor Soc* 2006;3:A469, abstracts issue.

Wilson SR, Yamada EG, Sudhakar R, Roberto L, Mannino D, Mejia C, Huss N. A controlled trial of an environmental tobacco smoke reduction intervention in low-income children with asthma. *Chest* 2001;120(5):1709–22.

Wolf RL, Berry CA, Quinn K. Development and validation of a brief pediatric screen for asthma and allergies among children. *Ann Allergy Asthma Immunol* 2003;90(5):500–7.

Woloshin S, Bickell NA, Schwartz LM, Gany F, Welch HG. Language barriers in medicine in the United States. *JAMA* 1995;273(9):724–8.

Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, Britton J, Strachan D, Howarth P, Altmann D, et al.; Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003;349(3):225–36.

Yawn BP. The impact of childhood asthma on daily life of the family—a qualititative study using recurrent thematic analysis. *Primary Care Respir J* 2003;12(3):82–5.

Yawn BP. Participatory research in rural primary care. *Minn Med* 2004;87(9):52–4.

Zeiger RS, Heller S, Mellon MH, Wald J, Falkoff R, Schatz M. Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits. *J Allergy Clin Immunol* 1991;87(6):1160–1168. Erratum in: *J Allergy Clin Immunol* 1992;90(2):278.

Zorc JJ, Scarfone RJ, Li Y, Hong T, Harmelin M, Grunstein L, Andre JB. Scheduled follow-up after a pediatric emergency department visit for asthma: a randomized trial. *Pediatrics* 2003;111(3):495–502.

SECTION 3, COMPONENT 3: CONTROL OF ENVIRONMENTAL FACTORS AND COMORBID CONDITIONS THAT AFFECT ASTHMA

KEY POINTS: CONTROL OF ENVIRONMENTAL FACTORS AND COMORBID CONDITIONS THAT AFFECT ASTHMA

- Exposure of patients who have asthma to allergens (Evidence A) or irritants (EPR—2 1997) to which they are sensitive has been shown to increase asthma symptoms and precipitate asthma exacerbations.

- For at least those patients who have persistent asthma, the clinician should evaluate the potential role of allergens, particularly indoor inhalant allergens (Evidence A):

  — Use the patient's medical history to identify allergen exposures that may worsen the patient's asthma.

  — Use skin testing or in vitro testing to reliably determine sensitivity to perennial indoor inhalant allergens to which the patient is exposed.

  — Assess the significance of positive tests in the context of the patient's medical history.

  — Use the patient's history to assess sensitivity to seasonal allergens.

- Patients who have asthma at any level of severity should:

  — Reduce, if possible, exposure to allergens to which the patient is sensitized and exposed.

  — Know that effective allergen avoidance requires a multifaceted, comprehensive approach; individual steps alone are generally ineffective (Evidence A).

  — Avoid exposure to environmental tobacco smoke and other respiratory irritants, including smoke from wood-burning stoves and fireplaces and, if possible, substances with strong odors (Evidence C).

  — Avoid exertion outdoors when levels of air pollution are high (Evidence C).

  — Avoid use of nonselective beta-blockers (Evidence C).

  — Avoid sulfite-containing and other foods to which they are sensitive (Evidence C).

  — Consider allergen immunotherapy when there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive (Evidence B). If use of allergen immunotherapy is elected, it should be administered only in a physician's office where facilities and trained personnel are available to treat any life-threatening reaction that can, but rarely does, occur.

- Adult patients who have severe persistent asthma, nasal polyps, or a history of sensitivity to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) should be counseled regarding the risk of severe and even fatal exacerbations from using these drugs (Evidence C).

- Clinicians should evaluate a patient for the presence of a chronic comorbid condition when the patient's asthma cannot be well controlled. Treating the conditions may improve asthma management: ABPA (Evidence A), gastroesophageal reflux (Evidence B), obesity (Evidence B, limited studies), OSA (Evidence D), rhinitis/sinusitis (Evidence B), chronic stress/depression (Evidence D).

- Consider inactivated influenza vaccination for patients who have asthma. It is safe for administration to children more than 6 months of age and adults (Evidence A). The Advisory Committee on Immunization Practices of the CDC recommends vaccination for persons who have asthma, because they are considered to be at risk for complications from influenza. However, the vaccine should not be given with the expectation that it will reduce either the frequency or severity of asthma exacerbations during the influenza season (Evidence B).

- Use of humidifiers and evaporative (swamp) coolers is not generally recommended in homes of patients who have asthma and are sensitive to house-dust mites or mold (Evidence C).

- Employed persons who have asthma should be queried about possible occupational exposures, particularly those who have new-onset disease (EPR—2 1997).

- There is insufficient evidence to recommend any specific environmental strategies to prevent the development of asthma.

KEY DIFFERENCES FROM 1997 EXPERT PANEL REPORT

- Evidence strengthens recommendations that reducing exposure to inhalant indoor allergens can improve asthma control and notes that a multifaceted approach is required; single steps to reduce exposure are generally ineffective.

- Formaldehyde and volatile organic compounds (VOCs) have been implicated as potential risk factors for asthma and wheezing.

- Evidence shows that influenza vaccine, while having other benefits, does not appear to reduce either the frequency or severity of asthma exacerbations during the influenza season.

- The section has been expanded to include discussion of ABPA, obesity, OSA, and stress as chronic comorbid conditions, in addition to rhinitis, sinusitis, and gastroesophageal reflux, that may interfere with asthma management.

Introduction

See section 1, "Overall Methods Used To Develop This Report," for literature search strategy and tally of results for the EPR—3: Full Report 2007 on this component, "Control of Environmental Factors and Comorbid Conditions That Affect Asthma." Two Evidence Tables were prepared: 9, Allergen Avoidance; and 10, Immunotherapy.

For successful long-term management of asthma, it is essential to identify and reduce exposures to relevant allergens and irritants and to control other factors that have been shown to increase asthma symptoms and/or precipitate asthma exacerbations. These factors are in five categories: inhalant allergens, occupational exposures, irritants, comorbid conditions, and other factors. Ways to reduce the effects of these factors on asthma are discussed in this component of asthma management.

Inhalant Allergens

The Expert Panel recommends that patients who have asthma at any level of severity should be queried about exposures to inhalant allergens, particularly indoor inhalant allergens, and their potential effect on the patient's asthma (Evidence A). Exposure of a person who has asthma to inhalant allergens to which the person is sensitive increases airway inflammation and symptoms. Substantially reducing such exposure may significantly reduce inflammation, symptoms, and need for medication (See a summary of the evidence in box 3–5.).

DIAGNOSIS—DETERMINE RELEVANT INHALANT SENSITIVITY

Demonstrating a patient's relevant sensitivity to inhalant allergens will enable the clinician to recommend specific environmental controls to reduce exposures. It will also help the patient understand the pathogenesis of asthma and the value of allergen avoidance.

The Expert Panel recommends that, given the importance of allergens and their control to asthma morbidity and asthma management, patients who have persistent asthma should be evaluated for the role of allergens as possible contributing factors as follows (EPR—2 1997):

- **Determine the patient's exposure to allergens, especially indoor inhalant allergens. (See relevant questions in figure 3–17.)**
- **Assess sensitivity to the allergens to which the patient is exposed.**
  - **Use the patient's medical history, which is usually sufficient, to determine sensitivity to seasonal allergens.**
  - **Use skin testing or in vitro testing to determine the presence of specific IgE antibodies to the indoor allergens to which the patient is exposed year round. (See figure 3–18 for a comparison of skin and in vitro tests.) Allergy testing is the only reliable way to determine sensitivity to perennial indoor allergens (See box 3–6 for further explanation.).**
  - **For selected patients who have asthma at any level of severity, detection of specific IgE sensitivity to seasonal or perennial allergens may be indicated as a basis for education about the role of allergens for avoidance and for immunotherapy.**
- **Assess the clinical significance of positive allergy tests in the context of the patient's medical history (See figure 3–19.).**

BOX 3–5. THE STRONG ASSOCIATION BETWEEN SENSITIZATION TO ALLERGENS AND ASTHMA: A SUMMARY OF THE EVIDENCE

The association of asthma and allergy has long been recognized. Recent studies confirm that sensitization among genetically susceptible populations to certain indoor allergens such as house-dust mite, animal dander, and cockroach or to the outdoor fungus Alternaria is a risk for developing asthma in children (Halonen et al. 1997; Sears et al. 1993; Sporik et al. 1990). Sensitization to outdoor pollens carries less risk for asthma (Sears et al. 1989), although exposure to grass (Reid et al. 1986) and ragweed (Creticos et al. 1996) pollen has been associated with seasonal asthma. It is widely accepted that the importance of inhalant sensitivity as a cause of asthma declines with advancing age (Pollart et al. 1989).

An allergic reaction in the airways, caused by natural exposure to allergens, has been shown to lead to an increase in inflammatory reaction, increased airway hyperresponsiveness (Boulet et al. 1983; Peroni et al. 1994; Piacentini et al. 1993), and increased eosinophils in bronchoalveolar lavage (Rak et al. 1991). Other research has demonstrated that asthma symptoms, pulmonary function, and need for medication in mite-sensitive asthma patients correlate with the level of house-dust mite exposure (Custovic et al. 1998; Huss et al. 2001; Sporik et al. 1990; Vervloet et al. 1991) and that reducing house-dust mite exposure reduces asthma symptoms, nonspecific bronchial hyperresponsiveness, and evidence of active inflammation (Morgan et al. 2004; Peroni et al. 2002; Piacentini et al. 1993; Simon et al. 1994). Inhalant allergen exposure to seasonal outdoor fungal spores (O'Hollaren et al. 1991; Targonski et al. 1995) and to indoor allergens (Call et al. 1994) has also been implicated in fatal exacerbations of asthma. These reports emphasize that allergen exposure must be considered in the treatment of asthma.

The important allergens for children and adults appear to be those that are inhaled. Food allergens are not a common precipitant of asthma symptoms. Foods are an important cause of anaphylaxis in adults and children (Golbert et al. 1969; Sampson et al. 1992), but significant lower respiratory tract symptoms are uncommon even with positive double-blind food challenges (James et al. 1994). However, asthma is a risk factor for fatal anaphylactic reactions to food or immunotherapy (Bernstein et al. 2004; Reid et al. 1993).

BOX 3–6. RATIONALE FOR ALLERGY TESTING FOR PERENNIAL INDOOR ALLERGENS

Determination of sensitivity to a perennial indoor allergen is usually not possible with a patient's medical history alone (Murray and Milner 1995). Increased symptoms during vacuuming or bed making and decreased symptoms when away from home on a business trip or vacation are suggestive but not sufficient. Allergy skin or in vitro tests are reliable in determining the presence of specific IgE (Dolen 2001; Yunginger et al. 2000), but these tests do not determine whether the specific IgE is responsible for the patient's symptoms. That is why patients should be tested only for sensitivity to the allergens to which they may be exposed, and why the third step in evaluating patients for allergen sensitivity calls for assessing the clinical relevance of the sensitivity.

The recommendation to do skin or in vitro tests for patients who have persistent asthma and are exposed to perennial indoor allergens will result in a limited number of allergy tests for about half of all asthma patients. This estimate is based on the prevalence of persistent asthma and the level of exposure to indoor allergens. Based on data on children in the United States, it is estimated that at least 70 percent of all patients who have asthma have persistent asthma (Squillace et al. 1997; Taylor and Newacheck 1992). About 80 percent of the U.S. population is exposed to house-dust mites (Arbes et al. 2003; Nelson and Fernandez-Caldas 1995), 60 percent to cat or dog, and a much smaller percentage to both animals (Ingram et al. 1995). Cockroaches are a consideration primarily in the inner-city and southern parts of the United States.

Skin or in vitro tests are necessary to educate patients about the role of allergens in their disease. Education is an essential prerequisite for convincing patients about the need for specific allergen avoidance. Current recommendations for avoidance measures for dust-mite, cat, or cockroach allergens are allergen specific, and it is only possible to convince patients to undertake the measures once they know to what they are allergic.

MANAGEMENT—REDUCE EXPOSURE

The Expert Panel recommends that patients should reduce exposure, as much as possible, to allergens to which the patient is sensitized and exposed:

- **The first and most important step in controlling allergen-induced asthma is to advise patients to reduce exposure to relevant indoor and outdoor allergens to which the patient is sensitive (Evidence A) (See Evidence Table 9, Allergen Avoidance.).**
- **Effective allergen avoidance requires a multifaceted, comprehensive approach; individual steps alone are generally ineffective (Evidence A).**
- **Consider multifaceted allergen-control education interventions provided in the home setting that have been proven effective for reducing exposures to cockroach, dust-mite, and rodent allergens for patients sensitive to those allergens (Evidence A). Further research to evaluate the feasibility of widespread implementation of such programs will be helpful (see "Component 2: Education for a Partnership in Asthma Care.").**

Effective ways patients can reduce their exposures to indoor and outdoor allergens are discussed below and summarized in figure 3–20, which also addresses irritants. Although these recommendations focus on the home environment, reductions in exposures to allergens and irritants are also appropriate in other environments where the patient spends extended periods of time, such as school, work, or daycare. For information about companies that distribute products to help reduce allergen exposure, contact the Asthma and Allergy Foundation of America toll-free hotline at 800–727–8462 or the Allergy and Asthma Network/Mothers of Asthmatics at 800–878–4403.

See "Component 2: Education for a Partnership in Asthma Care" for a description of allergen-control education programs that are delivered in patients' homes. Multifaceted programs that focus on educating patients and providing tools for reducing exposure to cockroach, dust-mite, and rodent allergens have demonstrated success in reducing exposure and reducing asthma morbidity. Further evaluation is needed of the cost-effectiveness and feasibility for widespread implementation of these interventions; however, the efficacy of the interventions warrants their consideration, if available, for patients sensitive to these allergens.

Animal allergens. The Expert Panel recommends the following actions to control animal antigens (Evidence D):

- **If the patient is sensitive to an animal, the treatment of choice is removal of the exposure from the home.**
- **If removal of the animal is not acceptable:**
  - **Keep the pet out of the patient's bedroom.**
  - **Keep the patient's bedroom door closed.**
  - **Remove upholstered furniture and carpets from the home, or isolate the pet from these items to the extent possible.**
  - **Mouse allergen exposure can be reduced by a combination of blocking access, low-toxicity pesticides, traps, and vacuuming and cleaning.**

All warm-blooded animals, including pets and rodents, produce dander, urine, feces, and saliva that can cause allergic reactions (de Blay et al. 1991b; Swanson et al. 1985). Given recent evidence that exposure to cat allergens can be significant in homes, schools, and offices without animals, the issue of allergen avoidance in sites without animals has become more relevant. Successful controlled trials of animal dander avoidance have now been reported for schools and for homes without an animal (Popplewell et al. 2000). Studies suggest that mouse and rat allergen exposure and sensitization are common in urban children who have asthma (Phipatanakul et al. 2004).

High-efficiency particulate air (HEPA) cleaners reduce airborne Can f 1 in homes with dogs. Furthermore, preventing the dog from having access to the bedroom, and possibly the living room, may reduce the total allergen load inhaled (Green et al. 1999). Weekly washing of the pet will remove large quantities of dander and dried saliva that will otherwise accumulate in the house; however, the role of washing in allergen avoidance is not established (Avner et al. 1997, de Blay et al. 1991a, Klucka et al. 1995).

House-dust mite allergen. The Expert Panel recommends the following mite-control measures; effective allergen avoidance requires a multifaceted approach (Evidence A).

- **Recommended actions to control mites include:**
  - **Encase the mattress in an allergen-impermeable cover.**
  - **Encase the pillow in an allergen-impermeable cover or wash it weekly.**
  - **Wash the sheets and blankets on the patient's bed weekly in hot water.**
  - **A temperature of >130 °F is necessary for killing house-dust mites. Prolonged exposure to dry heat or freezing can also kill mites but does not remove allergen. If high temperature water is not available, a considerable reduction in live mites and mite allergens can still be achieved with cooler water and using detergent and bleach.**
- **Actions to *consider* to control mites include:**
  - **Reduce indoor humidity to or below 60 percent, ideally between 30 and 50 percent.**
  - **Remove carpets from the bedroom.**
  - **Avoid sleeping or lying on upholstered furniture.**
  - **Remove from the home carpets that are laid on concrete.**
  - **In children's beds, minimize the number of stuffed toys, and wash them weekly.**

House-dust mites are universal in areas of high humidity (most areas of the United States) but are usually not present at high altitudes or in arid areas unless moisture is added to the indoor air (Platts-Mills et al. 1997). Mites depend on atmospheric moisture and human dander for survival. High levels of mites can be found in dust from mattresses, pillows, carpets, upholstered furniture, bed covers, clothes, and soft toys. The patient's bed is the most important source of dust mites to control. Washing bedding is advised, preferably in hot water, but cold water, detergent, and bleach can also be effective (Arlian et al. 2003; McDonald and Tovey 1992). Several recent studies support the efficacy of allergen avoidance in the treatment of asthma (Carter et al. 2001; Halken et al. 2003; Htut et al. 2001; Morgan et al. 2004; Peroni et al. 2002; Rijssenbeek-Nouwens et al. 2003; van der Heide et al. 1997). Other studies provide important insight into the details of allergen avoidance. For example, three studies reported that mattress covers without other measures were not effective (Luczynska et al. 2003; Terreehorst et al. 2003; Woodcock et al. 2003). Likewise, two well-conducted studies failed to show an effect of HEPA filters alone (Francis et al. 2003; Wood et al. 1998). Thus, the conclusion remains that effective allergen avoidance requires a comprehensive approach, and that individual steps alone are generally ineffective (Platts-Mills et al. 2000).

Chemical agents are available for killing mites and denaturing the antigen; however, the effects are not dramatic and do not appear to be maintained for long periods. Therefore, use of these agents in the homes of persons who have asthma and are sensitive to house-dust mites should not be recommended routinely (Woodfolk et al. 1995). Vacuuming removes mite allergen from carpets but is inefficient at removing live mites.

Room air-filtering devices are not recommended for control of mite allergens, because the allergens are associated with large particles which remain airborne for only a few minutes after disturbance. They are, therefore, not susceptible to removal by air filtration.

Cockroach allergen. The Expert Panel recommends that cockroach control measures should be instituted if the patient is sensitive to cockroaches and infestation is present in the home (Evidence B).

Cockroach sensitivity and exposure are common among patients who have asthma and live in inner cities (Call et al. 1992; Gelber et al. 1993; Huss et al. 2001; Kang et al. 1993). In a study of asthma in an inner-city area, asthma severity increased with increasing levels of cockroach antigen in the bedrooms of children who were sensitized (Rosenstreich et al. 1997). Another major study demonstrated efficacy of cockroach avoidance as part of an overall plan for allergen avoidance (Morgan et al. 2004). Patients should not leave food or garbage exposed. Poison baits, boric acid, and traps are preferred to other chemical agents, because the latter can be irritating when inhaled by persons who have asthma. If volatile chemical agents are used, the home should be well ventilated, and the person who has asthma should not return to the home until the odor has dissipated. Care should be taken so that young children do not have access to cockroach baits and poisons.

Indoor fungi (molds). The Expert Panel recommends consideration of measures to control indoor mold (Evidence C). Indoor fungi are particularly prominent in humid environments and homes that have problems with dampness. Children who live in homes with dampness problems have increased respiratory symptoms (Institute of Medicine 2004; Verhoeff et al. 1995), but the relative contribution of fungi, house-dust mites, or irritants is not clear. Because an association between indoor fungi and respiratory and allergic disease is suggested by some studies (Bjornsson et al. 1995; Smedje et al. 1996; Strachan 1988), measures to control dampness or fungal growth in the home may be beneficial.

Outdoor allergens (tree, grass, and weed pollen; seasonal mold spores). The Expert Panel recommends that patients who are sensitive to seasonal outdoor allergens consider staying indoors, if possible, during peak pollen times—particularly midday and afternoon (EPR—2 1997). The strongest associations between mold-spore exposure and asthma have been with the outdoor fungi, such as *Alternaria* (Halonen et al. 1997; O'Hollaren et al. 1991; Targonski et al. 1995). Patients can reduce exposure during peak pollen season by staying indoors with windows closed in an air-conditioned environment (Solomon et al. 1980), particularly during the midday and afternoon when pollen and some spore counts are highest (Long and Kramer 1972; Mullins et al. 1986; Smith and Rooks 1954). Conducting outdoor activities shortly after sunrise will result in less exposure to pollen. These actions may not be realistic for some patients, especially children.

IMMUNOTHERAPY

The Expert Panel recommends that allergen immunotherapy be considered for patients who have persistent asthma if evidence is clear of a relationship between symptoms and exposure to an allergen to which the patient is sensitive (Evidence B) (see Evidence Table 10, Immunotherapy).

Immunotherapy is usually reserved for patients whose symptoms occur all year or during a major portion of the year and in whom controlling symptoms with pharmacologic management is difficult because the medication is ineffective, multiple medications are required, or the patient is

not accepting the use of medication. Reports, however, that immunotherapy can prevent the development of new sensitivities in monosensitized children and adults (Des Roches et al. 1997; Pajno et al. 2001; Purello-D'Ambrosio et al. 2001) and that immunotherapy with birch and timothy pollen extracts can prevent the development of asthma in children who have allergic rhinitis (Moller et al. 2002), along with evidence of persisting effect for at least 3 years after discontinuation (Durham et al. 1999), suggest that immunotherapy should be considered when there is a significant allergic contribution to the patient's symptoms. Specific immunotherapy has been shown to induce a wide range of immunologic responses that include the modulation of T- and B-cell responses by the generation of allergen-specific Treg cells; increases in allergen-specific IgG4, IgG1, and IgA; decrease in IgE and decreased tissue infiltration of mast cells and eosinophils. The relevance of these immunologic changes to the clinical efficacy of specific immunotherapy has yet to be established (Akdis and Akdis 2007).

Controlled studies of immunotherapy, usually conducted with single allergens, have demonstrated reduction in asthma symptoms caused by exposure to grass, cat, house-dust mite, ragweed, *Cladosporium,* and *Alternaria* (Creticos et al. 1996; Horst et al. 1990; Malling et al. 1986; Olsen et al. 1997; Reid et al. 1986; Varney et al. 1997). A meta-analysis of 75 randomized, placebo-controlled studies has confirmed the effectiveness of immunotherapy in asthma, with a significant reduction in asthma symptoms and medication and with improvement in bronchial hyperreactivity (Abramson et al. 2003). This meta-analysis included 36 trials for allergy to house dust mites, 20 for pollen allergy, and 10 for animal dander. On the other hand, only three trials for mold allergy and only six trials with multiple allergen therapy were included. In the United States, standardized extracts are available for house-dust mites, grasses, short ragweed, and cat, and there are unstandardized extracts of other pollens and for dog that appear to have similar potency (Nelson 2007). Available extracts for cockroach and mold, on the other hand, are of very variable allergen content and allergenic potency, and their effectiveness in specific immunotherapy has not been demonstrated (Nelson 2007). Few studies have been reported on multiple-allergen mixes that are commonly used in clinical practice. One, which included high doses of all allergens to which the children were sensitive (Johnstone and Dutton 1968), demonstrated reduction in asthma symptoms compared to lower doses of the same allergens or placebo. Another study, in which the children were given optimal medical therapy and in which the only perennial allergen administered was house-dust mite, demonstrated no improvement in asthma symptoms between active and placebo therapy (Adkinson et al. 1997).

The course of allergen immunotherapy is typically of 3–5 years' duration. Severe and sometimes fatal reactions to immunotherapy, especially severe bronchoconstriction, are more frequent among patients who have asthma, particularly those who have poorly controlled asthma, compared with those who have allergic rhinitis (Bernstein et al. 2004; Reid et al. 1993). If use of allergen immunotherapy is elected, it should be administered only in a physician's office where facilities and trained personnel are available to treat any life-threatening reaction that can, but rarely does, occur (AAAI Board of Directors 1994). For this reason, enthusiasm for the use of immunotherapy in asthma differs considerably among experts (Abramson et al. 2003; Canadian Society of Allergy and Clinical Immunology 1995; Frew 1993).

In Europe, interest has increased in high-dose sublingual immunotherapy (Canonica and Passalacqua 2003). It has been reported to be effective in asthma, with benefit persisting 4–5 years after its discontinuation (Di Rienzo et al. 2003), and to be free of systemic reactions, thus allowing home administration. Comparative studies suggest it is less effective, however, than immunotherapy administered by subcutaneous injection (Khinchi et al. 2004; Lima et al. 2002).

ASSESSMENT OF DEVICES THAT MAY MODIFY INDOOR AIR

The Expert Panel recommends the following actions to modify indoor air:

- **Vacuuming carpets once or twice a week to reduce accumulation of house dust. Patients sensitive to components of house dust should avoid using conventional vacuum cleaners, and these patients should stay out of rooms where a vacuum cleaner is being or has just been used (EPR—2 1997;** Murray et al. 1983**).** If patients vacuum, they can use a dust mask, a central cleaner with the collecting bag outside the home, or a cleaner fitted with a HEPA filter or with a double bag (Popplewell et al. 2000; Woodfolk et al. 1993).

- **Air conditioning during warm weather, if possible, for patients who have asthma and are allergic to outdoor allergens (Evidence C),** because air conditioning allows windows and doors to stay closed, thus preventing entry of outdoor allergens (Solomon et al. 1980). Regular use of central air conditioning also will usually control humidity sufficiently to reduce house-dust mite growth during periods of high humidity (Arlian et al. 2001). Reducing relative humidity is a practical way to control house-dust mites and their allergens in homes in temperate climates (Arlian et al. 2001).

- **Use of a dehumidifier to reduce house-dust mite levels in areas where the humidity of the outside air remains high for most of the year (EPR—2 1997).** House-dust mite levels can be reduced by use of dehumidifiers to maintain levels to or below 60 percent, ideally 30–50 percent, relative humidity (Cabrera et al. 1995).

- **There is insufficient evidence to recommend indoor air cleaning devices. They may reduce some, but not all airborne allergens, but evidence is limited regarding their impact on asthma control.** Indoor air-cleaning devices cannot substitute for the more effective dust-mite and cockroach control measures described previously, because these heavy particles do not remain airborne (Custis et al. 2003). However, air-cleaning devices (i.e., HEPA and electrostatic precipitating filters) have been shown to reduce airborne dog allergen (Green et al. 1999), cat dander (de Blay et al. 1991a; Francis et al. 2003; Wood et al. 1998), mold spores (Maloney et al. 1987), and particulate tobacco smoke (EPA 1990). Use of an air cleaning device containing a HEPA filter may reduce exposure, especially if added to other avoidance measures (Green et al. 1999). However, most studies of air cleaners have failed to demonstrate an effect on asthma symptoms or pulmonary function (Nelson et al. 1988; Reisman et al. 1990; Warburton et al. 1994; Warner et al. 1993; Wood et al. 1998). Air cleaners that are designed to work by the generation of ozone and that emit ozone into the air should be avoided by persons who have asthma.

- **There is insufficient evidence to recommend cleaning air ducts of heating/ventilation/air conditioning systems (Evidence D).** Cleaning has been reported to decrease levels of airborne fungi in residences (Garrison et al. 1993). The effect on levels of house-dust mite or animal dander has not been studied. Limited evidence continues to preclude the Expert Panel's making a recommendation in this area.

The Expert Panel does not generally recommend use of humidifiers and evaporative (swamp) coolers for use in the homes of house-dust mite-sensitive patients who have asthma (Evidence C). If use of a humidifier is desired to avoid excessive dryness, the relative humidity in the home should be maintained below 60 percent, ideally between 30 and 50 percent. These machines are potentially harmful because increased humidity may

encourage the growth of both mold (Solomon 1976) and house-dust mites (Ellingson et al. 1995; McConnell et al. 2002). In addition, humidifiers may pose a problem because, if not properly cleaned, they can harbor and aerosolize mold spores (Solomon 1974).

Occupational Exposures

The Expert Panel recommends that clinicians query patients who are employed and have asthma about possible occupational exposures, particularly those who have new-onset disease (EPR—2 1997). Early recognition and control of exposures are particularly important in occupationally induced asthma, because the likelihood of complete resolution of symptoms decreases with time (Pisati et al. 1993). Occupational asthma is suggested by a correlation between asthma symptoms and work, as well as with improvement when away from work for several days. Other indications of workplace exposure are listed in figure 3–21. The patient may fail to recognize the relationship with work, because symptoms often begin several hours after exposure. Recently, common jobs—such as domestic cleaner, laboratory technician, and house painter—have been associated with the disease (Moscato et al. 1995). Serial peak flow records at work and away from work can confirm the association between work and asthma (Nicholson et al. 2005).

Workplace exposure to sensitizing chemicals, allergens, or dusts can induce asthma which often persists after the exposures are terminated (Pisati et al. 1993). This effect should be distinguished from allergen- or irritant-induced aggravation of preexisting asthma.

Patient confidentiality issues are particularly important in work-related asthma. Because even general inquiries about the potential adverse health effects of work exposures may occasionally result in reprisals against the patient (e.g., job loss), patients who have asthma need to be informed of this possibility and be full partners in the decision to approach management regarding the effects or control of workplace exposures. This situation may require referral to an occupational asthma specialist.

Irritants

The Expert Panel recommends that clinicians query patients who have asthma at any level of severity about exposures to irritants that may cause their asthma to worsen, and advise them accordingly about reducing relevant exposures (EPR—2 1997). Sample assessment questions are in figure 3–17.

ENVIRONMENTAL TOBACCO SMOKE

The Expert Panel recommends that clinicians advise persons who have asthma not to smoke or be exposed to ETS (Evidence C). Query patients about their smoking status and specifically consider referring to smoking cessation programs adults who smoke and have young children who have asthma in the household (Evidence B).

Exposure to ETS is common in the United States (Gergen et al. 1998). ETS is associated with increased symptoms, decreased lung function, and greater use of health services among those who have asthma (Sippel et al. 1999) in all age groups, although exact negative effects may vary by age (Mannino et al. 2001). Exposure to maternal smoking has been shown to be a risk factor for the development of asthma in infancy and childhood (Henderson et al. 1995; Martinez et al. 1995; Soyseth et al. 1995). Effects of ETS on a child's asthma are greater when the mother smokes than when others in the household smoke (Agabiti et al. 1999; Austin and

Russell 1997; Ehrlich et al. 2001). Heavy smokers may be more unaware than those who smoke less of the effects of ETS exposure on children (Crombie et al. 2001). The primary modes of exposure to ETS for adults who have asthma may be when they are at work (Radon et al. 2002) or traveling (Eisner and Blanc 2002). ETS exposure operates as a cofactor in wheezing, along with other insults such as infections (Gilliland et al. 2001). Smoking out of doors to avoid exposing others may not adequately reduce exposure for children (Bahceciler et al. 1999). See "Component 2: Education for a Partnership in Asthma Care" for discussion of programs to encourage parents of children who have asthma not to smoke.

As a routine part of their asthma care, patients should be counseled concerning the negative effects of smoking and ETS.

INDOOR/OUTDOOR AIR POLLUTION AND IRRITANTS

The Expert Panel recommends that clinicians advise patients to avoid, to the extent possible, exertion or exercise outside when levels of air pollution are high (Evidence C).

Increased pollution levels—especially of particulate matter ≤10 micrometers (PM10) (Abbey et al. 1993; Atkinson et al. 2001; Gent et al. 2003; Koenig et al. 1993; Ostro et al. 1995; Pope et al. 1991; Schwartz et al. 1993; Slaughter et al. 2003; Walters et al. 1994) and ozone (Abbey et al. 1993; Cody et al. 1992; Kesten et al. 1995; Ostro et al. 1995; Ponka 1991; Romieu et al. 1995; Thurston et al. 1992; White et al. 1994), but also of SO_2 (Moseholm et al. 1993) and nitric oxide (NO_2) (Kesten et al. 1995; Moseholm et al. 1993)—have been reported to precipitate symptoms of asthma (Abbey et al. 1993; Koenig et al. 1987; Moseholm et al. 1993; Pope et al. 1991), increase SABA use (Gent et al. 2003), and increase ED visits and hospitalizations for asthma (Cody et al. 1992; Kesten et al. 1995; Ponka 1991; Romieu et al. 1995; Schwartz et al. 1993; Thurston et al. 1992; Walters et al. 1994; White et al. 1994).

High exposure to NO_2 in the week before the start of a respiratory viral infection, at levels within current air quality standards, may increase the severity of virus-induced asthma exacerbations (Chauhan et al. 2003).

Exposure to pollutants may increase airway inflammation (Hiltermann et al. 1999) and enhance the risk of allergic sensitization through simultaneous exposure to aeroallergens (Diaz-Sanchez et al. 1999; Fujieda et al. 1998; Jenkins et al. 1999). The propensity for particulate pollution to enhance allergic sensitization may be genetically regulated (Gilliland et al. 2004; Peden 2005).

Formaldehyde and Volatile Organic Compounds

Formaldehyde and VOCs—which can arise from sources such as new linoleum flooring, synthetic carpeting, particleboard, wall coverings, furniture, and recent painting—have been implicated as potential risk factors for the onset of asthma and wheezing (Garrett et al. 1999; Jaakkola et al. 2004; Rumchev et al. 2004). Clinicians should advise patients to be aware of the potential irritating effects of newly installed furnishings and finishes.

Gas Stoves and Appliances

The Expert Panel recommends that clinicians advise patients to avoid, if possible, exposure to gas stoves and appliances that are not vented to the outside, fumes from wood-burning appliances or fireplaces, sprays, or strong odors (Evidence C).

Use of unvented gas stoves and appliances results in increased indoor levels of NO_2. Use of gas stoves for cooking has been associated with increased respiratory symptoms, including wheezing in school children (Garrett et al. 1998; Withers et al. 1998) and increased prevalence of bronchial hyperresponsiveness in atopic adults (Kerkhof et al. 1999). However, data from the National Health and Nutrition Examination Survey III (NHANES III) did not suggest any impact of gas-stove use on pulmonary function or respiratory symptoms in adults who have asthma (Eisner and Blanc 2003). Infants at high risk for asthma who were exposed to higher levels of NO_2—but levels which currently are not considered to be harmful—had increased days of wheezing and shortness of breath (van Strien et al. 2004). In school-aged children, increased levels of NO_2 were associated with increased bronchitis, wheeze, and asthma in girls but not boys (Shima and Adachi 2000). When unflued gas heaters in schools were replaced, NO_2 levels decreased by two-thirds, accompanied by significant reduction in both daytime and nighttime asthma symptoms (Pilotto et al. 2004). Exposure to gas heaters and appliances in infancy has been found to be a risk for wheezing, asthma, and bronchial hyperresponsiveness as well as sensitization to house-dust mites in school-aged children (Phoa et al. 2004; Ponsonby et al. 2000, 2001). Current use of gas appliances also was found to be a risk for decreased FEV_1 in children sensitized to house-dust mites (Glasgow et al. 2001). Fumes from wood-burning appliances or fireplaces can precipitate symptoms in persons who have asthma (Ostro et al. 1994). Sprays and strong odors, particularly perfumes, can also irritate the lungs and precipitate asthma symptoms.

Comorbid Conditions

The Expert Panel recommends that clinicians evaluate a patient for presence of a chronic comorbid condition when the patient's asthma cannot be well controlled. Treating the following conditions may improve asthma management: ABPA (Evidence A), gastroesophageal reflux (Evidence B), obesity (Evidence B, limited studies), OSA (Evidence D), rhinitis/sinusitis (Evidence B), chronic stress/depression (Evidence D). Several chronic comorbid conditions have been demonstrated to impede asthma management. Evidence suggests that if the conditions are treated appropriately, asthma control can improve, although clearly some conditions are more readily addressed than others. Clinical judgment is needed to weigh the level of asthma control and patient circumstances to determine the appropriate approach.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

The Expert Panel recommends that ABPA should be suspected in patients who have asthma and have the presence or a history of pulmonary infiltrates. It should also be specifically considered in patients who have evidence of IgE sensitization to *Aspergillus* (positive prick skin test or in vitro tests) and in corticosteroid-dependent patients who have asthma (Evidence A). ABPA complicates both asthma and cystic fibrosis (Greenberger 2002). The fungus grows saphrophytically in bronchial mucus in the bronchi. Although there is no tissue invasion, a surrounding, predominantly eosinophilic inflammation occurs and often leads to damage to the bronchial wall and development of the typical proximal bronchiectasis, which may be varicose (beaded), cylindrical, or saccular (cystic). The classic clinical presentation includes transient migratory lung shadows on chest x ray or computer tomography (CT), peripheral blood eosinophilia, pyrexia, and sputum containing brown plugs or flecks. Occasionally, the same presentation is produced by another organism, usually another fungus.

Clear diagnostic criteria for ABPA are lacking; minimum criteria for the diagnosis of ABPA complicating asthma include (Greenberger 2002):

- Positive immediate skin test to *Aspergillus*
- Total serum IgE >417 IU (1,000 ng/mL)
- Elevated serum IgE and/or immunoglobulin G (IgG) to *Aspergillus*
- Central bronchiectasis (inner two-thirds of the chest CT fields)

An earlier form of the disease, before it has progressed to produce central bronchiectasis, can be diagnosed based on the first three criteria above in patients who have asthma. Additional supporting findings for a diagnosis of ABPA include a history of pulmonary infiltrates, serum precipitating antibodies to *Aspergillus,* peripheral blood eosinophilia, and production of mucus plugs containing *Aspergillus.*

The standard treatment for ABPA is prednisone, initially 0.5 mg per kilogram, with gradual tapering monitored by repeat chest x rays and measurement of total serum IgE concentrations (Greenberger 2002). Azole antifungal agents have also been tried as adjunctive treatment in patients who are stable and who have ABPA (Wark et al. 2003). Itraconazole administered orally for 16 weeks reduced sputum eosinophilia, serum IgE and IgG levels, and the number of exacerbations requiring oral corticosteroids (Stevens et al. 2000).

GASTROESOPHAGEAL REFLUX DISEASE

The Expert Panel recommends that medical management of GERD be instituted for patients who have asthma and complain of frequent heartburn or pyrosis, particularly those who have frequent episodes of nocturnal asthma (Evidence B).

For patients who have poorly controlled asthma, particularly with a nocturnal component, investigation for GERD may be warranted even in the absence of suggestive symptoms (Irwin et al. 1989; Kiljander et al. 1999).

Medical management of GERD includes:

- Avoiding heavy meals, fried food, caffeine, and alcohol.
- Avoiding food and drink within 3 hours of retiring (Nelson 1984).
- Elevating the head of the bed on 6- to 8-inch blocks (Nelson 1984).
- Using appropriate pharmacologic therapy (Harding 1999).

For patients who have persistent reflux symptoms following optimal therapy, further evaluation is indicated.

The symptoms of GERD are common in both children and adults who have asthma (Harding 1999). Reflux during sleep can contribute to nocturnal asthma (Avidan et al. 2001; Cibella and Cuttitta 2001; Davis et al. 1983; Martin et al. 1982). Although a systematic review concluded that there was no overall improvement in asthma following medical treatment for GERD (Gibson et al. 2003), treatment with a proton pump inhibitor was reported to reduce nocturnal symptoms (Kiljander et al. 1999), reduce asthma exacerbations, and improve quality of life related to asthma (Littner et al. 2005). Surgical treatment has been reported to reduce the symptoms of asthma and the requirement for medication (Field et al. 1999; Perrin-Fayolle et al. 1989; Sontag et al. 2003).

OBESITY

The Expert Panel recommends that clinicians consider advising asthma patients who are overweight or obese that weight loss, in addition to improving overall health, might also improve their asthma control (Evidence B, limited studies).

Obesity has been associated with asthma persistence and severity in both children and adults (Camargo et al. 1999; Schaub and von Mutius 2005; Shore and Fredberg 2005; Weiss 2005; Weiss and Shore 2004). Although obesity itself causes alterations in pulmonary physiology that can lead to dyspnea, studies have documented specific increases in asthma among overweight and obese persons.

Increased risk from obesity appears to be greatest in postpubertal women and is associated with more severe symptoms, enhanced airway inflammation, and new-onset or persistent disease (Camargo et al. 1999; Guerra et al. 2004). Presently, the relationship of obesity to allergy is controversial.

The effects of obesity on asthma appear to be independent of diet and physical activity, although these three factors are clearly interrelated. Many epidemiologic studies have controlled for potential effects of diet and physical activity when examining the relationship of obesity to asthma onset (Camargo et al. 1999).

The few RCTs that have been done are small, but they show that weight loss in adults resulted in improvement in pulmonary mechanics, improved FEV_1, reductions in exacerbations and courses of oral corticosteroids, and improved quality of life (Stenius-Aarniala et al. 2000). Weight loss following gastric bypass surgery improved self-reported asthma severity (Simard et al. 2004).

OBSTRUCTIVE SLEEP APNEA

The Expert Panel recommends that clinicians consider evaluating patients who have unstable, not-well-controlled asthma, particularly those who are overweight or obese, to ascertain whether they have symptoms that suggest OSA (Evidence D).

OSA and nocturnal asthma are distinct entities that fall within the broad classification of sleep-disordered breathing. Patients who have OSA and nocturnal asthma may have similar clinical presentations. Both conditions may involve repetitive sleep arousals associated with changes in oronasal airflow, ventilatory effort, and decreases in oxygen saturation (SaO_2) during sleep. Consequently, each of these disorders may be mistaken for the other in some patients. Moreover, asthma and OSA may coexist in a significant number of patients. Congestion of the nasopharynx, with resultant mouth breathing, may heighten the expression of both conditions. OSA-induced hypoxemia may predispose to increased bronchial reactivity, and vagal tone is increased during obstructive apneas (Denjean et al. 1988; Tilkian et al. 1978). On the other hand, sleep disruption secondary to nocturnal asthma could cause periodic breathing and decreased upper airway muscle activity, contributing to upper airway obstruction during sleep. A high prevalence of OSA has been reported in patients who have unstable asthma (Yigla et al. 2003).

Patients who have unstable asthma **and** sleep apnea demonstrated improvement when treated with nasal continuous positive airway pressure (CPAP). Morning and evening PEF before and after SABA significantly improved (Chan et al. 1988). However, nocturnal nasal CPAP in

individuals who have asthma and who do not have apnea is associated with disrupted sleep architecture (Martin and Pak 1991). Thus, confirmation of diagnosis is important.

RHINITIS/SINUSITIS

The Expert Panel recommends that clinicians evaluate patients who have asthma regarding the presence of rhinitis/sinusitis diagnosis or symptoms (Evidence B). It is important for clinicians to appreciate the connection between upper and lower airway conditions and the part the connection plays in asthma management.

There is considerable evidence for the interrelationship of the upper and lower airway and the concept of the airway as a continuum. Varied epidemiologic studies support a substantial association between allergic rhinitis and asthma (Guerra et al. 2002; Leynaert et al. 1999; Linneberg et al. 2002). Those persons who treat asthma need to concern themselves with the best therapy for the upper airway to optimize overall therapy for their patients.

In addition to the general similarity of normal nasal and bronchial mucosa, these mucosa may show similar changes when inflamed, including erosion of the epithelium, thickening of the basement membrane, and cellular infiltrate that is often eosinophilic (Ponikau et al. 2003). In patients who have allergic rhinitis, nasal allergen challenge has been shown to induce adhesion molecule expression and inflammatory mediators in bronchial mucosa and sputum (Beeh et al. 2003; Braunstahl et al. 2001). Segmental bronchial allergen challenge causes inflammatory changes in both nasal and bronchial mucosa (Braunstahl et al. 2000, 2001).

Treatment of allergic rhinitis and asthma with intranasal corticosteroids has decreased exhaled NO and H_2O_2, markers of lower airway inflammation (Sandrini et al. 2003). Review of the literature on antihistamine therapy in the treatment of asthma reveals positive results (Nelson 2003). Both intranasal steroids and second-generation antihistamines with or without decongestants have been reported to decrease ED visits for asthma (Adams et al. 2002; Corren et al. 2004; Crystal-Peters et al. 2002). However, the validity of the statistical approach used to arrive at this conclusion, in at least one of these articles, has been questioned (Suissa and Ernst 2005). Immunotherapy may also be considered for the treatment of allergic rhinitis (See previous section “Immunotherapy.”)

A similar manifestation of “the airway as a continuum” exists in patients who have sinusitis and asthma. A direct relationship can be seen between severity of CT of sinus, markers of lower airway inflammation including eosinophils in peripheral blood and sputum, level of exhaled NO, as well as decreases in pulmonary function (ten Brinke et al. 2002). In children who have asthma and are treated with intranasal corticosteroids and antibiotics for rhinosinusitis, improvement in respiratory symptoms has been shown to be accompanied by decreases in inflammatory cells and mediators in the nose (Tosca et al. 2003). Studies of sinus surgery in patients who have chronic rhinosinusitis and asthma have shown mixed results (Dunlop et al. 1999; Uri et al. 2002).

STRESS, DEPRESSION, AND PSYCHOSOCIAL FACTORS IN ASTHMA

The Expert Panel recommends that clinicians consider inquiring about the potential role of chronic stress or depression in complicating asthma management for patients whose asthma is not well controlled (Evidence C); additional patient education may be helpful (Evidence D). Clinical trials are needed to evaluate the effect of stress and stress reduction on asthma control, but observational studies demonstrate an association between increased stress

and worsening asthma. See ”Component 2: Education for a Partnership in Asthma Care” for strategies to help improve patients’ coping skills and support for asthma management.

The role of stress and psychological factors in asthma is important but not fully defined. Emerging evidence indicates that stress can play an important role in precipitating exacerbations of asthma and possibly act as a risk factor for an increase in prevalence of asthma (Busse et al. 1995; Sandberg et al. 2004; Wright et al. 2002). Chronic stressors increase the risk of asthma exacerbations, especially in children who have severely negative life events and those who have brittle asthma (Miles et al. 1997; Sandberg et al. 2000).

The mechanisms involved in this process have yet to be fully established and may involve enhanced generation of pro-inflammatory cytokines (Friedman et al. 1994). In a prospective study of a birth cohort predisposed to atopy, higher caregiver stress in the first 6 months after birth was significantly associated with an increased atopic immune profile in the children (high total IgE level, increased production of tumor necrosis factor-alpha (TNF-α) and a suggested trend between higher stress and reduced interferon-gamma (IFN-γ production) (Wright et al. 2004a). Equally important are psychosocial factors that are associated with poor outcome (e.g., conflict between patients and family and the medical staff, inappropriate asthma self-care, depressive symptoms, behavioral problems, emotional problems, and disregard of perceived asthma symptoms) (Brush and Mathé 1993; Strunk et al. 1985; Strunk 1993). Asthma severity can be affected by personal or parental factors, and both should be evaluated in cases of poorly controlled asthma. For example, maternal depression is common among inner-city mothers of children who have asthma and has been associated with increased ED visits and poor adherence to therapy by these children (Bartlett et al. 2001, 2004). Furthermore, in a large prospective study of inner-city children who had asthma, increased exposure to violence, as reported by caretakers, predicted a higher number of symptom days in their children, with caregivers’ perceived stress mediating some, although not all, of this effect (Wright et al. 2004b). It may also be important to evaluate psychosocial and socioenvironmental factors in children who have repeated hospitalizations; however, it is not clear whether psychosocial factors affect or result from the frequent hospitalizations (Chen et al. 2003).

Other Factors

MEDICATION SENSITIVITIES

Aspirin

The Expert Panel recommends that clinicians query adult patients who have asthma regarding precipitation of bronchoconstriction by aspirin and other NSAIDs (Evidence C). If patients have experienced a reaction to any of these drugs, they should be informed of the potential for all of these drugs to precipitate severe and even fatal exacerbations. Adult patients who have severe persistent asthma or nasal polyps should be counseled regarding the risk of using these drugs (Evidence C). Alternatives to aspirin that usually do not cause acute bronchoconstriction in aspirin-sensitive patients include acetaminophen (7 percent cross-sensitivity) (Jenkins et al. 2004), salsalate (Settipane et al. 1995; Szczeklik et al. 1977), or the COX-2 inhibitor celecoxib (Gyllfors et al. 2003). Aspirin desensitization treatment, followed by daily aspirin, is a potential option to decrease disease activity and reduce corticosteroid requirements (Berges-Gimeno et al. 2003a,b).

As many as 21 percent of adults and 5 percent of children who have asthma have aspirin-induced asthma, especially when identified through oral provocation testing rather than

verbal history (Jenkins et al. 2004). In one study, 39 percent of adults who had asthma and were admitted to an asthma-referral hospital were reported to experience severe and even fatal exacerbations of asthma after taking aspirin or certain other NSAIDs (Spector et al. 1979). The prevalence of aspirin sensitivity increases with increasing age and severity of asthma (Chafee and Settipane 1974; Spector et al. 1979).

Beta-Blockers

The Expert Panel recommends that clinicians advise asthma patients to avoid nonselective beta-blockers, including those in ophthalmological preparations (Evidence B). Nonselective beta-blockers can cause asthma symptoms (Odeh et al. 1991; Schoene et al. 1984), although cardioselective beta-blockers, such as betaxolol, may be tolerated (Dunn et al. 1986). A recent systematic review, primarily of single dose or short-term studies in younger subjects, indicates that patients who have mild to moderate airway obstruction can tolerate cardioselective beta-blockers; therefore, if needed for managing cardiovascular disorders, these agents may be administered after careful evaluation (Salpeter et al. 2002).

SULFITE SENSITIVITY

The Expert Panel recommends that clinicians advise patients who have asthma symptoms associated with eating processed potatoes, shrimp, or dried fruit or with drinking beer or wine to avoid these products (Evidence C). These products contain sulfites, which are used to preserve foods and beverages. Sulfites have caused severe asthma exacerbations, particularly in patients who have severe persistent asthma (Taylor et al. 1988).

INFECTIONS

Viral Respiratory Infections

It is well established that viral respiratory infections can exacerbate asthma, particularly in children under age 10 who have asthma (Busse et al. 1993). Respiratory syncytial virus (RSV), rhinovirus, and influenza virus have been implicated (Busse et al. 1993), with rhinovirus being implicated in the majority of the exacerbations of asthma in children (Johnston et al. 1995). The role of infections causing exacerbations of asthma also appears to be important in adults (Nicholson et al. 1993). Rhinovirus, considered to be mainly an upper airway pathogen, has recently been demonstrated in the lower airways in patients who have asthma (Mosser et al. 2005). Rhinovirus infections in patients who have asthma may induce exacerbations due to abnormalities in epithelial cells' innate immune responses to infection (Wark et al. 2005).

Viral infections are the most frequent precipitants of wheezing during infancy and asthma exacerbations during childhood. Many infants and toddlers who wheeze with viral infections are predisposed to have bronchial obstruction during these illnesses because of very small airway size (Martinez et al. 1995), and they will not have further exacerbations during later childhood.

However, chronic asthma also may start as early as the first year of life among infants who have a family history of asthma, persistent rhinorrhea, atopic dermatitis, or high IgE levels. Early identification of these infants would allow institution of environmental controls to reduce exposure to tobacco smoke, animal dander, and house-dust mites and, thus, potentially reduce symptoms. RSV infections severe enough to require hospitalization during infancy and early childhood may be a risk factor for subsequent chronic asthma (Sigurs et al. 2005).

Bacterial Infections

Recent studies in both children and adults suggest that infections with both *Mycoplasma* and *Chlamydia,* in addition to viral infections, may contribute to exacerbation rates and disease chronicity and severity (Cunningham et al. 1998; Esposito et al. 2000; Kraft et al. 2002). Studies to confirm and expand upon these initial observations have been impeded due to the lack of definitive serologic markers to document current or past infection, as well as the inherent difficulties in obtaining biologic specimens from the lower airway to confirm the presence of these infectious agents (Martin et al. 2001).

Influenza Infection

The Expert Panel recommends that clinicians consider inactivated influenza vaccination for patients who have asthma. It is safe to administer in children over 6 months and adults who have asthma (Evidence A), and the Advisory Committee on Immunization Practices of the CDC recommends the vaccine for persons who have asthma because they may be at increased risk for complications from influenza. However, the vaccine should not be given with the expectation that it will reduce either the frequency or severity of asthma exacerbations during the influenza season (Evidence B).

Recent evaluations in both children and adults have yielded inconsistent and unconvincing results regarding the ability of influenza vaccination to reduce either overall rates of asthma exacerbations or exacerbations specifically related to influenza infection during the influenza season (Abadoglu et al. 2004; Bueving et al. 2004; Cates et al. 2004; Kramarz et al. 2001). The Advisory Committee on Immunization Practices recommends inactivated influenza vaccine for persons who have chronic disorders of the pulmonary systems, including asthma, because they are considered to be at increased risk for complications from influenza, such as hospitalizations and increased requirements for antibiotics (CDC 2006).

Administration of partially inactivated influenza vaccine is safe in both adults and children who have asthma (American Lung Association Asthma Clinical Research Centers 2001). Vaccination with cold-adapted, live, attenuated influenza vaccine has also been demonstrated to be safe in school-aged, adolescent, and adult patients who have asthma (Belshe et al. 2004). However, the observation of an increased risk of asthma/reactive airway disease in children <36 months of age is of potential concern (Bergen et al. 2004). In patients who have documented histories of anaphylactic reactions after ingestion of egg protein and documented evidence of current allergic sensitization to eggs (skin testing or in vitro antigen-specific IgE antibody testing), the risk/benefit ratio of administration of influenza vaccine should be reviewed carefully. If the decision is made to administer the live, attenuated vaccine, a subspecialist familiar with appropriate challenge testing and published safe administration protocols should be consulted prior to administration (Zeiger 2002).

FEMALE HORMONES AND ASTHMA

In the opinion of the Expert Panel, no recommendation can be made at this time regarding female hormones and asthma.

There is considerable interest in the effects of female hormones on asthma severity. Studies are not totally concordant in their findings, but most evidence suggests that some women have worsening of their asthma during the premenstrual and menstrual times of the cycle (Haggerty et al. 2003; Shames et al. 1998). Two ED studies, however, suggest that many women

experience asthma exacerbations during the preovulatory phase (Brenner et al. 2005; Zimmerman et al. 2000). Studies on hormone replacement therapy (HRT) after menopause also demonstrate apparent discordance. A cross-sectional study reported better pulmonary function and less frequent asthma exacerbations (Kos-Kudla et al. 2001), whereas a prospective cohort study found higher risk of adult-onset asthma (Barr et al. 2004).

Although associations between female hormones and asthma severity are not uniform or clear, it may be useful for clinicians, as they develop action plans with their patients, to appreciate the role that female hormone levels may have in the course of asthma.

DIET

In the opinion of the Expert Panel, there is insufficient evidence to make specific recommendations with regard to dietary constituents that should be consumed or avoided to affect asthma.

Patients have great interest in whether dietary factors may influence the onset, persistence, or severity of asthma. Although people who have asthma frequently experience bronchoconstriction as part of an acute IgE-mediated reaction to a food, food allergy is rarely the main aggravating factor in chronic asthma in children and even more rarely in adults (Sampson 2003).

Preliminary evidence suggests that antioxidant vitamins (Currie et al. 2005; Devereux et al. 2002; Kaur et al. 2001; Martindale et al. 2005; McKeever et al. 2004; Pearson et al. 2004; Shaheen et al. 2001) and omega-3 fatty acids (Broadfield et al. 2004; Dunstan et al. 2003; Kompauer et al. 2004; Mihrshahi et al. 2003, 2004; Peat et al. 2004; Woods et al. 2004) reduce asthma development and symptom severity, but no conclusive evidence shows that any dietary factors prevent or exacerbate the disease.

Physicians and patients are encouraged to promote a varied diet consistent with the Dietary Guidelines for Americans (DHHS and USDA 2005). In brief, most Americans need to consume diets with more fruits, vegetables, and whole grains, and eat less solid fats (saturated fat, *trans* fat), salt, and added sugars.

Primary Prevention of Allergic Sensitization and Asthma

In the opinion of the Expert Panel, there is insufficient evidence to recommend any specific strategies to prevent the development of asthma.

Primary prevention of asthma—preventing initial development—is an active area of investigation. Although a number of trials have investigated dietary and environmental manipulations as preventive measures for asthma and allergy, clinical trials have not been uniform in their approaches, making firm conclusions difficult. Also, most of these interventions have been evaluated over a relatively short period of time, thus limiting their weight for any long-term implications.

Evaluations of dust-mite mitigation in homes of children of atopic parents show effectiveness of interventions in decreasing dust-mite levels as well as decreased incidence of wheezing (Custovic et al. 2001; Tsitoura et al. 2002). Prospective assessment of dust-mite reduction and cow's milk avoidance (breastfeeding or hydrolysate) appears to show protective effects at

8-year followup (Arshad et al. 2003), while breastfeeding, dust-mite and pet avoidance, and tobacco smoke avoidance were protective at 7-year followup (Chan-Yeung et al. 2005).

Trials evaluating breastfeeding have generally shown protective benefit (Chandra 1997; Gdalevich et al. 2001; Oddy et al. 1999), although there are conflicting studies (Sears et al. 2003; Wright et al. 2001). Pet exposure as preventive or provocative is controversial (Celedon et al. 2002; Ownby et al. 2002). Although interesting data support the development of tolerance rather than clinical disease after exposure to cat (Platts-Mills et al. 2001), there is also contrary information (Brussee et al. 2005).

Dietary modification or supplementation with antioxidants or omega-3 polyunsaturated fatty acids to reduce the likelihood of asthma and allergic diseases requires further research (Devereux and Seaton 2005). Preliminary studies with probiotics show promise (Kalliomaki et al. 2001; Rautava et al. 2005) but require further study.

Several recent studies have suggested that acetaminophen may contribute to the pathogenesis of asthma and asthma-related symptoms. The effect has been observed in both children and adults in population-based, birth-cohort, and case-control studies. A comprehensive review of this topic has been published (Eneli et al. 2005). However, one potential limitation of many studies on intake of commonly available over-the-counter analgesics, such as acetaminophen, is the potential for confounding by indication (Signorello et al. 2002). In summary, preliminary evidence appears to indicate a possible association between acetaminophen intake and wheeze, but the data are limited and potentially confounded. Although choice of analgesic/antipyretic should always be made carefully, at the current time, it would be premature to recommend avoidance of acetaminophen.

Exposure to daycare in early childhood may be beneficial, while tobacco smoke exposure both in utero and in early childhood is a risk factor for asthma (Becker et al. 2004; Gergen et al. 1998; Gilliland et al. 2001). Larger family size may be preventive, with the incidence of asthma decreasing with an increasing number of siblings (Bodner et al. 1998; Mattes et al. 1999; Rona et al. 1997). The weight of evidence regarding larger family size, daycare exposure with more likelihood of respiratory infection, and country living is in keeping with the hygiene hypothesis of the origin of atopy and asthma. This hypothesis purports that more developed societies are more prone to higher incidence of allergy and asthma because their cleanliness downregulates immune processes for fighting infection in favor of those that cause atopic disease. Rural lifestyle may be protective compared to urban living (Bibi et al. 2002; Kauffmann et al. 2002).

FIGURE 3–17. ASSESSMENT QUESTIONS* FOR ENVIRONMENTAL AND OTHER FACTORS THAT CAN MAKE ASTHMA WORSE

Inhalant Allergens

Does the patient have symptoms year round? (If yes, ask the following questions. If no, see next set of questions.)

- Does the patient keep pets indoors? What type?
- Does the patient have moisture or dampness in any room of his or her home (e.g., basement)? (Suggests house-dust mites, molds.)
- Does the patient have mold visible in any part of his or her home? (Suggests molds.)
- Has the patient seen cockroaches or rodents in his or her home in the past month? (Suggests significant cockroach exposure.)
- Assume exposure to house-dust mites unless patient lives in a semiarid region. However, if a patient living in a semiarid region uses a swamp cooler, exposure to house-dust mites must still be assumed.

Do symptoms get worse at certain times of the year? (If yes, ask when symptoms occur.)

- Early spring? (trees)
- Late spring? (grasses)
- Late summer to autumn? (weeds)
- Summer and fall? (*Alternaria*, *Cladosporium,* mites)
- Cold months in temperate climates? (animal dander)

Tobacco Smoke

- Does the patient smoke?
- Does anyone smoke at home or work?
- Does anyone smoke at the child's daycare?

Indoor/Outdoor Pollutants and Irritants

- Is a wood-burning stove or fireplace used in the patient's home?
- Are there unvented stoves or heaters in the patient's home?
- Does the patient have contact with other smells or fumes from perfumes, cleaning agents, or sprays?
- Have there been recent renovations or painting in the home?

Workplace Exposures

- Does the patient cough or wheeze during the week, but not on weekends when away from work?
- Do the patient's eyes and nasal passages get irritated soon after arriving at work?
- Do coworkers have similar symptoms?
- What substances are used in the patient's worksite? (Assess for sensitizers.)

Rhinitis

- Does the patient have constant or seasonal nasal congestion, runny nose, and/or postnasal drip?

Gastroesophageal Reflux Disease (GERD)

- Does the patient have heartburn?
- Does food sometimes come up into the patient's throat?
- Has the patient had coughing, wheezing, or shortness of breath at night in the past 4 weeks?
- Does the infant vomit, followed by cough, or have wheezy cough at night? Are symptoms worse after feeding?

Sulfite Sensitivity

- Does the patient have wheezing, coughing, or shortness of breath after eating shrimp, dried fruit, or processed potatoes or after drinking beer or wine?

Medication Sensitivities and Contraindications

- What medications does the patient use now (prescription and nonprescription)?
- Does the patient use eyedrops? What type?
- Does the patient use any medications that contain beta-blockers?
- Does the patient ever take aspirin or other nonsteroidal anti-inflammatory drugs?
- Has the patient ever had symptoms of asthma after taking any of these medications?

*These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed.

FIGURE 3–18. COMPARISON OF SKIN TESTS WITH IN VITRO TESTS

Advantages of Skin Tests

- Less expensive than in vitro tests.
- Results are available within 1 hour.
- Equally sensitive as in vitro tests.
- Results are visible to the patient. This may encourage compliance with environmental control measures.

Advantages of RAST and Other In Vitro Tests

- Do not require knowledge of skin testing technique.
- Do not require availability of allergen extracts.
- Can be performed on patients who are taking medications that suppress the immediate skin test (antihistamines, antidepressants).
- No risk of systemic reactions.
- Can be done for patients who have extensive eczema.

FIGURE 3–19. PATIENT INTERVIEW QUESTIONS* FOR ASSESSING THE CLINICAL SIGNIFICANCE OF POSITIVE ALLERGY TESTS

- **Animal dander.** If pets are in the patient's home and the patient is sensitive to dander of that species of animal, the likelihood that animal dander allergy is contributing to asthma symptoms is increased if answers to the following questions are affirmative. However, absence of positive responses does not exclude a contribution of animal dander to the patient's symptoms.
  - Do nasal, eye, or chest symptoms appear when the patient is in a room where carpets are being or have just been vacuumed?
  - Do nasal or chest symptoms improve when the patient is away from home for a week or longer?
  - Do the patient's symptoms become worse during the first 24 hours after returning home?
- **House-dust mites.** Mite allergy is more likely to be a contributing factor to asthma severity if answers to the following questions are affirmative. However, absence of a positive response does not exclude a contribution of mite allergen to the patient's symptoms.
  - Do nasal, eye, or chest symptoms appear when the patient is in a room where carpets are being or have just been vacuumed?
  - Does making a bed cause nasal or chest symptoms in the patient?
  - Does the patient sneeze repeatedly in the morning?
- **Indoor fungi (molds).** Contribution of indoor molds in causing asthma symptoms is suggested by a positive answer to this question:
  - Do nasal, eye, or chest symptoms appear when the patient is in damp or moldy rooms, such as basements?
- **Outdoor allergens (pollens and outdoor molds).** Contribution of pollens and outdoor molds in causing asthma symptoms is suggested by a positive answer to this question:
  - Is asthma worse in a specific season or at a time when the patient has hay fever symptoms in spring, summer, fall, or parts of the growing season?
  - Usually, if pollen or mold spores are causing increased asthma symptoms, the patient will also have symptoms of allergic rhinitis—sneezing, itching nose and eyes, runny and obstructed nose.

*These questions are provided as examples for the clinician. The validity and reliability of these questions have not been assessed.

FIGURE 3–20. SUMMARY OF MEASURES TO CONTROL ENVIRONMENTAL FACTORS THAT CAN MAKE ASTHMA WORSE

Allergens

Reduce or eliminate exposure to the allergen(s) the patient is sensitive to, including:

- **Animal dander:** Remove animal from house or, at a minimum, keep animal out of the patient's bedroom.
- **House-dust mites:**
  - **Recommended:** Encase mattress in an allergen-impermeable cover; encase pillow in an allergen-impermeable cover or wash it weekly; wash sheets and blankets on the patient's bed in hot water weekly (water temperature of >130 °F is necessary for killing mites): cooler water and detergent and bleach will still reduce live mites and allergen level. Prolonged exposure to dry heat or freezing can also kill mites but does not remove allergen.
  - **Desirable:** Reduce indoor humidity to or below 60 percent, ideally 30–50 percent; remove carpets from the bedroom; avoid sleeping or lying on upholstered furniture; remove carpets that are laid on concrete.
- **Cockroaches:** Use poison bait or traps to control insects, but intensive cleaning is necessary to reduce reservoirs. Do not leave food or garbage exposed.
- **Pollens (from trees, grass, or weeds) and outdoor molds:** If possible, adults who have allergies should stay indoors, with windows closed, during periods of peak pollen exposure, which are usually during the midday and afternoon.
- **Indoor mold:** Fix all leaks and eliminate water sources associated with mold growth; clean moldy surfaces. Consider reducing indoor humidity to or below 60 percent, ideally 30–50 percent. Dehumidify basements if possible.
- It is recommended that allergen immunotherapy be considered for patients who have asthma if evidence is clear of a relationship between symptoms and exposure to an allergen to which the patient is sensitive.

Tobacco Smoke

Advise patients and others in the home who smoke to stop smoking or to smoke outside the home. Discuss ways to reduce exposure to other sources of tobacco smoke, such as from daycare providers and the workplace.

Indoor/Outdoor Pollutants and Irritants

Discuss ways to reduce exposures to the following:

- Wood-burning stoves or fireplaces
- Unvented gas stoves or heaters
- Other irritants (e.g., perfumes, cleaning agents, sprays)
- Volatile organic compounds (VOCs) such as new carpeting, particle board, painting

FIGURE 3–21. EVALUATION AND MANAGEMENT OF WORK-AGGRAVATED ASTHMA AND OCCUPATIONAL ASTHMA

Evaluation

Potential for workplace-related symptoms:

- Recognized sensitizers (e.g., isocyanates, plant or animal products).
- Irritants* or physical stimuli (e.g., cold/heat, dust, humidity).
- Coworkers may have similar symptoms.

Patterns of symptoms (in relation to work exposures):

- Improvement occurs during vacations or days off (may take a week or more).
- Symptoms may be immediate (<1 hour), delayed (most commonly, 2–8 hours after exposure), or nocturnal.
- Initial symptoms may occur after high-level exposure (e.g., spill).

Documentation of work-relatedness of airflow limitation:

- Serial charting for 2–3 weeks (2 weeks at work and up to 1 week off work, as needed to identify or exclude work-related changes in PEF):
  - Record when symptoms and exposures occur.
  - Record when a bronchodilator is used.
  - Measure and record peak flow (or FEV_1) every 2 hours while awake.
- Immunologic tests.
- Referral for further confirmatory evaluation (e.g., bronchial challenges).

Management

Work-aggravated asthma:

- Work with onsite health care providers or managers/supervisors.
- Discuss avoidance, ventilation, respiratory protection, tobacco smoke-free environment.

Occupationally induced asthma:

- Recommend complete cessation of exposure to initiating agent.

*Material Safety Data Sheets may be helpful for identifying respiratory irritants, but many sensitizers are not listed.

Key: FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow

References

Abadoglu O, Mungan D, Pasaoglu G, Celik G, Misirligil Z. Influenza vaccination in patients with asthma: effect on the frequency of upper respiratory tract infections and exacerbations. *J Asthma* 2004;41(3):279–83.

Abbey DE, Petersen F, Mills PK, Beeson WL. Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a nonsmoking population. *Arch Environ Health* 1993;48(1):33–46.

Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003;(4):CD001186.

Adams RJ, Fuhlbrigge AL, Finkelstein JA, Weiss ST. Intranasal steroids and the risk of emergency department visits for asthma. *J Allergy Clin Immunol* 2002;109(4):636–42.

Adkinson NF Jr, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, Hamilton RG, Weiss ME, Arshad H, Meinert CL, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336(5):324–31.

Agabiti N, Mallone S, Forastiere F, Corbo GM, Ferro S, Renzoni E, Sestini P, Rusconi F, Ciccone G, Viegi G, et al. The impact of parental smoking on asthma and wheezing. SIDRIA Collaborative Group. Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente. *Epidemiology* 1999;10(6):692–8.

Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2007;119(4):780–9. Epub February 2007.

American Academy of Allergy and Immunology Board of Directors. Guidelines to minimize the risk from systemic reactions caused by immunotherapy with allergenic extracts. *J Allergy Clin Immunol* 1994;93(4):811–2.

American Lung Association Asthma Clinical Research Centers. The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med* 2001;345(21):1529–36.

Arbes SJ Jr, Cohn RD, Yin M, Muilenberg ML, Burge HA, Friedman W, Zeldin DC. House dust mite allergen in US beds: results from the First National Survey of Lead and Allergens in Housing. *J Allergy Clin Immunol* 2003;111(2):408–14.

Arlian LG, Neal JS, Morgan MS, Vyszenski-Moher DL, Rapp CM, Alexander AK. Reducing relative humidity is a practical way to control dust mites and their allergens in homes in temperate climates. *J Allergy Clin Immunol* 2001;107(1):99–104.

Arlian LG, Vyszenski-Moher DL, Morgan MS. Mite and mite allergen removal during machine washing of laundry. *J Allergy Clin Immunol* 2003;111(6):1269–73.

Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003;58(6):489–93.

Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, Boumghar A, Forastiere F, Forsberg B, Touloumi G, et al. Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European Approach. *Am J Respir Crit Care Med* 2001;164(10 Pt 1):1860–6.

Austin JB, Russell G. Wheeze, cough, atopy, and indoor environment in the Scottish Highlands. *Arch Dis Child* 1997;76(1):22–6.

Avidan B, Sonnenberg A, Schnell TG, Sontag SJ. Temporal associations between coughing or wheezing and acid reflux in asthmatics. *Gut* 2001;49(6):767–72.

Avner DB, Perzanowski MS, Platts-Mills TA, Woodfolk JA. Evaluation of different techniques for washing cats: quantitation of allergen removed from the cat and the effect on airborne Fel d 1. *J Allergy Clin Immunol* 1997;100(3):307–12.

Bahceciler NN, Barlan IB, Nuhoglu Y, Basaran MM. Parental smoking behavior and the urinary cotinine levels of asthmatic children. *J Asthma* 1999;36(2):171–5.

Barr RG, Wentowski CC, Grodstein F, Somers SC, Stampfer MJ, Schwartz J, Speizer FE, Camargo CA Jr. Prospective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. *Arch Intern Med* 2004;164(4):379–86.

Bartlett SJ, Kolodner K, Butz AM, Eggleston P, Malveaux FJ, Rand CS. Maternal depressive symptoms and emergency department use among inner-city children with asthma. *Arch Pediatr Adolesc Med* 2001;155(3):347–53.

Bartlett SJ, Krishnan JA, Riekert KA, Butz AM, Malveaux FJ, Rand CS. Maternal depressive symptoms and adherence to therapy in inner-city children with asthma. *Pediatrics* 2004;113(2):229–37.

Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. The Canadian asthma primary prevention study: outcomes at 2 years of age. *J Allergy Clin Immunol* 2004;113(4):650–6.

Beeh KM, Beier J, Kornmann O, Meier C, Taeumer T, Buhl R. A single nasal allergen challenge increases induced sputum inflammatory markers in non-asthmatic subjects with seasonal allergic rhinitis: correlation with plasma interleukin-5. *Clin Exp Allergy* 2003;33(4):475–82.

Belshe R, Lee MS, Walker RE, Stoddard J, Mendelman PM. Safety, immunogenicity and efficacy of intranasal, live attenuated influenza vaccine. *Expert Rev Vaccines* 2004;3(6):643–54.

Bergen R, Black S, Shinefield H, Lewis E, Ray P, Hansen J, Walker R, Hessel C, Cordova J, Mendelman PM. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. *Pediatr Infect Dis J* 2004;23(2):138–44.

Berges-Gimeno MP, Simon RA, Stevenson DD. Early effects of aspirin desensitization treatment in asthmatic patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2003a;90(3):338–41.

Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2003b;111(1):180–6.

Bernstein DI, Wanner M, Borish L, Liss GM; Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113(6):1129–36.

Bibi H, Shoseyov D, Feigenbaum D, Nir P, Shiachi R, Scharff S, Peled R. Comparison of positive allergy skin tests among asthmatic children from rural and urban areas living within small geographic area. *Ann Allergy Asthma Immunol* 2002;88(4):416–20.

Bjornsson E, Norback D, Janson C, Widstrom J, Palmgren U, Strom G, Boman G. Asthmatic symptoms and indoor levels of micro-organisms and house dust mites. *Clin Exp Allergy* 1995;25(5):423–31.

Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. The Aberdeen WHEASE Group. *Thorax* 1998;53(1):28–32.

Boulet LP, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. *J Allergy Clin Immunol* 1983;71(4):399–406.

Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;161(6):2051–7.

Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001;107(3):469–76.

Brenner BE, Holmes TM, Mazal B, Camargo CA Jr. Relation between phase of the menstrual cycle and asthma presentations in the emergency department. *Thorax* 2005;60(10):806–9.

Broadfield EC, McKeever TM, Whitehurst A, Lewis SA, Lawson N, Britton J, Fogarty A. A case-control study of dietary and erythrocyte membrane fatty acids in asthma. *Clin Exp Allergy* 2004;34(8):1232–6.

Brush J, Mathé A. Psychiatric aspects. In: Weiss EB, Stein M, eds. *Bronchial Asthma.* Boston: Little, Brown and Company, 1993. pp. 1121–31.

Brussee JE, Smit HA, van Strien RT, Corver K, Kerkhof M, Wijga AH, Aalberse RC, Postma D, Gerritsen J, Grobbee DE, et al. Allergen exposure in infancy and the development of sensitization, wheeze, and asthma at 4 years. *J Allergy Clin Immunol* 2005;115(5):946–52.

Bueving HJ, Bernsen RM, de Jongste JC, Suijlekom-Smit LW, Rimmelzwaan GF, Osterhaus AD, Rutten-van Molken MP, Thomas S, van der Wouden JC. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. *Am J Respir Crit Care Med* 2004;169(4):488–93.

Busse WW, Kiecolt-Glaser JK, Coe C, Martin RJ, Weiss ST, Parker SR. NHLBI Workshop summary. Stress and asthma. *Am J Respir Crit Care Med* 1995;151(1):249–52. Review.

Busse WW, Lemanske RF Jr, Stark JM, Calhoun WJ. The role of respiratory infections in asthma. In: Holgate ST, Austen KF, Lichtenstein LM, Kay AB, eds. *Asthma: Physiology, Immunopharmacology and Treatment.* London: Academic Press, 1993. Ch. 26, pp. 345–53.

Cabrera P, Julia-Serda G, Rodriguez de Castro F, Caminero J, Barber D, Carrillo T. Reduction of house dust mite allergens after dehumidifier use. *J Allergy Clin Immunol* 1995;95(2):635–6.

Call RS, Smith TF, Morris E, Chapman MD, Platts-Mills TA. Risk factors for asthma in inner city children. *J Pediatr* 1992;121(6):862–6.

Call RS, Ward G, Jackson S, Platts-Mills TA. Investigating severe and fatal asthma. *J Allergy Clin Immunol* 1994;94(6 Pt 1):1065–72.

Camargo CA Jr, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med* 1999;159(21):2582–8.

Canadian Society of Allergy and Clinical Immunology. Guidelines for the use of allergen immunotherapy. *CMAJ* 1995;152(9):1413–9.

Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. *J Allergy Clin Immunol* 2003;111(3):437–48, quiz 449.

Carter MC, Perzanowski MS, Raymond A, Platts-Mills TA. Home intervention in the treatment of asthma among inner-city children. *J Allergy Clin Immunol* 2001;108(5):732–737.

Cates CJ, Jefferson TO, Bara AI, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev* 2004;(2):CD000364.

Celedon JC, Litonjua AA, Ryan L, Platts-Mills T, Weiss ST, Gold DR. Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. *Lancet* 2002;360(9335):781–2.

Centers for Disease Control and Prevention, Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;55(RR-10):1–42. Erratum in: *MMWR Morb Mortal Wkly Rep* 2006;55(29):800.

Chafee FH, Settipane GA. Aspirin intolerance. I. Frequency in an allergic population. *J Allergy Clin Immunol* 1974;53:193–9.

Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: role of snoring and obstructive sleep apnea. *Am Rev Respir Dis* 1988;137(6):1502–4.

Chandra RK. Five-year follow-up of high-risk infants with family history of allergy who were exclusively breast-fed or fed partial whey hydrolysate, soy, and conventional cow's milk formulas. *J Pediatr Gastroenterol Nutr* 1997;24(4):380–8.

Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, Dybuncio A, Becker A. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005;116(1):49–55.

Chauhan AJ, Inskip HM, Linaker CH, Smith S, Schreiber J, Johnston SL, Holgate ST. Personal exposure to nitrogen dioxide (NO_2) and the severity of virus-induced asthma in children. *Lancet* 2003;361(9373):1939–44.

Chen E, Bloomberg GR, Fisher EB Jr, Strunk RC. Predictors of repeat hospitalizations in children with asthma: the role of psychosocial and socioenvironmental factors. *Health Psychol* 2003;22(1):12–8.

Cibella F, Cuttitta G. Nocturnal asthma and gastroesophageal reflux. *Am J Med* 2001;111(Suppl 8A):31S–36S.

Cody RP, Weisel CP, Birnbaum G, Lioy PJ. The effect of ozone associated with summertime photochemical smog on the frequency of asthma visits to hospital emergency departments. *Environ Res* 1992;58(2):184–94.

Corren J, Manning BE, Thompson SF, Hennessy S, Strom BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol* 2004;113(3):415–9.

Creticos PS, Reed CE, Norman PS, Khoury J, Adkinson NF Jr, Buncher CR, Busse WW, Bush RK, Gadde J, Li JT, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;334(8):501–6.

Crombie IK, Wright A, Irvine L, Clark RA, Slane PW. Does passive smoking increase the frequency of health service contacts in children with asthma? *Thorax* 2001;56(1):9–12.

Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002;109(1):57–62.

Cunningham AF, Johnston SL, Julious SA, Lampe FC, Ward ME. Chronic *Chlamydia pneumoniae* infection and asthma exacerbations in children. *Eur Respir J* 1998;11(2):345–9.

Currie GP, Lee DK, Anderson WJ. Vitamin E supplements in asthma. *Thorax* 2005;60(2):171–2, author reply 172.

Custis NJ, Woodfolk JA, Vaughan JW, Platts-Mills TA. Quantitative measurement of airborne allergens from dust mites, dogs, and cats using an ion-charging device. *Clin Exp Allergy* 2003;33(7):986–91.

Custovic A, Simpson A, Woodcock A. Importance of indoor allergens in the induction of allergy and elicitation of allergic disease. *Allergy* 1998;53(48 Suppl):115–20.

Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A; NAC Manchester Asthma and Allergy Study Group. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet* 2001;358(9277):188–93.

Davis RS, Larsen GL, Grunstein MM. Respiratory response to intraesophageal acid infusion in asthmatic children during sleep. *J Allergy Clin Immunol* 1983;72(4):393–8.

de Blay F, Chapman MD, Platts-Mills TA. Airborne cat allergen (Fel d I). Environmental control with the cat in situ. *Am Rev Respir Dis* 1991a;143(6):1334–9.

de Blay F, Heymann PW, Chapman MD, Platts-Mills TA. Airborne dust mite allergens: comparison of group II allergens with group I mite allergen and cat-allergen Fel d I. *J Allergy Clin Immunol* 1991b;88(6):919–26.

Denjean A, Roux C, Herve P, Bonniot JP, Comoy E, Duroux P, Gaultier C. Mild isocapnic hypoxia enhances the bronchial response to methacholine in asthmatic subjects. *Am Rev Respir Dis* 1988;138(4):789–93.

Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;99(4):450–3.

Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. *Clin Exp Allergy* 2002;32(1):43–50.

Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005;115(6):1109–1117, quiz 1118. Review.

Diaz-Sanchez D, Garcia MP, Wang M, Jyrala M, Saxon A. Nasal challenge with diesel exhaust particles can induce sensitization to a neoallergen in the human mucosa. *J Allergy Clin Immunol* 1999;104(6):1183–8.

Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, Canonica GW, Passalacqua G. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003;33(2):206–10.

Dolen WK. Skin testing and immunoassays for allergen-specific IgE. *Clin Rev Allergy Immunol* 2001;21(2–3):229–39.

Dunlop G, Scadding GK, Lund VJ. The effect of endoscopic sinus surgery on asthma: management of patients with chronic rhinosinusitis, nasal polyposis, and asthma. *Am J Rhinol* 1999;13(4):261–5.

Dunn TL, Gerber MJ, Shen AS, Fernandez E, Iseman MD, Cherniack RM. The effect of topical ophthalmic instillation of timolol and betaxolol on lung function in asthmatic subjects. *Am Rev Respir Dis* 1986;133(2):264–8.

Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL. Maternal fish oil supplementation in pregnancy reduces interleukin-13 levels in cord blood of infants at high risk of atopy. *Clin Exp Allergy* 2003;33(4):442–8.

Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, Till SJ, Hamid QA, Nouri-Aria KT. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341(7):468–75.

Ehrlich R, Jordaan E, Du TD, Potter P, Volmink J, Zwarenstein M, Weinberg E. Household smoking and bronchial hyperresponsiveness in children with asthma. *J Asthma* 2001;38(3):239–51.

Eisner MD, Blanc PD. Environmental tobacco smoke exposure during travel among adults with asthma. *Chest* 2002;122(3):826–8.

Eisner MD, Blanc PD. Gas stove use and respiratory health among adults with asthma in NHANES III. *Occup Environ Med* 2003;60(10):759–64.

Ellingson AR, LeDoux RA, Vedanthan PK, Weber RW. The prevalence of *Dermatophagoides* mite allergen in Colorado homes utilizing central evaporative coolers. *J Allergy Clin Immunol* 1995;96(4):473–9.

Eneli I, Sadri K, Camargo C Jr, Barr RG. Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. *Chest* 2005;127(2):604–12.

EPR—2. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

Esposito S, Blasi F, Arosio C, Fioravanti L, Fagetti L, Droghetti R, Tarsia P, Allegra L, Principi N. Importance of acute *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections in children with wheezing. *Eur Respir J* 2000;16(6):1142–6.

Field SK, Gelfand GA, McFadden SD. The effects of antireflux surgery on asthmatics with gastroesophageal reflux. *Chest* 1999;116(3):766–74.

Francis H, Fletcher G, Anthony C, Pickering C, Oldham L, Hadley E, Custovic A, Niven R. Clinical effects of air filters in homes of asthmatic adults sensitized and exposed to pet allergens. *Clin Exp Allergy* 2003;33(1):101–5.

Frew AJ. Injection immunotherapy. British Society for Allergy and Clinical Immunology Working Party. *BMJ* 1993;307(6909):919–23.

Friedman EM, Coe CL, Ershler WB. Bidirectional effects of interleukin-1 on immune responses in rhesus monkeys. *Brain Behav Immun* 1994;8(2):87–99.

Fujieda S, Diaz-Sanchez D, Saxon A. Combined nasal challenge with diesel exhaust particles and allergen induces in vivo IgE isotype switching. *Am J Respir Cell Mol Biol* 1998;19(3):507–12.

Garrett MH, Hooper MA, Hooper BM, Abramson MJ. Respiratory symptoms in children and indoor exposure to nitrogen dioxide and gas stoves. *Am J Respir Crit Care Med* 1998;158(3):891–5.

Garrett MH, Hooper MA, Hooper BM, Rayment PR, Abramson MJ. Increased risk of allergy in children due to formaldehyde exposure in homes. *Allergy* 1999;54(4):330–7.

Garrison RA, Robertson LD, Koehn RD, Wynn SR. Effect of heating-ventilation-air conditioning system sanitation on airborne fungal populations in residential environments. *Ann Allergy* 1993;71(6):548–56.

Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001;139(2):261–6.

Gelber LE, Seltzer LH, Bouzoukis JK, Pollart SM, Chapman MD, Platts-Mills TA. Sensitization and exposure to indoor allergens as risk factors for asthma among patients presenting to hospital. *Am Rev Respir Dis* 1993;147(3):573–8.

Gent JF, Triche EW, Holford TR, Belanger K, Bracken MB, Beckett WS, Leaderer BP. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. *JAMA* 2003;290(14):1859–67.

Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD. The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. *Pediatrics* 1998;101(2):E8.

Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. *Cochrane Database Syst Rev* 2003;(2):CD001496.

Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001;163(2):429–36.

Gilliland FD, Li YF, Saxon A, Diaz-Sanchez D. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study. *Lancet* 2004;363(9403):119–25.

Glasgow NJ, Ponsonby AL, Yates RE, McDonald T, Attewell R. Asthma screening as part of a routine school health assessment in the Australian Capital Territory. *Med J Aust* 2001;174(8):384–8.

Golbert TM, Patterson R, Pruzansky JJ. Systemic allergic reactions to ingested antigens. *J Allergy* 1969;44(2):96–107.

Green R, Simpson A, Custovic A, Faragher B, Chapman M, Woodcock A. The effect of air filtration on airborne dog allergen. *Allergy* 1999;54(5):484–8.

Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2002;110(5):685–92.

Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002;109(3):419–25.

Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004;170(1):78–85.

Gyllfors P, Bochenek G, Overholt J, Drupka D, Kumlin M, Sheller J, Nizankowska E, Isakson PC, Mejza F, Lefkowith JB, et al. Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgetic drug celecoxib. *J Allergy Clin Immunol* 2003;111(5):1116–21.

Haggerty CL, Ness RB, Kelsey S, Waterer GW. The impact of estrogen and progesterone on asthma. *Ann Allergy Asthma Immunol* 2003;90(3):284–91.

Halken S, Host A, Niklassen U, Hansen LG, Nielsen F, Pedersen S, Osterballe O, Veggerby C, Poulsen LK. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol* 2003;111(1):169–76.

Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997;155(4):1356–61.

Harding SM. Gastroesophageal reflux and asthma: insight into the association. *J Allergy Clin Immunol* 1999;104(2 Pt 1):251–9.

Henderson FW, Henry MM, Ivins SS, Morris R, Neebe EC, Leu SY, Stewart PW. Correlates of recurrent wheezing in school-age children. The Physicians of Raleigh Pediatric Associates. *Am J Respir Crit Care Med* 1995;151(6):1786–93.

Hiltermann JT, Lapperre TS, van Bree L, Steerenberg PA, Brahim JJ, Sont JK, Sterk PJ, Hiemstra PS, Stolk J. Ozone-induced inflammation assessed in sputum and bronchial lavage fluid from asthmatics: a new noninvasive tool in epidemiologic studies on air pollution and asthma. *Free Radic Biol Med* 1999;27(11−12):1448–54.

Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized *Alternaria* extract. *J Allergy Clin Immunol* 1990;85(2):460–72.

Htut T, Higenbottam TW, Gill GW, Darwin R, Anderson PB, Syed N. Eradication of house dust mite from homes of atopic asthmatic subjects: a double-blind trial. *J Allergy Clin Immunol* 2001;107(1):55–60.

Huss K, Adkinson NF Jr, Eggleston PA, Dawson C, Van Natta ML, Hamilton RG. House dust mite and cockroach exposure are strong risk factors for positive allergy skin test responses in the Childhood Asthma Management Program. *J Allergy Clin Immunol* 2001;107(1):48–54.

Ingram JM, Sporik R, Rose G, Honsinger R, Chapman MD, Platts-Mills TA. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens: relation to sensitization and asthma among children living in Los Alamos, New Mexico. *J Allergy Clin Immunol* 1995;96(4):449–56.

Institute of Medicine. *Damp Indoor Spaces and Health.* Washington, DC: The National Academies Press, 2004.

Irwin RS, Zawacki JK, Curley FJ, French CL, Hoffman PJ. Chronic cough as the sole presenting manifestation of gastroesophageal reflux. *Am Rev Respir Dis* 1989;140(5):1294–300.

Jaakkola JJ, Parise H, Kislitsin V, Lebedeva NI, Spengler JD. Asthma, wheezing, and allergies in Russian schoolchildren in relation to new surface materials in the home. *Am J Public Health* 2004;94(4):560–2.

James JM, Bernhisel-Broadbent J, Sampson HA. Respiratory reactions provoked by double-blind food challenges in children. *Am J Respir Crit Care Med* 1994;149(1):59–64.

Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004;328(7437):434.

Jenkins HS, Devalia JL, Mister RL, Bevan AM, Rusznak C, Davies RJ. The effect of exposure to ozone and nitrogen dioxide on the airway response of atopic asthmatics to inhaled allergen: dose- and time-dependent effects. *Am J Respir Crit Care Med* 1999;160(1):33–9.

Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrrell DA, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995;310(6989):1225–9.

Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children—a 14-year study. *Pediatrics* 1968;42(5):793–802.

Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357(9262):1076–9.

Kang BC, Johnson J, Veres-Thorner C. Atopic profile of inner-city asthma with a comparative analysis on the cockroach-sensitive and ragweed-sensitive subgroups. *J Allergy Clin Immunol* 1993;92(6):802–11.

Kauffmann F, Oryszczyn MP, Maccario J. The protective role of country living on skin prick tests, immunoglobulin E and asthma in adults from the Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyper-responsiveness and atopy. *Clin Exp Allergy* 2002;32(3):379–86.

Kaur B, Rowe BH, Ram FS. Vitamin C supplementation for asthma. *Cochrane Database Syst Rev* 2001;(4):CD000993. Review. Update in: *Cochrane Database Syst Rev* 2004;(3):CD000993.

Kerkhof M, De Monchy JG, Rijken B, Schouten JP. The effect of gas cooking on bronchial hyperresponsiveness and the role of immunoglobulin E. *Eur Respir J* 1999;14(4):839–844.

Kesten S, Szalai J, Dzyngel B. Air quality and the frequency of emergency room visits for asthma. *Ann Allergy Asthma Immunol* 1995;74(3):269–73.

Khinchi MS, Poulsen LK, Carat F, Andre C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;59(1):45–53.

Kiljander TO, Salomaa ER, Hietanen EK, Terho EO. Gastroesophageal reflux in asthmatics: a double-blind, placebo-controlled crossover study with omeprazole. *Chest* 1999;116(5):1257–64.

Klucka CV, Ownby DR, Green J, Zoratti E. Cat shedding of Fel d I is not reduced by washings, Allerpet-C spray, or acepromazine. *J Allergy Clin Immunol* 1995;95(6):1164–71.

Koenig JQ, Covert DS, Marshall SG, Van Belle G, Pierson WE. The effects of ozone and nitrogen dioxide on pulmonary function in healthy and in asthmatic adolescents. *Am Rev Respir Dis* 1987;136(5):1152–7.

Koenig JQ, Larson TV, Hanley QS, Rebolledo V, Dumler K, Checkoway H, Wang SZ, Lin D, Pierson WE. Pulmonary function changes in children associated with fine particulate matter. *Environ Res* 1993;63(1):26–38.

Kompauer I, Demmelmair H, Koletzko B, Bolte G, Linseisen J, Heinrich J. n6/n3 hypothesis and allergies: biologically plausible, but not confirmed. *Eur J Med Res* 2004;9(8):378–82.

Kos-Kudla B, Ostrowska Z, Marek B, Ciesielska-Kopacz N, Kajdaniuk D, Kudla M. Effects of hormone replacement therapy on endocrine and spirometric parameters in asthmatic postmenopausal women. *Gynecol Endocrinol* 2001;15(4):304–11.

Kraft M, Cassell GH, Pak J, Martin RJ. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in asthma: effect of clarithromycin. *Chest* 2002;121(6):1782–8.

Kramarz P, DeStefano F, Gargiullo PM, Chen RT, Lieu TA, Davis RL, Mullooly JP, Black SB, Shinefield HR, Bohlke K, et al.; Vaccine Safety Datalink Team. Does influenza vaccination prevent asthma exacerbations in children? *J Pediatr* 2001;138(3):306–10.

Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;104(2 Pt 1):301–4.

Lima MT, Wilson D, Pitkin L, Roberts A, Nouri-Aria K, Jacobson M, Walker S, Durham S. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. *Clin Exp Allergy* 2002;32(4):507–14.

Linneberg A, Henrik NN, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2002;57(11):1048–52.

Littner MR, Leung FW, Ballard ED, Huang B, Samra NK. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. *Chest* 2005;128(3):1128–35.

Long DL, Kramer CL. Air spora of two contrasting ecological sites in Kansas. *J Allergy Clin Immunol* 1972;49(5):255–66.

Luczynska C, Tredwell E, Smeeton N, Burney P. A randomized controlled trial of mite allergen-impermeable bed covers in adult mite-sensitized asthmatics. *Clin Exp Allergy* 2003;33(12):1648–53.

Malling HJ, Dreborg S, Weeke B. Diagnosis and immunotherapy of mould allergy. V. Clinical efficacy and side effects of immunotherapy with *Cladosporium herbarum*. *Allergy* 1986;41(7):507–19.

Maloney MJ, Wray BB, DuRant RH, Smith L, Smith L. Effect of an electronic air cleaner and negative ionizer on the population of indoor mold spores. *Ann Allergy* 1987;59(3):192–4.

Mannino DM, Moorman JE, Kingsley B, Rose D, Repace J. Health effects related to environmental tobacco smoke exposure in children in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Pediatr Adolesc Med* 2001;155(1):36–41.

Martin ME, Grunstein MM, Larsen GL. The relationship of gastroesophageal reflux to nocturnal wheezing in children with asthma. *Ann Allergy* 1982;49(6):318–22.

Martin RJ, Kraft M, Chu HW, Berns EA, Cassell GH. A link between chronic asthma and chronic infection. *J Allergy Clin Immunol* 2001;107(4):595–601.

Martin RJ, Pak J. Nasal CPAP in nonapneic nocturnal asthma. *Chest* 1991;100(4):1024–7.

Martindale S, McNeill G, Devereux G, Campbell D, Russell G, Seaton A. Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life. *Am J Respir Crit Care Med* 2005;171(2):121–128. Epub November 2004.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133–8.

Mattes J, Karmaus W, Storm van's Gravesande K, Moseler M, Forster J, Kuehr J. Pulmonary function in children of school age is related to the number of siblings in their family. *Pediatr Pulmonol* 1999;28(6):414–7.

McConnell R, Berhane K, Gilliland F, Islam T, Gauderman WJ, London SJ, Avol E, Rappaport EB, Margolis HG, Peters JM. Indoor risk factors for asthma in a prospective study of adolescents. *Epidemiology* 2002;13(3):288–95.

McDonald LG, Tovey E. The role of water temperature and laundry procedures in reducing house dust mite populations and allergen content of bedding. *J Allergy Clin Immunol* 1992;90(4 Pt 1):599–608.

McKeever TM, Lewis SA, Smit H, Burney P, Britton J, Cassano PA. Serum nutrient markers and skin prick testing using data from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2004;114(6):1398–402.

Mihrshahi S, Peat JK, Marks GB, Mellis CM, Tovey ER, Webb K, Britton WJ, Leeder SR; Childhood Asthma Prevention Study. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). *J Allergy Clin Immunol* 2003;111(1):162–8. Erratum in: *J Allergy Clin Immunol* 2003; 111(4):735.

Mihrshahi S, Peat JK, Webb K, Oddy W, Marks GB, Mellis CM; CAPS Team. Effect of omega-3 fatty acid concentrations in plasma on symptoms of asthma at 18 months of age. *Pediatr Allergy Immunol* 2004;15(6):517–22.

Miles JF, Garden GM, Tunnicliffe WS, Cayton RM, Ayres JG. Psychological morbidity and coping skills in patients with brittle and non-brittle asthma: a case-control study. *Clin Exp Allergy* 1997;27(10):1151–9.

Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, Koivikko A, Koller DY, Niggemann B, Norberg LA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;109(2):251–6.

Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R III, Stout J, Malindzak G, Smartt E, Plaut M, et al.; Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351(11):1068–80.

Moscato G, Godnic-Cvar J, Maestrelli P, Malo JL, Burge PS, Coifman R. Statement on self-monitoring of peak expiratory flows in the investigation of occupational asthma. Subcommittee on Occupational Allergy of the European Academy of Allergology and Clinical Immunology. American Academy of Allergy and Clinical Immunology. European Respiratory Society. American College of Allergy, Asthma and Immunology. *Eur Respir J* 1995;8(9):1605–10.

Moseholm L, Taudorf E, Frosig A. Pulmonary function changes in asthmatics associated with low-level SO_2 and NO_2 air pollution, weather, and medicine intake. An 8-month prospective study analyzed by neural networks. *Allergy* 1993;48(5):334–44.

Mosser AG, Vrtis R, Burchell L, Lee WM, Dick CR, Weisshaar E, Bock D, Swenson CA, Cornwell RD, Meyer KC, et al. Quantitative and qualitative analysis of rhinovirus infection in bronchial tissues. *Am J Respir Crit Care Med* 2005;171(6):645–51.

Mullins J, White J, Davies BH. Circadian periodicity of grass pollen. *Ann Allergy* 1986;57(5):371–4.

Murray AB, Ferguson AC, Morrison BJ. Diagnosis of house dust mite allergy in asthmatic children: what constitutes a positive history? *J Allergy Clin Immunol* 1983;71(1 Pt 1):21–8.

Murray AB, Milner RA. The accuracy of features in the clinical history for predicting atopic sensitization to airborne allergens in children. *J Allergy Clin Immunol* 1995;96(5 Pt 1):588–96.

Nelson HS. Gastroesophageal reflux and pulmonary disease. *J Allergy Clin Immunol* 1984;73(5 Pt 1):547–56.

Nelson HS. Prospects for antihistamines in the treatment of asthma. *J Allergy Clin Immunol* 2003;112(4 Suppl):S96–S100.

Nelson HS. Allergen immunotherapy: Where is it now? *J Allergy Clin Immunol* 2007;119(4):769–77. Epub March 2007.

Nelson HS, Fernandez-Caldas E. Prevalence of house dust mites in the Rocky Mountain states. *Ann Allergy Asthma Immunol* 1995;75(4):337–9.

Nelson HS, Hirsch SR, Ohman JL Jr, Platts-Mills TA, Reed CE, Solomon WR. Recommendations for the use of residential air-cleaning devices in the treatment of allergic respiratory diseases. *J Allergy Clin Immunol* 1988;82(4):661–9.

Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ* 1993;307(6910):982–6.

Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;62(5):290–9.

Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, Kendall GE, Burton PR. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *BMJ* 1999;319(7213):815–9.

Odeh M, Oliven A, Bassan H. Timolol eyedrop-induced fatal bronchospasm in an asthmatic patient. *J Fam Pract* 1991;32(1):97–8.

O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, Sachs MI. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991;324(6):359–63.

Olsen OT, Larsen KR, Jacobsan L, Svendsen UG. A 1-year, placebo-controlled, double-blind house-dust-mite immunotherapy study in asthmatic adults. *Allergy* 1997;52(8):853–9.

Ostro BD, Lipsett MJ, Mann JK, Braxton-Owens H, White MC. Air pollution and asthma exacerbations among African-American children in Los Angeles. *Inhal Toxicol* 1995;7:711–22.

Ostro BD, Lipsett MJ, Mann JK, Wiener MB, Selner J. Indoor air pollution and asthma. Results from a panel study. *Am J Respir Crit Care Med* 1994;149(6):1400–6.

Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *JAMA* 2002;288(8):963–72.

Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001;31(9):1392–7.

Pearson PJ, Lewis SA, Britton J, Fogarty A. Vitamin E supplements in asthma: a parallel group randomised placebo controlled trial. *Thorax* 2004;59(8):652–6.

Peat JK, Mihrshahi S, Kemp AS, Marks GB, Tovey ER, Webb K, Mellis CM, Leeder SR. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. *J Allergy Clin Immunol* 2004;114(4):807–13.

Peden DB. The epidemiology and genetics of asthma risk associated with air pollution. *J Allergy Clin Immunol* 2005;115(2):213–9.

Peroni DG, Boner AL, Vallone G, Antolini I, Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1994;149(6):1442–6.

Peroni DG, Piacentini GL, Costella S, Pietrobelli A, Bodini A, Loiacono A, Aralla R, Boner AL. Mite avoidance can reduce air trapping and airway inflammation in allergic asthmatic children. *Clin Exp Allergy* 2002;32(6):850–5.

Perrin-Fayolle M, Gormand F, Braillon G, Lombard-Platet R, Vignal J, Azzar D, Forichon J, Adeleine P. Long-term results of surgical treatment for gastroesophageal reflux in asthmatic patients. *Chest* 1989;96(1):40–5.

Phipatanakul W, Cronin B, Wood RA, Eggleston PA, Shih MC, Song L, Tachdjian R, Oettgen HC. Effect of environmental intervention on mouse allergen levels in homes of inner-city Boston children with asthma. *Ann Allergy Asthma Immunol* 2004;92(4):420–5.

Phoa LL, Toelle BG, Ng K, Marks GB. Effects of gas and other fume emitting heaters on the development of asthma during childhood. *Thorax* 2004;59(9):741–5.

Piacentini GL, Martinati L, Fornari A, Comis A, Carcereri L, Boccagni P, Boner AL. Antigen avoidance in a mountain environment: influence on basophil releasability in children with allergic asthma. *J Allergy Clin Immunol* 1993;92(5):644–50.

Pilotto LS, Nitschke M, Smith BJ, Pisaniello D, Ruffin RE, McElroy HJ, Martin J, Hiller JE. Randomized controlled trial of unflued gas heater replacement on respiratory health of asthmatic schoolchildren. *Int J Epidemiol* 2004;33(1):208–14.

Pisati G, Baruffini A, Zedda S. Toluene diisocyanate induced asthma: outcome according to persistence or cessation of exposure. *Br J Ind Med* 1993;50(1):60–4.

Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001;357(9258):752–6.

Platts-Mills TA, Vaughan JW, Carter MC, Woodfolk JA. The role of intervention in established allergy: avoidance of indoor allergens in the treatment of chronic allergic disease. *J Allergy Clin Immunol* 2000;106(5):787–804.

Platts-Mills TA, Vervloet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma: report of the Third International Workshop. *J Allergy Clin Immunol* 1997;100(6 Pt 1):S2–S24.

Pollart SM, Chapman MD, Fiocco GP, Rose G, Platts-Mills TA. Epidemiology of acute asthma: IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. *J Allergy Clin Immunol* 1989;83(5):875–82.

Ponikau JU, Sherris DA, Kephart GM, Kern EB, Gaffey TA, Tarara JE, Kita H. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? *J Allergy Clin Immunol* 2003;112(5):877–82.

Ponka A. Asthma and low level air pollution in Helsinki. *Arch Environ Health* 1991;46(5):262–270.

Ponsonby AL, Couper D, Dwyer T, Carmichael A, Kemp A, Cochrane J. The relation between infant indoor environment and subsequent asthma. *Epidemiology* 2000;11(2):128–35.

Ponsonby AL, Dwyer T, Kemp A, Couper D, Cochrane J, Carmichael A. A prospective study of the association between home gas appliance use during infancy and subsequent dust mite sensitization and lung function in childhood. *Clin Exp Allergy* 2001;31(10):1544–52.

Pope CA III, Dockery DW, Spengler JD, Raizenne ME. Respiratory health and PM10 pollution. A daily time series analysis. *Am Rev Respir Dis* 1991;144(3 Pt 1):668–74.

Popplewell EJ, Innes VA, Lloyd-Hughes S, Jenkins EL, Khdir K, Bryant TN, Warner JO, Warner JA. The effect of high-efficiency and standard vacuum-cleaners on mite, cat and dog allergen levels and clinical progress. *Pediatr Allergy Immunol* 2000;11(3):142–8.

Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, Ricciardi L. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy* 2001;31(8):1295–302.

Radon K, Busching K, Heinrich J, Wichmann HE, Jorres RA, Magnussen H, Nowak D. Passive smoking exposure: a risk factor for chronic bronchitis and asthma in adults? *Chest* 2002;122(3):1086–90.

Rak S, Bjornson A, Hakanson L, Sorenson S, Venge P. The effect of immunotherapy on eosinophil accumulation and production of eosinophil chemotactic activity in the lung of subjects with asthma during natural pollen exposure. *J Allergy Clin Immunol* 1991;88(6):878–88.

Rautava S, Kalliomaki M, Isolauri E. New therapeutic strategy for combating the increasing burden of allergic disease: Probiotics-A Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota (NAMI) Research Group report. *J Allergy Clin Immunol* 2005;116(1):31–7.

Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985–1989. *J Allergy Clin Immunol* 1993;92(1 Pt 1):6–15.

Reid MJ, Moss RB, Hsu YP, Kwasnicki JM, Commerford TM, Nelson BL. Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. *J Allergy Clin Immunol* 1986;78(4 Pt 1):590–600.

Reisman RE, Mauriello PM, Davis GB, Georgitis JW, DeMasi JM. A double-blind study of the effectiveness of a high-efficiency particulate air (HEPA) filter in the treatment of patients with perennial allergic rhinitis and asthma. *J Allergy Clin Immunol* 1990;85(6):1050–7.

Rijssenbeek-Nouwens LH, Oosting AJ, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Anti-allergic mattress covers in asthma: to do or not to do? *Clin Exp Allergy* 2003;33(12):1613–7.

Romieu I, Meneses F, Sienra-Monge JJ, Huerta J, Ruiz Velasco S, White MC, Etzel RA, Hernandez-Avila M. Effects of urban air pollutants on emergency visits for childhood asthma in Mexico City. *Am J Epidemiol* 1995;141(6):546–53.

Rona RJ, Duran-Tauleria E, Chinn S. Family size, atopic disorders in parents, asthma in children, and ethnicity. *J Allergy Clin Immunol* 1997;99(4):454–60.

Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 1997;336(19):1356–63.

Rumchev K, Spickett J, Bulsara M, Phillips M, Stick S. Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax* 2004;59(9):746–51.

Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137(9):715–25.

Sampson HA. Adverse reactions to foods. *Middleton's Allergy Principles and Practice.* 6th ed. Philadelphia: Mosby, Inc., 2003. Ch. 89.

Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327(6):380–84.

Sandberg S, Jarvenpaa S, Penttinen A, Paton JY, McCann DC. Asthma exacerbations in children immediately following stressful life events: a Cox's hierarchical regression. *Thorax* 2004;59(12):1046–1051. Erratum in: *Thorax* 2005;60(3):261.

Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR, Oja H. The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000;356(9234):982–87.

Sandrini A, Ferreira IM, Jardim JR, Zamel N, Chapman KR. Effect of nasal triamcinolone acetonide on lower airway inflammatory markers in patients with allergic rhinitis. *J Allergy Clin Immunol* 2003;111(2):313–20.

Schaub B, von Mutius E. Obesity and asthma, what are the links? *Curr Opin Allergy Clin Immunol* 2005;5(2):185–93.

Schoene RB, Abuan T, Ward RL, Beasley CH. Effects of topical betaxolol, timolol, and placebo on pulmonary function in asthmatic bronchitis. *Am J Ophthalmol* 1984;97(1):86–92.

Schwartz J, Slater D, Larson TV, Pierson WE, Koenig JQ. Particulate air pollution and hospital emergency room visits for asthma in Seattle. *Am Rev Respir Dis* 1993;147(4):826–31.

Sears MR, Burrows B, Herbison GP, Holdaway MD, Flannery EM. Atopy in childhood. II. Relationship to airway responsiveness, hay fever and asthma. *Clin Exp Allergy* 1993;23(11):949–56.

Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349(15):1414–22.

Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989;19(4):419–24.

Settipane RA, Schrank PJ, Simon RA, Mathison DA, Christiansen SC, Stevenson DD. Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects. *J Allergy Clin Immunol* 1995;96(4):480–85.

Shaheen SO, Sterne JA, Thompson RL, Songhurst CE, Margetts BM, Burney PG. Dietary antioxidants and asthma in adults: population-based case-control study. *Am J Respir Crit Care Med* 2001;164(10 Pt 1):1823–8.

Shames RS, Heilbron DC, Janson SL, Kishiyama JL, Au DS, Adelman DC. Clinical differences among women with and without self-reported perimenstrual asthma. *Ann Allergy Asthma Immunol* 1998;81(1):65–72.

Shima M, Adachi M. Effect of outdoor and indoor nitrogen dioxide on respiratory symptoms in schoolchildren. *Int J Epidemiol* 2000;29(5):862–70.

Shore SA, Fredberg JJ. Obesity, smooth muscle, and airway hyperresponsiveness. *J Allergy Clin Immunol* 2005;115(5):925–7.

Signorello LB, McLaughlin JK, Lipworth L, Friis S, Sorensen HT, Blot WJ. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Ther* 2002;9(3):199–205. Review.

Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, Kjellman B. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;171(2):137–41. Epub October 2004.

Simard B, Turcotte H, Marceau P, Biron S, Hould FS, Lebel S, Marceau S, Boulet LP. Asthma and sleep apnea in patients with morbid obesity: outcome after bariatric surgery. *Obes Surg* 2004;14(10):1381–8.

Simon HU, Grotzer M, Nikolaizik WH, Blaser K, Schoni MH. High altitude climate therapy reduces peripheral blood T lymphocyte activation, eosinophilia, and bronchial obstruction in children with house-dust mite allergic asthma. *Pediatr Pulmonol* 1994;17(5):304–11.

Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML. Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. *Chest* 1999;115(3):691–6.

Slaughter JC, Lumley T, Sheppard L, Koenig JQ, Shapiro GG. Effects of ambient air pollution on symptom severity and medication use in children with asthma. *Ann Allergy Asthma Immunol* 2003;91(4):346–53.

Smedje G, Norbäck D, Wessén B, Edling C. Asthma among school employees in relation to the school environment. Indoor Air 96. Proceedings; vol. 1:611–6, 7th International Conference on Indoor Air Quality and Climate; 1996 July 21–26, Nagoya, Japan.

Smith RD, Rooks R. The diurnal variation of air-borne ragweed pollen as determined by a continuous recording particle sampler and implications of the study. *J Allergy* 1954;25(1):36–45.

Solomon WR. Fungus aerosols arising from cold-mist vaporizers. *J Allergy Clin Immunol* 1974;54(4):222–8.

Solomon WR. A volumetric study of winter fungus prevalence in the air of midwestern homes. *J Allergy Clin Immunol* 1976;57(1):46–55.

Solomon WR, Burge HA, Boise JR. Exclusion of particulate allergens by window air conditioners. *J Allergy Clin Immunol* 1980;65(4):305–8.

Sontag SJ, O'Connell S, Khandelwal S, Greenlee H, Schnell T, Nemchausky B, Chejfec G, Miller T, Seidel J, Sonnenberg A. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies. *Am J Gastroenterol* 2003;98(5):987–99.

Soyseth V, Kongerud J, Boe J. Postnatal maternal smoking increases the prevalence of asthma but not of bronchial hyperresponsiveness or atopy in their children. *Chest* 1995;107(2):389–94.

Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J Allergy Clin Immunol* 1979;64(6 Pt 1):500–6.

Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990;323(8):502–7.

Squillace SP, Sporik RB, Rakes G, Couture N, Lawrence A, Merriam S, Zhang J, Platts-Mills AE. Sensitization to dust mites as a dominant risk factor for asthma among adolescents living in central Virginia. Multiple regression analysis of a population-based study. *Am J Respir Crit Care Med* 1997;156(6):1760–4.

Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000;320(7238):827–32. Erratum in: *BMJ* 2000;320(7240):984.

Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, Bamberger DM, Weinmann AJ, Tuazon CU, Judson MA, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med* 2000;342(11):756–62.

Strachan DP. Damp housing and childhood asthma: validation of reporting of symptoms. *BMJ* 1988;297(6658):1223–6. Erratum in: *BMJ* 1988:10;297(6662):1500.

Strunk RC. Death due to asthma. New insights into sudden unexpected deaths, but the focus remains on prevention. *Am Rev Respir Dis* 1993;148(3):550–2.

Strunk RC, Mrazek DA, Fuhrmann GS, LaBrecque JF. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. A case-controlled study. *JAMA* 1985;254(9):1193–8.

Suissa S, Ernst P. Bias in observational study of the effectiveness of nasal corticosteroids in asthma. *J Allergy Clin Immunol* 2005;115(4):714–9.

Swanson MC, Agarwal MK, Reed CE. An immunochemical approach to indoor aeroallergen quantitation with a new volumetric air sampler: studies with mite, roach, cat, mouse, and guinea pig antigens. *J Allergy Clin Immunol* 1985;76(5):724–9.

Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. *J Allergy Clin Immunol* 1977;60(5):276–84.

Targonski PV, Persky VW, Ramekrishnan V. Effect of environmental molds on risk of death from asthma during the pollen season. *J Allergy Clin Immunol* 1995;95(5 Pt 1):955–61.

Taylor SL, Bush RK, Selner JC, Nordlee JA, Wiener MB, Holden K, Koepke JW, Busse WW. Sensitivity to sulfited foods among sulfite-sensitive subjects with asthma. *J Allergy Clin Immunol* 1988;81(6):1159–67.

Taylor WR, Newacheck PW. Impact of childhood asthma on health. *Pediatrics* 1992;90(5):657–62.

ten Brinke A, Grootendorst DC, Schmidt JT, De Bruine FT, van Buchem MA, Sterk PJ, Rabe KF, Bel EH. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002;109(4):621–26.

Terreehorst I, Hak E, Oosting AJ, Tempels-Pavlica Z, De Monchy JG, Bruijnzeel-Koomen CA, Aalberse RC, Gerth van Wijk R. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. *N Engl J Med* 2003;349(3):237–46.

Thurston GD, Ito K, Kinney PL, Lippmann M. A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: results for 1988 and 1989 summers. *J Expo Anal Environ Epidemiol* 1992;2(4):429–50.

Tilkian AG, Motta J, Guilleminault C. Sleep apnea syndromes. In: Tilkian AG, Motta J, Guilleminault C, eds. *Cardiac Arrhythmias in Sleep Apnea.* New York: Alan R. Liss, Inc., 1978. pp. 197–210.

Tosca MA, Cosentino C, Pallestrini E, Caligo G, Milanese M, Ciprandi G. Improvement of clinical and immunopathologic parameters in asthmatic children treated for concomitant chronic rhinosinusitis. *Ann Allergy Asthma Immunol* 2003;91(1):71–8.

Tsitoura S, Nestoridou K, Botis P, Karmaus W, Botezan C, Bojarskas J, Arshad H, Kuehr J, Forster J. Randomized trial to prevent sensitization to mite allergens in toddlers and preschoolers by allergen reduction and education: one-year results. *Arch Pediatr Adolesc Med* 2002;156(10):1021–7.

U.S. Department of Health and Human Services (DHHS) and U.S. Department of Agriculture (USDA). *Dietary Guidelines for Americans, 2005.* 6th ed. Washington, DC, U.S. Government Printing Office, January 2005.

U.S. Environmental Protection Agency (EPA). *Residential Air-Cleaning Devices: A Summary of Available Information.* Washington, DC, Office of Air and Radiation, U.S. Environmental Protection Agency, 1990.

Uri N, Cohen-Kerem R, Barzilai G, Greenberg E, Doweck I, Weiler-Ravell D. Functional endoscopic sinus surgery in the treatment of massive polyposis in asthmatic patients. *J Laryngol Otol* 2002;116(3):185–9.

van der Heide S, Kauffman HF, Dubois AE, De Monchy JG. Allergen reduction measures in houses of allergic asthmatic patients: effects of air-cleaners and allergen-impermeable mattress covers. *Eur Respir J* 1997;10(6):1217–23.

van Strien RT, Gent JF, Belanger K, Triche E, Bracken MB, Leaderer BP. Exposure to NO_2 and nitrous acid and respiratory symptoms in the first year of life. *Epidemiology* 2004;15(4):471–8.

Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy* 1997;27(8):860–7.

Verhoeff AP, van Strien RT, van Wijnen JH, Brunekreef B. Damp housing and childhood respiratory symptoms: the role of sensitization to dust mites and molds. *Am J Epidemiol* 1995;141(2):103–10.

Vervloet D, Charpin D, Haddi E, N'guyen A, Birnbaum J, Soler M, Van der Brempt X. Medication requirements and house dust mite exposure in mite-sensitive asthmatics. *Allergy* 1991;46(7):554–8.

Walters S, Griffiths RK, Ayres JG. Temporal association between hospital admissions for asthma in Birmingham and ambient levels of sulphur dioxide and smoke. *Thorax* 1994;49(2):133–40.

Warburton CJ, Niven RM, Pickering CA, Fletcher AM, Hepworth J, Francis HC. Domiciliary air filtration units, symptoms and lung function in atopic asthmatics. *Respir Med* 1994;88(10):771–6.

Wark PA, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database Syst Rev* 2003;(3):CD001108.

Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, Holgate ST, Davies DE. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005;201(6):937–47.

Warner JA, Marchant JL, Warner JO. Double blind trial of ionisers in children with asthma sensitive to the house dust mite. *Thorax* 1993;48(4):330–3.

Weiss ST. Obesity: insight into the origins of asthma. *Nat Immunol* 2005;6(6):537–9.

Weiss ST, Shore S. Obesity and asthma: directions for research. *Am J Respir Crit Care Med* 2004;169(8):963–8.

White MC, Etzel RA, Wilcox WD, Lloyd C. Exacerbations of childhood asthma and ozone pollution in Atlanta. *Environ Res* 1994;65(1):56–68.

Withers NJ, Low L, Holgate ST, Clough JB. The natural history of respiratory symptoms in a cohort of adolescents. *Am J Respir Crit Care Med* 1998;158(2):352–7.

Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. *Am J Respir Crit Care Med* 1998;158(1):115–20.

Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, Britton J, Strachan D, Howarth P, Altmann D, et al.; Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003;349(3):225–36.

Woodfolk JA, Hayden ML, Couture N, Platts-Mills TA. Chemical treatment of carpets to reduce allergen: comparison of the effects of tannic acid and other treatments on proteins derived from dust mites and cats. *J Allergy Clin Immunol* 1995;96(3):325–33.

Woodfolk JA, Luczynska CM, de Blay F, Chapman MD, Platts-Mills TA. The effect of vacuum cleaners on the concentration and particle size distribution of airborne cat allergen. *J Allergy Clin Immunol* 1993;91(4):829–37.

Woods RK, Raven JM, Walters EH, Abramson MJ, Thien FC. Fatty acid levels and risk of asthma in young adults. *Thorax* 2004;59(2):105–10.

Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001;56(3):192–7.

Wright RJ, Cohen S, Carey V, Weiss ST, Gold DR. Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. *Am J Respir Crit Care Med* 2002;165(3):358–65.

Wright RJ, Finn P, Contreras JP, Cohen S, Wright RO, Staudenmayer J, Wand M, Perkins D, Weiss ST, Gold DR. Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. *J Allergy Clin Immunol* 2004a;113(6):1051–7.

Wright RJ, Mitchell H, Visness CM, Cohen S, Stout J, Evans R, Gold DR. Community violence and asthma morbidity: the Inner-City Asthma Study. *Am J Public Health* 2004b;94(4):625–32.

Yigla M, Tov N, Solomonov A, Rubin AH, Harlev D. Difficult-to-control asthma and obstructive sleep apnea. *J Asthma* 2003;40(8):865–71.

Yunginger JW, Ahlstedt S, Eggleston PA, Homburger HA, Nelson HS, Ownby DR, Platts-Mills TA, Sampson HA, Sicherer SH, Weinstein AM, et al. Quantitative IgE antibody assays in allergic diseases. *J Allergy Clin Immunol* 2000;105(6 Pt 1):1077–84.

Zeiger RS. Current issues with influenza vaccination in egg allergy. *J Allergy Clin Immunol* 2002;110(6):834–40.

Zimmerman JL, Woodruff PG, Clark S, Camargo CA. Relation between phase of menstrual cycle and emergency department visits for acute asthma. *Am J Respir Crit Care Med* 2000;162(2 Pt 1):512–5.

SECTION 3, COMPONENT 4: MEDICATIONS

KEY POINTS: MEDICATIONS

Medications for asthma are categorized into two general classes: long-term control medications used to achieve and maintain control of persistent asthma and quick-relief medications used to treat acute symptoms and exacerbations.

Long-term control medications (listed in alphabetical order)

- **Corticosteroids:** Block late-phase reaction to allergen, reduce airway hyperresponsiveness, and inhibit inflammatory cell migration and activation. They are the most potent and effective anti-inflammatory medication currently available (Evidence A). ICSs are used in the long-term control of asthma. Short courses of oral systemic corticosteroids are often used to gain prompt control of the disease when initiating long-term therapy; long-term oral systemic corticosteroid is used for severe persistent asthma.

- **Cromolyn sodium and nedocromil:** Stabilize mast cells and interfere with chloride channel function. They are used as alternative, but not preferred, medication for the treatment of mild persistent asthma (Evidence A). They can also be used as preventive treatment prior to exercise or unavoidable exposure to known allergens.

- **Immunomodulators:** Omalizumab (anti-IgE) is a monoclonal antibody that prevents binding of IgE to the high-affinity receptors on basophils and mast cells. Omalizumab is used as adjunctive therapy for patients ≥12 years of age who have allergies and severe persistent asthma (Evidence B). Clinicians who administer omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur (see discussion in text).

- **Leukotriene modifiers:** Include LTRAs and a 5-lipoxygenase inhibitor. Two LTRAs are available—montelukast (for patients >1 year of age) and zafirlukast (for patients ≥7 years of age). The 5-lipoxygenase pathway inhibitor zileuton is available for patients ≥12 years of age; liver function monitoring is essential. LTRAs are alternative, but not preferred, therapy for the treatment of mild persistent asthma (Step 2 care) (Evidence A). LTRAs can also be used as adjunctive therapy with ICSs, but for youths ≥12 years of age and adults they are not the preferred adjunctive therapy compared to the addition of LABAs (Evidence A). Zileuton can be used as alternative but not preferred adjunctive therapy in adults (Evidence D).

- **LABAs:** Salmeterol and formoterol are bronchodilators that have a duration of bronchodilation of at least 12 hours after a single dose.

  — LABAs are not to be used as monotherapy for long-term control of asthma (Evidence A).

  — LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma (step 3 care or higher in children ≥5 years of age and adults) (Evidence A for ≥12 years of age, Evidence B for 5–11 years of age).

— Of the adjunctive therapies available, LABA is the preferred therapy to combine with ICS in youths ≥12 years of age and adults (Evidence A).

— In the opinion of the Expert Panel, the beneficial effects of LABA in combination therapy for the great majority of patients who require more therapy than low-dose ICS alone to control asthma (i.e., require step 3 care or higher) should be weighed against the increased risk of severe exacerbations, although uncommon, associated with the daily use of LABAs (see discussion in text).

  ♦ For patients ≥5 years of age who have moderate persistent asthma or asthma inadequately controlled on low-dose ICS, the option to increase the ICS dose should be given equal weight to the option of adding LABA.

  ♦ For patients ≥5 years of age who have severe persistent asthma or asthma inadequately controlled on step 3 care, the combination of LABA and ICS is the preferred therapy.

— LABA may be used before exercise to prevent EIB (Evidence A), but duration of action does not exceed 5 hours with chronic regular use. Frequent and chronic use of LABA for EIB is discouraged, because this use may disguise poorly controlled persistent asthma (Evidence D).

— In the opinion of the Expert Panel, the use of LABA for the treatment of acute symptoms or exacerbations is not currently recommended (Evidence D).

■ **Methylxanthines:** Sustained-release theophylline is a mild to moderate bronchodilator used as alternative, not preferred, adjunctive therapy with ICS (Evidence A). Theophylline may have mild anti-inflammatory effects. Monitoring of serum theophylline concentration is essential.

Quick-relief medications (listed in alphabetical order)

■ **Anticholinergics:** Inhibit muscarinic cholinergic receptors and reduce intrinsic vagal tone of the airway. Ipratropium bromide provides additive benefit to SABA in moderate-to-severe asthma exacerbations. May be used as an alternative bronchodilator for patients who do not tolerate SABA (Evidence D).

■ **SABAs:** Albuterol, levalbuterol, and pirbuterol are bronchodilators that relax smooth muscle. Therapy of choice for relief of acute symptoms and prevention of EIB (Evidence A).

■ **Systemic corticosteroids:** Although not short acting, oral systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations (Evidence A).

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- Information about asthma medications has been updated based on review of evidence published since 1997. *This updated report* (EPR—3: Full Report 2007) *continues to emphasize that the most effective medications for long-term therapy are those shown to have anti-inflammatory effects.*
- New medications—immunomodulators—are available for long-term control of asthma.
- New data on the safety of LABAs are discussed, and the position of LABA in therapy has been revised (see text). The most significant difference is that for youths ≥12 years of age and adults who have moderate persistent asthma or asthma inadequately controlled on low-dose ICS, the option of increasing the dose of medium-dose ICS should be given equal weight to the option of adding LABA to low-dose ICS.
- The estimated clinical comparability of different ICS preparations has been updated. (See Section 4, "Managing Asthma Long-Term," figures 4–4b and 4–8b.) The significant role of ICSs in asthma therapy continues to be supported.

Introduction

See Section 1, "Overall Methods Used To Develop This Report," for the literature search strategies and tallies of results used to update each class of medication discussed in this section. Evidence Tables were prepared for: 11, Inhaled Corticosteroids: Combination Therapy; 12, Inhaled Corticosteroids: Dosing Strategies; 13, Immunomodulators: Anti-IgE; 14, Leukotriene Receptor Antagonists: Monotherapy/Effectiveness Studies; 15, Bronchodilators: Safety of Long-Acting Beta$_2$-Agonists; 16, Bronchodilators: Levalbuterol.

Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction. Recommendations in this "Component 4: Medications," reflect the scientific concepts that asthma is a chronic disorder with recurrent episodes of airflow limitation, mucus production, and cough and that the severity of the underlying asthma may vary over time. Asthma medications are categorized into two general classes: long-term control medications taken daily on a long-term basis to achieve and maintain control of persistent asthma (these medications are also known as long-term preventive, controller, or maintenance medications) and quick-relief medications taken to provide prompt reversal of acute airflow obstruction and relief of accompanying bronchoconstriction (these medications are also known as reliever or rescue medications). Patients who have persistent asthma require both classes of medication. Figures 3–22 and 3–23 present summaries of the indications, mechanisms, potential adverse effects, and therapeutic issues for currently available long-term control and quick-relief medications. The discussion in this component includes the following: an overview of asthma medications—both long-term control and quick-relief—and an overview of complementary alternative medicine strategies.

Overview of the Medications

LONG-TERM CONTROL MEDICATIONS

The Expert Panel recommends that long-term control medications be taken daily on a long-term basis to achieve and maintain control of persistent asthma. The most effective long-term-control medications are those that attenuate the underlying inflammation characteristic of asthma (Evidence A).

Long-term control medications include ICSs, inhaled long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators. Because eosinophilic and lymphocytic inflammation is a constant feature of the mucosa of the airways in asthma, the most effective long-term control medications are those that attenuate inflammation (Haahtela et al. 1991; Kerrebijn et al. 1987; Van Essen-Zandvliet et al. 1992). The Expert Panel defines anti-inflammatory medications as those that cause a reduction in the markers of airway inflammation in airway tissue or airway secretions (e.g., eosinophils, mast cells, activated lymphocytes, macrophages, and cytokines; or ECP and tryptase; or extravascular leakage of albumin, fibrinogen, or other vascular protein) and thus decrease the intensity of airway hyperresponsiveness. Because many factors contribute to the inflammatory response in asthma, many drugs may be considered anti-inflammatory. It is not yet established, however, which anti-inflammatory actions are responsible for therapeutic effects, such as reduction in symptoms, improvement in expiratory flow, reduction in airway hyperresponsiveness, prevention of exacerbations, or prevention of airway wall remodeling.

Inhaled Corticosteroids

Mechanism

The Expert Panel concludes that ICSs are the most potent and consistently effective long-term control medication for asthma (Evidence A). The broad action of ICSs on the inflammatory process may account for their efficacy as preventive therapy. Their clinical effects include reduction in severity of symptoms; improvement in asthma control and quality of life; improvement in PEF and spirometry; diminished airway hyperresponsiveness; prevention of exacerbations; reduction in systemic corticosteroid courses, ED care, hospitalizations, and deaths due to asthma; and possibly the attenuation of loss of lung function in adults (Barnes et al. 1993; Barnes and Pedersen 1993; Dahl et al. 1993; Fabbri et al. 1993; Gustafsson et al. 1993; Haahtela et al. 1991; Jeffery et al. 1992; Kamada et al. 1996; Pauwels et al. 2003; Rafferty et al. 1985; Suissa et al. 2000; Van Essen-Zandvliet et al. 1992).

Which of these clinical effects depend on specific anti-inflammatory actions of corticosteroids is not yet clear. Corticosteroids suppress the generation of cytokines, recruitment of airway eosinophils, and release of inflammatory mediators. These anti-inflammatory actions of corticosteroids have been noted in clinical trials and analyses of airway histology (Booth et al. 1995; Busse 1993; Djukanovic et al. 1992; Duddridge et al. 1993; Laitinen et al. 1991, 1992; Levy et al. 1995; McGill et al. 1995). The anti-inflammatory effects of corticosteroids are mediated through receptors that modulate inflammatory gene expression.

ICSs do not have the same bioavailability as oral systemic corticosteroids; hence, the risk of potential side effects is substantially reduced with ICSs.

Inhaled Corticosteroid Insensitivity

The Expert Panel concludes that sensitivity and consequently clinical response to ICS can vary among patients (Evidence B).

Variation in sensitivity to ICS therapy may be related to high levels of inflammation, corticosteroid-insensitive pathways, or structural changes refractory to corticosteroid therapy (Leung and Bloom 2003). Corticosteroid responsiveness is decreased in smokers (Chalmers et al. 2002; Chaudhuri et al. 2003) and persons who have asthma with predominantly neutrophilic inflammation (Gauvreau et al. 2002; Green et al. 2002). Also, African American children who have poor control of their asthma appear to have an increased risk for corticosteroid insensitivity; this could be related to diminished glucocorticoid responsiveness at the cellular level, specifically T lymphocytes (Chan et al. 1998; Federico et al. 2005).

Efficacy of Inhaled Corticosteroids as Compared to Other Long-Term Control Medications as Monotherapy

The Expert Panel concludes that studies demonstrate that ICSs improve asthma control more effectively in both children and adults than LTRAs or any other single long-term control medication (Evidence A).

For the EPR—3: Full Report 2007, the evidence of the efficacy of ICS therapy compared to other single daily long-term control medications in patients ≥5 years of age was obtained from nine randomized trials, most of which compared ICS to LTRA; five of these trials had placebo control groups (Garcia-Garcia et al. 2005; Ostrom et al. 2005; Szefler et al. 2002, 2005; Zeiger et al. 2006). These studies confirm findings discussed in EPR—Update 2002. Patients who have mild or moderate persistent asthma and are treated with ICS, compared to other single long-term control medications, demonstrate greater improvements in prebronchodilator FEV_1; reduced airway hyperresponsiveness, symptom scores, exacerbation rates, and symptom frequency; as well as less use of supplemental SABA, fewer courses of oral systemic corticosteroids, and less use of hospitalization. The evidence does not suggest, however, that ICS use is associated with improved long-term postbronchodilator FEV_1 (CAMP 2000).

Studies comparing ICS to cromolyn or theophylline are limited, but available evidence shows that neither of these long-term control medications appears to be as effective as ICS in improving asthma outcomes.

Efficacy of Inhaled Corticosteroid and Adjunctive Therapy (Combination Therapy)

The Expert Panel recommends that when patients ≥12 years of age require more than low-dose ICS alone to control asthma (i.e., step 3 care or higher), a therapeutic option is to add LABA to ICS (Evidence A). Alternative, but not preferred adjunctive therapies include LTRA (Evidence B), theophylline (Evidence B), or, in adults, zileuton (Evidence D). (See Evidence Table 11, Inhaled Corticosteroids: Combination Therapy.) For children 0–11 years of age, LABA, LTRA, and, in children 5–11 years of age, theophylline may be considered as adjunctive therapies in combination with ICS (Evidence B, based on extrapolation from studies in older children and adults; see also section 4, "Managing Asthma Long Term" for recommendations on adjunctive therapies at different steps of care for different age groups in children).

Although numerous studies have examined adjunctive therapy in adults, adjunctive therapy has not been studied adequately in children 5–11 years of age, and it has not been evaluated at all in children less than 4 years of age. An extensive review of the literature on this topic, conducted for the EPR—Update 2002, concluded that strong evidence in adults and older children indicates that the combination of ICS and LABA leads to improvements in lung function and symptoms and reduced need for quick-relief SABA. Adding an LTRA or theophylline to ICS or doubling the dose of ICS also was shown to improve outcomes, but the evidence was not as substantial as with the addition of LABA (EPR—Update 2002).

The current review of the evidence supports this conclusion. The 2006 evidence review included studies comparing the combination of ICS and LABA to either baseline dose of ICS (two articles) or increasing doses of ICS (eight articles); comparing the combination of ICS and LTRA to baseline doses of ICS (three articles) or increasing doses of ICS (one article); comparing the combination of ICS and LABA to ICS and LTRA (seven articles); and comparing the combination of ICS and one LABA to another LABA (two articles), as well as three Cochrane Review meta-analyses (See Evidence Table 11, Inhaled Corticosteroids: Combination Therapy for complete citations.). The weight of the evidence reviewed continues to demonstrate that the addition of LABA to ICS leads to greater improvement in lung function, symptoms, and less use of SABA than increasing the dose of ICS or using LTRA as adjunctive therapy. Studies on the addition of LTRA to ICS have limitations that preclude conclusions, although the studies reveal a trend showing that LTRA improved lung function and some but not all trials report improvements in some measures of asthma control (See also the section below on “Leukotriene Modifiers.”). Recent data indicate potential risks that need to be considered for uncommon but life-threatening exacerbations associated with the daily use of LABAs (See the section below on “Safety of Inhaled Long-Acting Beta$_2$-Agonists.”). See also section 4 on “Managing Asthma Long Term” for a discussion of issues to consider regarding combination therapy compared to increasing the dose of ICS.

Dose-Response and Delivery Device

The Expert Panel concludes that dosages for ICSs vary, depending upon the specific product and delivery devices. (See figure 3–24 for issues on delivery devices; see figures 4–4b, and 4–8b in section 4, “Managing Asthma Long Term,” for comparative ICS dosages.) For all ICS preparations, the dose-response relationship appears to flatten in patients who have mild or moderate asthma for most clinical parameters and lung function in the low- to medium-dose range (Evidence C).

Although most of the benefits of treatment are achieved with a low dose, the dose-response to ICS may vary, based on the response measured (e.g., improvement in lung function, prevention of exacerbations, or improvement in bronchial hyperresponsiveness, individual variability in response to ICS, and disease severity). Several studies show that for patients who have mild or moderate persistent asthma, use of higher doses improves asthma control modestly if at all (Bousquet et al. 2002; Holt et al. 2001; Kemp et al. 2000; Masoli et al. 2004a; Nayak et al. 2000; Powell and Gibson 2003; Szefler and Eigen 2002). However, the dose-response continued to improve at a higher dose for patients who have severe asthma (Masoli et al. 2004b). This efficacy of low-dose ICS therapy may account for the success of once-per-day treatment of patients who have mild or moderate persistent asthma, using several ICS preparations—both ICS alone (Casale et al. 2003; Jonasson et al. 2000; Jones et al. 1994; Noonan et al. 2001; Pincus et al. 1995) and in combination with LABA (Buhl et al. 2003). This efficacy may also account for the finding that mild and moderate asthma are as well controlled by starting treatment with a low, standard dose of an ICS as by starting with a high dose (Chanez et al.

2001; Reddel et al. 2000). These generalizations may not apply to patients who have more severe, uncontrolled asthma or to patients who have frequent, severe exacerbations. In these patients, twice-daily therapy with a higher dose may be necessary (Noonan et al. 1995; Pauwels et al. 1997), although control is achieved in a higher proportion of patients, and at a lower ICS dose, when it is given in combination with a LABA (Bateman et al. 2003, 2004).

Variability in Response and Adjustable Dose Therapy

The Expert Panel recommends that, given the variations over time in the severity of the pathophysiologic processes underlying asthma, it may be useful to adjust anti-inflammatory therapy accordingly (Evidence B). (See Evidence Table 12, Inhaled Corticosteroids: Dosing Strategies.)

Several studies have shown that, for most patients whose asthma has been well controlled for at least 2 months by a high dose of an ICS alone, a 50 percent reduction in dose does not lead to loss of control (Aalbers et al. 2004; Hawkins et al. 2003; Leuppi et al. 2003; Thoonen et al. 2003). This finding does not mean, however, that treatment with an ICS can be stopped altogether, for studies show that asthma control in most patients can worsen within a few weeks when treatment is discontinued (CAMP 2000; Dahl et al. 2002). Trials are now focusing on clinical features or “biomarkers” to distinguish between those patients who need continued treatment and those in whom it can be reduced or discontinued (Deykin et al. 2005; Leuppi et al. 2003).

Whether ICS treatment should be increased temporarily in response to some index of worsening asthma is also being examined. The effectiveness of this adjustable dose approach may be a function of timing or of dose. When asthma symptoms have worsened to the point of qualifying as an asthma exacerbation (See section 5 on “Managing Exacerbations of Asthma” for definition.), simply doubling the regular maintenance dose of ICS treatment does not appear to be effective (FitzGerald et al. 2004; Harrison et al. 2004). Studies that have shown benefit to patients from treatment with an adjustable dose regimen have employed greater increase in the dose of ICS (e.g., fourfold) and/or have made this adjustment earlier, at the first appearance of worsening symptoms (Aalbers et al. 2004; Boushey et al. 2005; Foresi et al. 2000; Harrison et al. 2004; Ind et al. 2004; Leuppi et al. 2003; Reddel and Barnes 2006; Thoonen et al. 2003). An interesting application of this approach was made possible by the development of an inhaler containing both budesonide (an ICS) and formoterol (a LABA with a rapid onset of action). Although this product does not have approved labeling for use as an acute quick-relief medication, one study has shown that use of a low dose of budesonide from this combination inhaler twice daily (maintenance therapy) plus additional use for relief of symptoms (adjustable therapy) was associated with a lower rate of asthma exacerbations and a lower cumulative dose of budesonide than was twice daily treatment with a fourfold greater dose of budesonide alone (Bisgaard et al. 2006; O'Byrne et al. 2005; Rabe et al. 2006).

Another approach to adjustable therapy with an ICS is to link the dose adjustments to measurement of a biomarker of airway inflammation. Three biomarkers have been examined: bronchial reactivity to methacholine (Sont et al. 1999), sputum eosinophils (Green et al. 2002), and the concentration of nitric oxide in exhaled air (FeNO) (Smith et al. 2005). In these studies, biomarker-adjusted therapy reduced the rate of asthma exacerbations. In two of the studies (Green et al. 2002; Smith et al. 2005), the cumulative dose of ICS was reduced as well as in comparison to standard maintenance therapy alone.

Safety of Inhaled Corticosteroids

KEY POINTS: SAFETY OF INHALED CORTICOSTEROIDS

- ICSs are the most effective long-term therapy available for mild, moderate, or severe persistent asthma; in general, ICSs are well tolerated and safe at the recommended dosages (Evidence A).
- The potential but small risk of adverse events from the use of ICS treatment is well balanced by their efficacy (Evidence A).
- The dose-response curve for ICS treatment begins to flatten for many measures of efficacy at low to medium doses, although some data suggest that higher doses may reduce the risk of exacerbations. Most benefit is achieved with relatively low doses, whereas the risk of adverse effects increases with dose (Evidence B).
- To reduce the potential for adverse effects, the following measures are recommended:
  - Spacers or valved holding chambers (VHCs) used with non-breath-activated MDIs reduce local side effects (Evidence A), but there are no data on use of spacers with ultra fine particle hydrofluoroalkane (HFA) MDIs.
  - Advise patients to rinse their mouths (rinse and spit) after inhalation (Evidence B).
  - Use the lowest dose of ICS that maintains asthma control. Evaluate patient adherence and inhaler technique as well as environmental factors that may contribute to asthma severity before increasing the dose of ICS (Evidence B).
  - To achieve or maintain control of asthma, consider adding a LABA to a low or medium dose of ICS rather than using a higher dose of ICS (Evidence A).
  - For children, monitor growth (Evidence A). See "Key Points: Inhaled Corticosteroids and Linear Growth in Children."
  - In adult patients, consider supplements of calcium (1,000–1,500 mg per day) and vitamin D (400–800 units a day), particularly in perimenopausal women (Evidence D). Bone-sparing therapy (e.g., bisphosphonate), where appropriate, may be considered for patients on medium or high doses of ICS, particularly for those who are at risk of osteoporosis or who have low bone mineral density (BMD) scores by dual energy x ray absorptiometry (or DEXA) scan (Evidence C). In children, age-appropriate dietary intake of calcium and exercise should be reviewed with the child's caregivers (Evidence D).

The Expert Panel concludes that ICSs are the most effective long-term therapy available for patients who have persistent asthma and, in general, ICSs are well tolerated and safe at the recommended dosages (Evidence A). Systemic activity has been identified, particularly at high doses (See figures 4–4b and 4–8b.), for a definition of high-, medium-, and low-dose ICSs), but their clinical significance remains unclear (Leone et al. 2003). Furthermore, there may be interindividual variations in dose-response effects; thus, some patients may

experience effects at lower doses. See Key Points, above, for a summary of recommendations to minimize the potential for adverse effects. In general, the potential for adverse effects must be weighed against the risk of uncontrolled asthma; to date, evidence supports the use of ICS, especially at low and medium doses (Barnes et al. 1993; CAMP 2000; EPR—Update 2002; Leone et al. 2003; Tinkelman et al. 1993; Van Essen-Zandvliet et al. 1992).

The Expert Panel recommends the following actions to minimize potential adverse effects of ICS. Specific recommendations and evidence rank are presented under "Prevention and Treatment."

Local Adverse Effects

Oral candidiasis (thrush) is one of the most common adverse effects of ICSs. Positive throat cultures of *Candida* can be identified in about 45–58 percent of patients, whereas clinical thrush is diagnosed in only 0–34 percent of patients (Rinehart et al. 1975; Shaw and Edmunds 1986; Toogood et al. 1980). With lower dosages of ICS, candidiasis is uncommon (5 percent) (Rinehart et al. 1975), although it is more frequent in adults than in children. **Prevention and Treatment:** Use a spacer or VHC with a non-breath-activated MDI to reduce the incidence of colonization and clinical thrush; rinse mouth with water after inhalation (Selroos and Halme 1991). No data are available on the use of spacers or VHCs with ultrafine-particle-generated HFA MDIs. Administer ICS less frequently (bid versus qid). Topical or oral antifungal agents should be used to treat active infections (EPR—2 1997).

Dysphonia is reported in 5–50 percent of patients who use an ICS and is associated with vocal stress and increasing dosages of ICS (Toogood et al. 1980). **Prevention and Treatment:** Use a spacer or VHC with a non-breath-activated MDI, temporarily reduce dosage, or rest for vocal stress (EPR—2 1997).

Reflex cough and bronchospasm. **Prevention and Treatment:** These effects can be reduced by slower rates of inspiration and/or use of a spacer or valved holding chamber or by pretreatment with SABA. There is no convincing evidence that the routine use of a SABA before each dose of ICS increases intrapulmonary delivery of the ICS or reduces dosage requirement (EPR—2 1997).

Systemic Adverse Effects

Linear growth. A reduction in growth velocity may occur in children or adolescents as a result of inadequate control of chronic diseases such as asthma or from the use of corticosteroids for treatment. Overall, however, the available cumulative data about children suggest that, although low or medium doses of ICS may have the potential of decreasing growth velocity, the effects are small, nonprogressive, and may be reversible (CAMP 2000; Guilbert et al. 2006; Leone et al. 2003). Furthermore, studies of early intervention with low- or medium-dose ICS showed significantly improved asthma outcomes, despite a small reduction in growth velocity (Guilbert et al. 2006; Pauwels et al. 2003).

The long-term prospective studies on growth involved budesonide, the retrospective analyses included studies on beclomethasone, and several shorter term studies have been performed on a variety of moieties, but the results have been generalized to include all ICS preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies on numerous preparations suggest that the effect of ICS on growth is a drug-class effect. When high doses of ICS are necessary to achieve satisfactory asthma

control, the use of adjunctive long-term control therapy should be initiated to reduce the dose of ICS and thus minimize possible dose-related long-term effects on growth. **Prevention and Treatment:** Physicians should monitor the growth of children and adolescents who are taking corticosteroids by any route and should weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression or delay if a child's or an adolescent's growth appears slowed (Evidence D).

KEY POINTS: INHALED CORTICOSTEROIDS AND LINEAR GROWTH IN CHILDREN

In the opinion of the Expert Panel:

- The potential risks of ICSs are well balanced by their benefits.
- Growth rates are highly variable in children. Short-term evaluations may not be predictive of final adult height attained.
- Poorly controlled asthma may delay growth in children.
- In general, children who have asthma tend to have longer periods of reduced growth rates before puberty (males more than females).
- The potential for adverse effects on linear growth from ICS appears to be dose dependent. In treatment of children who have *mild or moderate persistent asthma*, low- to medium-dose ICS therapy may be associated with a possible, but not predictable, adverse effect on linear growth. The clinical significance of this potential systemic effect has yet to be determined. High doses of ICS have greater potential for growth suppression.
- Use of high doses of ICS by children who have *severe persistent asthma* has significantly less potential than use of oral systemic corticosteroids for having an adverse effect on linear growth.
- Studies in which growth has been carefully monitored suggest the growth-velocity effect of ICS occurs in the first several months of treatment and is generally small and nonprogressive.
- In general, the efficacy of ICSs is sufficient to outweigh any concerns about growth or other systemic effects. However, ICSs, as with any medications, should be titrated to as low a dose as needed to maintain good control of the child's asthma.

Bone mineral density. Low and medium doses of ICS appear to have no serious adverse effects on BMD in children (CAMP 2000; Roux et al. 2003). A small, dose-dependent reduction in BMD may be associated with ICS use in patients older than 18 years of age (Ip et al. 1994; Israel et al. 2001), but the clinical significance of these findings is not clear. A large observational study of older patients (>65 years of age) with prolonged use of ICS showed that, at <2,000 mcg/day of beclomethasone or equivalent, there was no increase in the risk of fractures (Suissa et al. 2004). Data in adults suggest a cumulative dose relationship to the

effects of ICS on BMD (Wong et al. 2000). **Prevention and Treatment:** In patients who have risk factors for osteoporosis or low BMD scores, consideration can be given to bone-protecting therapies (e.g., bisphosphonates), although data are mixed in supporting the use of these therapies specifically in asthma patients who are taking ICS (Campbell et al. 2004; Kasayama et al. 2005) (Evidence C). Measuring BMD may be considered every 1–2 years, depending on duration and dose of ICS and oral corticosteroid treatment as well as previous BMD scores (Evidence D).

Disseminated varicella. Although high doses of ICS theoretically present risks similar to those of systemic corticosteroid treatment, the reports of disseminated varicella in patients receiving only ICS are rare, causality is *not* clear, and there is no evidence that recommended doses of the ICSs are immunosuppressive. Cases have been reported of children who have severe persistent asthma, and are taking immunosuppressive doses of systemic corticosteroids, developing fatal disseminated disease from varicella infection (Kasper and Howe 1990; Silk et al. 1988). Other case reports indicate complications for patients who have *Strongyloides* or tuberculosis and who take high doses of systemic corticosteroids. **Prevention and Treatment of Varicella:** Children who require episodic therapy with systemic corticosteroids and who have not had clinical varicella should receive the varicella vaccine (EPR—2 1997). The vaccine should not be administered to patients who are receiving immunosuppressive doses of systemic corticosteroids (2 mg/kg or more of prednisone equivalent or 20 mg/day of prednisone for more than 1 month), unless this dosage is discontinued for at least 1 month. Children who have completed a short prednisone course may receive varicella vaccine without delay (American Academy of Pediatrics 1995; CDC 1994). Children and adults on treatment with immunosuppressive doses of corticosteroids who have not been immunized against varicella and are exposed to varicella infection are candidates for oral antiviral therapy (e.g., valacyclovir). If they develop clinical varicella, intravenous antiviral therapy should be given (EPR—2 1997).

Dermal thinning and increased ease of skin bruising. These effects have been observed in patients treated with ICS. The effect is dose dependent, but the threshold dose is variable (Capewell et al. 1990).

Ocular effects. In children, low- and medium-dose ICS therapy appears to have no significant effects on the incidence of subcapsular cataracts or glaucoma (CAMP 2000). In adults, high cumulative lifetime exposure (greater than 2,000 mg of beclomethasone dipropionate or equivalent) to ICS may increase the prevalence of cataracts, as suggested in three retrospective studies of adult and elderly patients (Evidence C) (Cumming et al. 1997; Garbe et al. 1998; Jick et al. 2001). A retrospective, case-control study showed an association between long-term ICS use and the development of glaucoma (Garbe et al. 1997). A subsequent cross-sectional, retrospective study in adults reported an association between elevated intraocular pressure and glaucoma in patients who had a family history of glaucoma and used ICS, particularly at higher doses (defined in this study as more than 4 puffs per day). There was no increase in risk in ICS users who did not have a family history of glaucoma (Mitchell et al. 1999). **Prevention and Treatment:** These data suggest the advisability of periodic assessments and treatments, if indicated, for increased intraocular pressures in asthma patients who use ICS, particularly at higher doses, and have a family history of glaucoma (Evidence C).

Hypothalamic-pituitary-adrenal axis function. The available evidence indicates that, on average, children may experience only clinically insignificant, if any, effects of low- or medium-dose ICS on the hypothalamic-pituitary-adrenal (HPA) axis (Leone et al. 2003). Rarely, however, some individuals may be more susceptible to the effects of ICS even at conventional doses.

Glucose metabolism. In a study of children, ICS at dosages from 400 to 1,000 mcg/day (budesonide) did not affect fasting glucose or glycosolated hemoglobin. At 1,000 mcg/day, a significantly greater rise in fasting serum insulin levels and glucose during a glucose tolerance test was noted, but results remained within normal limits (Turpeinen et al. 1991).

Oral Systemic Corticosteroids

The Expert Panel recommends that chronic administration of oral systemic corticosteroids as a long-term-control medication be used only for the most severe, difficult-to-control asthma because of well-documented risk for side effects (EPR—2 1997).

The Expert Panel recommends that, because the magnitude of adverse effects is often related to the dose, frequency of administration, and the duration of corticosteroid use (Evidence A), every consideration should be given to minimize systemic corticosteroid doses and maximize other modes of therapy (Evidence D). It is necessary, therefore, to monitor for the development and progression of adverse effects and to take appropriate steps to minimize the risk and impact of adverse corticosteroid effects (Evidence D).

Oral systemic corticosteroids suppress, control, and reverse airway inflammation. However, side effects with chronic administration include adrenal suppression, growth suppression, dermal thinning, hypertension, Cushing's syndrome, cataracts, and muscle weakness. Chronic corticosteroid use can also result in immunologic attenuation with loss of delayed-type hypersensitivity, diminished immunoglobulin G (IgG) levels without change in functional antibody response, potential for reactivation of latent tuberculosis infection, and possible increased risk for infection, especially the development of severe varicella (Spahn et al. 2003).

Cromolyn Sodium and Nedocromil

Cromolyn and nedocromil are alternative, not preferred, medications for the treatment of mild persistent asthma (Evidence A). They can also be used as preventive treatment before exercise or unavoidable exposure to known allergens (EPR—2 1997)**.** Although cromolyn and nedocromil have distinct properties (Clark 1993), they have similar anti-inflammatory actions. The mechanism of cromolyn and nedocromil appears to involve the blockade of chloride channels (Alton and Norris 1996) and modulate mast cell mediator release and eosinophil recruitment (Eady 1986). The two compounds are equally effective against allergen challenge (Gonzalez and Brogden 1987), although nedocromil appears to be more potent than cromolyn in inhibiting bronchospasm provoked by exercise (de Benedictis et al. 1995; Novembre et al. 1994), by cold dry air (Juniper et al. 1987), and by bradykinin aerosol (Dixon and Barnes 1989).

Dosing recommendations for both nedocromil and cromolyn are for administration four times a day, although nedocromil has been shown to be clinically effective with twice-daily dosing (Creticos et al. 1995; EPR—2 1997).

Cromolyn sodium and nedocromil have been shown to provide symptom control greater than placebo in some but not all clinical trials (Konig 1997; Petty et al. 1989; Tasche et al. 2000) and to confer protection against exacerbations of asthma leading to hospitalization, particularly in children (Donahue et al. 1997), and ED visits (Adams et al. 2001). These results, along with the excellent safety profile, justify consideration of cromolyn and nedocromil as treatment options. However, a systematic review (van der Wouden et al. 2003) concluded that insufficient evidence existed to conclude that cromolyn had a beneficial effect on maintenance treatment of childhood

asthma. Compared to placebo, nedocromil reduces both urgent care visits as well as the need for prednisone, which are meaningful clinical outcomes. However, nedocromil is no different than placebo on all other outcome measures (CAMP 2000). Overall, nedocromil is significantly less effective than ICS in improving outcomes measures (CAMP 2000). Nedocromil has not been studied adequately in children younger than 5 years of age. As a result of these disparate findings (i.e., some, but limited, effectiveness and strong safety profile), the Expert Panel's opinion is that cromolyn for children of all ages and nedocromil for children ≥5 years of age could be considered in the treatment of persistent asthma for children of all ages, but they are not preferred therapies. The Expert Panel's review of the literature in 2006 found that no new studies have been published that would change these conclusions.

Immunomodulators

Many different pharmaceutical agents have been tested for their ability to provide long-term control and/or steroid-sparing effects. These agents are loosely defined as immunomodulators. New information is available and discussed here on methotrexate, soluble interleukin-4 (IL-4) receptor, anti-IL-5, recombinant IL-12, cyclosporin A, intravenous immunoglobulin (IVIG), clarithromycin, omalizumab (anti-IgE), and others. For discussion of immunotherapy as an asthma management strategy, see "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma."

Omalizumab

The Expert Panel recommends that omalizumab may be considered as adjunctive therapy in step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA (Evidence B). (See Evidence Table 13, Immunomodulators: Anti-IgE.)

Omalizumab, a recombinant DNA-derived humanized monoclonal antibody to the Fc portion of the IgE antibody, binds to that portion preventing the binding of IgE to its high-affinity receptor (FcεRI) on mast cells and basophils. The decreased binding of IgE on the surface of mast cells leads to a decrease in the release of mediators in response to allergen exposure. Omalizumab also decreases FcεRI expression on basophils and airway submucosal cells (Djukanovic et al. 2004; Lin et al. 2004). That study also showed significant decreases in sputum and bronchial eosinophils as well as in CD3+, CD4+, and CD8+ T cells in bronchial biopsy (Djukanovic et al. 2004). The vast majority of patients in clinical trials of omalizumab had moderate or severe persistent asthma incompletely controlled with ICS (Walker et al. 2004); all had atopy and IgE ≥30 IU/mL. Adding omalizumab to ICS therapy generally produced a significant reduction in asthma exacerbations (Busse et al. 2001a; Soler et al. 2001; Vignola et al. 2004) but not always (Holgate et al. 2004; Milgrom et al. 2001). (See Evidence Table 13, Immunomodulators: Anti-IgE.) Omalizumab, added to ICS, was associated with a small but significant improvement in lung function (Busse et al. 2001a; Soler et al. 2001). In two trials, one open-label, in patients who had severe persistent asthma inadequately controlled on ICS plus LABAs, omalizumab reduced asthma exacerbations and ED visits (Ayres et al. 2004; Humbert et al. 2005). Omalizumab appears to have a modest steroid-sparing effect, allowing a median reduction of 25 percent over that of placebo in the trials (Busse et al. 2001a; Holgate et al. 2004; Milgrom et al. 2001; Soler et al. 2001). Omalizumab has not been compared in clinical trials to the other adjunctive therapies for moderate persistent asthma (LABAs, leukotriene modifiers, and theophylline), all of which improve outcomes and allow reduction of ICS dose. Omalizumab is the only adjunctive therapy, however, to demonstrate added efficacy to high-dose ICS plus LABA in patients who have severe persistent allergic asthma (Humbert et al. 2005). In studies

of patients who have severe persistent asthma, omalizumab resulted in clinically relevant improvements in quality-of-life scores in significantly more patients (approximately 60 percent) than did placebo (approximately 43 percent) (Holgate et al. 2004; Humbert et al. 2005).

Omalizumab is approved for patients 12 years and older who have proven sensitivity to aeroallergens: studies have been done in patients who have sensitivity to dust mite, cockroach, cat, or dog. One study of omalizumab in children 6–12 years of age demonstrated nonsignificant reductions in exacerbations and no improvement in lung function but did show small but significant reduction in ICS dose compared to placebo (Milgrom et al. 2001).

Urticaria and anaphylactic reactions have been reported in 0.1 percent of cases (Berger et al. 2003; FDA 2003; Holgate et al. 2004; Lanier et al. 2003). Postmarketing surveys have identified anaphylaxis in an estimated 0.2 percent of treated patients, which resulted in an FDA alert (FDA 2007). Most of these reactions occurred within 2 hours of the omalizumab injection, and after the first, second, or third injections. However, reactions have occurred after many injections and after many hours. Therefore, clinicians who administer omalizumab are advised to be prepared and equipped for the identification and treatment of anaphylaxis that may occur, to observe patients for an appropriate period of time following each injection (the optimal length of the observation is not established), and to educate patients about the risks of anaphylaxis and how to recognize and treat it if it occurs (e.g., using prescription auto injectors for emergency self-treatment, and seeking immediate medical care) (FDA 2007).

Adverse effects reported from omalizumab in the trials have also included injection-site pain and bruising in up to 20 percent of patients (Holgate et al. 2004). In the trials reported to the FDA, twice as many patients receiving omalizumab had malignancies (20 of 48,127, or 0.5 percent) as did those receiving placebo (5 of 2,236, or 0.2 percent), but there were no trends for a specific tumor type.

Antibiotics

In the opinion of the Expert Panel, the data at present are insufficient to support a recommendation about the use of macrolide in chronic asthma.

Some, but not all, data—including a recent controlled trial—have shown an effect of the macrolide antibiotic, clarithromycin, in the treatment of asthma (Kostadima et al. 2004; Kraft et al. 2002). Although it has been shown that clarithromycin can interfere with the clearance of methylprednisolone (Fost et al. 1999), this did not appear to be the mode of action. Preliminary data suggest that clarithromycin may enhance glucocorticoid effect on lymphocyte activation (Spahn et al. 2001).

Recent evidence suggesting that telithromycin may provide benefit in recovery from acute exacerbations has not linked the benefit with antibiotic activity of the drug (Johnston et al. 2006). Macrolide antibiotics, however, have potential risk for liver toxicity.

Others

The Expert Panel concludes that current evidence does not support the use of methotrexate, soluble IL-4 receptor, humanized monoclonal antibody against IL-5 or IL-12, cyclosporin A, IVIG, gold, troleandomycin (TAO), or colchicine for asthma treatment (Evidence B).

For methotrexate, the evidence from a new meta-analysis does not support use of the treatment, given the side effects of the drug (Aaron et al. 1998; Davies et al. 2000).

Use of soluble IL-4 receptor gave promising initial results on moderate to severe asthma (Borish et al. 1999), but subsequent trials were less successful, and it is unlikely to be marketed (Borish et al. 2001).

A humanized monoclonal antibody directed against IL-5 depleted eosinophils from blood and induced sputum but had no effect on airway hyperresponsiveness, on the late asthmatic reaction to inhaled allergen, or in patients who have severe persistent asthma (Flood-Page et al. 2003; Kips et al. 2003; Leckie et al. 2000). Recombinant IL-12 also reduced blood and sputum eosinophils, but it had no significant effects on airway hyperresponsiveness or the late asthmatic reaction to allergen (Bryan et al. 2000). These findings suggest that neither biological will be useful in clinical asthma.

Despite further interesting studies on the mechanism of action of cyclosporin A (Khan et al. 2000), data from controlled trials are not convincing (Evans et al. 2001); given the toxicity of the drug, the data make it difficult to recommend.

Data from open-label trials of IVIG have shown clinical and biomarker benefit in steroid-dependent asthma (Landwehr et al. 1998; Mazer and Gelfand 1991; Spahn et al. 1999). Two controlled trials, however, have failed to establish a clinical benefit of IVIG in such patients (Kishiyama et al. 1999; Niggemann et al. 1998) and showed significant adverse effects. The Expert Panel concludes, from available data, that the use of IVIG in asthma is not recommended.

Trials have suggested limited or no usefulness for oral gold (Bernstein et al. 1996), TAO (Nelson et al. 1993), and colchicine (Fish et al. 1997; Newman et al. 1997).

Leukotriene Modifiers

The Expert Panel recommends that LTRAs are an alternative, not preferred, treatment option for mild persistent asthma (Step 2 care) (Evidence A). LTRAs can also be used as adjunct therapy with ICS, but for youths ≥12 years of age and adults they are not the preferred, adjunct therapy compared to the addition of LABAs (Evidence A). A 5-lipoxygenase inhibitor (zileuton) is an alternative treatment option that is less desirable than LTRAs due to more limited efficacy data and the need for liver function monitoring (Evidence D). (See Evidence Table 14, Leukotriene Receptor Antagonists: Monotherapy/Effectiveness Studies.)

Leukotrienes are potent biochemical mediators—released from mast cells, eosinophils, and basophils—that contract airway smooth muscle, increase vascular permeability, increase mucus secretions, and attract and activate inflammatory cells in the airways of patients who have asthma (Henderson 1994).

Three leukotriene modifiers—montelukast, zafirlukast, and zileuton—are available as oral tablets for the treatment of asthma. Leukotriene modifiers comprise two pharmacologic classes of compounds: 5-lipoxygenase pathway inhibitors (e.g., zileuton), and LTRAs (e.g., montelukast and zafirlukast, which block the effects of the CysLT1 receptor). Only montelukast (for children as young as 1 year of age) and zafirlukast (for children as young as 7 years of age) are approved for use in children.

Leukotriene receptor antagonists. The LTRAs have been demonstrated to provide statistically significant but modest improvement in lung function when used as monotherapy in both adults and children as young as 5 years of age as well as in asthma control outcomes other than lung function in patients as young as 2 years of age (Bisgaard et al. 2005; Bleecker et al. 2000; Busse et al. 2001b,c; Garcia-Garcia et al. 2005; Jenkins et al. 2005; Ostrom et al. 2005; Pearlman et al. 2000; Szefler et al. 2005; Zeiger et al. 2005, 2006) (see Evidence Table 14). In general, these studies included patients who had either mild or moderate persistent asthma, although the classification of severity was not always clear in the studies, nor was it consistently applied. When comparing overall efficacy of LTRA to ICS in both children and adult patients who have persistent asthma, most outcome measures (e.g., reduction in exacerbations, improvements in symptom-free days and FEV_1) significantly and clearly favored ICS (Busse et al. 2001b,c; Ducharme et al. 2003; Garcia-Garcia et al. 2005; Jenkins et al. 2005; Ostrom et al. 2005; Sorkness et al. 2007; Zeiger et al. 2006). See Evidence Table 14: Leukotriene Receptor Antagonists: Monotherapy/Effectiveness Studies.

Three randomized, controlled, double-blind studies in children 5–15 years of age demonstrated the greater effectiveness of ICS (fluticasone) compared to montelukast (Garcia-Garcia et al. 2005; Ostrom et al. 2005; Sorkness et al. 2007). All three reported significantly greater improvements in lung function and total symptom scores as well as reduction in exacerbations; one demonstrated that montelukast was not inferior to fluticasone in rescue-free days (defined in the study as any day without asthma rescue medication and with no asthma-related resource use) (Garcia-Garcia et al. 2005), but the other two showed superiority of fluticasone compared to montelukast for percentage of rescue-free days.

A randomized, cross-over, double-blind study of 140 children 6–17 years of age, in which children received either ICS or LTRA (montelukast) for 8 weeks followed by 8 weeks of the other medication, examined what factors might predict individual variation in response to different medications. The study suggests that children who have higher levels of eosinophilic/allergic airway inflammation (nitric oxide, IgE levels, total eosinophil levels) or low pulmonary function (measured by FEV_1/FVC or FEV_1) are more likely to respond favorably to ICS than to LTRA. Children who do not have these markers appeared to respond equally to treatment with ICS or LTRA (Szefler et al. 2005; Zeiger et al. 2006).

LTRAs have been demonstrated to attenuate EIB (Mastalerz et al. 2002; Moraes and Selvadurai 2004).

LTRAs may be considered as an alternative treatment option for patients whose response to ICSs may be compromised. For example, a controlled trial noted that active cigarette smoking impairs the efficacy of short-term ICS treatment in adults who had mild asthma (Chalmers et al. 2002). However, patients who smoke should be advised to quit smoking. See “Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma” and “Component 2: Education for a Partnership in Care.”

Zafirlukast, an LTRA, has been demonstrated to attenuate the late response to inhaled allergen and post-allergen-induced bronchial responsiveness (Dahlen et al. 1994; Taylor et al. 1991). A study comparing zafirlukast to placebo in patients who have mild or moderate asthma demonstrated that patients treated with zafirlukast experienced modest improvement in FEV_1 (mean improvement of 11 percent above placebo), had improved symptom scores, and reduced albuterol use (average decline of 1 puff/day) (Spector et al. 1994). Zafirlukast can cause a significant increase in the half-life of warfarin. Consequently, for those individuals receiving zafirlukast and warfarin, it will be necessary to closely monitor prothrombin times and adjust

doses of warfarin accordingly. Cases of hepatic dysfunction have occurred with zafirlukast. Although most patients improved with discontinuation of zafirlukast, some have gone on to fulminate hepatic failure resulting in receiving a transplant or in death. Patients should be advised to be alert for signs and symptoms of hepatitis (anorexia, abdominal pain, nausea, jaundice, and pruritis); if these occur, they should discontinue zafirlukast and have liver enzymes (ALT) monitored.

The use of LTRA as adjunctive therapy in moderate or severe asthma has not been studied adequately in children 5–11 years of age and has not been studied at all in children less than 4 years of age. Limitations in the studies comparing addition of LTRA to a fixed dose of ICS (i.e., adding LTRA when patients are not adequately controlled with ICS alone) preclude definitive conclusions, although they reveal a trend showing that LTRA improved lung function and some but not all measures of asthma control (Laviolette et al. 1999; Robinson et al. 2001; Simons et al. 2001; Vaquerizo et al. 2003). One study in adults compared the combination of LTRA and ICS to increasing the dose of ICS and reported similar outcomes for the two approaches (Price et al. 2003). In a 24-week trial in patients who had poorly controlled asthma, the addition of theophylline or montelukast led to small improvement in lung function but did not improve episodes of poor asthma control, symptoms, or quality of life (American Lung Association Asthma Clinical Research Centers 2007). Studies comparing LTRA to LABA as adjunctive therapy in adults show significantly greater improvement in lung function and other asthma control measures with the LABA adjunctive therapy (EPR—Update 2002; Ram et al. 2005).

5-lipoxygenase inhibitor. Zileuton has not been studied in patients less than 12 years of age. It has been demonstrated to provide immediate and sustained improvements in FEV_1 (mean increase of 15 percent above placebo) in placebo-controlled trials in patients who have mild or moderate asthma (Israel et al. 1993, 1996). Compared to placebo, the patients who had moderate asthma treated with zileuton experienced significantly fewer exacerbations requiring oral systemic corticosteroids (Israel et al. 1996), thus suggesting anti-inflammatory action. Zileuton is capable of attenuating bronchoconstriction from exercise (Meltzer et al. 1996) and from aspirin in aspirin-sensitive individuals (Israel et al. 1993). One large, randomized, open label, study in adults who had asthma (Lazarus et al. 1998) and one small cross-over study in aspirin-sensitive adults who had asthma (Dahlen et al. 1998) demonstrated clinical benefits to adding zileuton to existing therapy; the large trial also reported elevated liver enzymes. Because liver toxicity has been found in some subjects receiving zileuton, it is recommended that hepatic enzymes (ALT) be monitored in patients who take this medication. Furthermore, zileuton is a microsomal cytochrome P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline; doses of these drugs should be monitored accordingly. Due to the limited efficacy data and the need for liver function monitoring, zileuton is a less desirable alternative than LTRAs.

Inhaled Long-Acting Beta$_2$-Agonists

The principal action of beta$_2$-agonists is to relax airway smooth muscle by stimulating beta$_2$-receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. Due to their increased lipophilicity prolonging retention in lung tissue, the LABAs have a duration of bronchodilation of at least 12 hours after a single dose (Kips and Pauwels 2001). The LABAs effectively block EIB for 12 hours after a single dose; however, with chronic regular administration, this effect does not exceed 5 hours (Ramage et al. 1994; Simons et al. 1997).

The Expert Panel concludes the following regarding the use of LABAs:

- **LABAs are used as an adjunct to ICS therapy for providing long-term control of symptoms (Evidence A). Of the adjunctive therapies available, LABA is the preferred treatment to combine with ICS in youths ≥12 years of age and adults (Evidence A).**

- **LABAs are not recommended for use as monotherapy for long-term control of persistent asthma (Evidence A).**

- **Use of LABA is not currently recommended to treat acute symptoms or exacerbations of asthma (Evidence D).** Studies are underway examining the potential use of formoterol in acute exacerbations and in adjustable-dose therapy in combination with ICS; see the discussion below in the section on "Quick-Relief Medications" and on "Inhaled Short-Acting Beta$_2$-Agonists."

- **LABA may be used before exercise to prevent EIB (Evidence B), but frequent and chronic use of LABA for EIB may indicate poorly controlled asthma which should be managed with daily anti-inflammatory therapy.**

- **Safety issues have been raised regarding LABAs. The Expert Panel reviewed the safety data provided to the FDA Pulmonary and Allergy Drugs Advisory Committee as well as the extensive accumulation of clinical trials and meta-analyses on the use of LABA, both as monotherapy and in conjunction with ICS. The Expert Panel concluded that LABAs should not be used as monotherapy as long-term control medication in persistent asthma but that LABAs should continue to be considered for adjunctive therapy in patients ≥5 years of age who have asthma that requires more than low-dose ICS. For patients inadequately controlled on low-dose ICS, the option to increase the ICS dose should be given equal weight to the addition of a LABA. For patients who have more severe persistent asthma (i.e., those who require step 4 care or higher), the Expert Panel continues to endorse the use of a combination of LABA and ICS as the most effective therapy. The basis of this opinion is discussed below.** (See Evidence Table 15, Bronchodilators: Safety of Long-Acting Beta$_2$-Agonists.)

Safety of Long-Acting Beta$_2$-Agonists

KEY POINTS: SAFETY OF INHALED LONG-ACTING BETA$_2$-AGONISTS

- The addition of LABA (salmeterol or formoterol) to the treatment of patients whose asthma is not well controlled on low- or medium-dose ICS improves lung function, decreases symptoms, and reduces exacerbations and use of SABA for quick relief in most patients (EPR—Update 2002; Greenstone et al. 2005; Masoli et al. 2005).
- A large clinical trial comparing daily treatment with salmeterol or placebo added to usual asthma therapy (Nelson et al. 2006) resulted in an increased risk of asthma-related deaths in patients treated with salmeterol (13 deaths out of 13,176 patients treated for 28 weeks with salmeterol versus 3 deaths out of 13,179 patients with placebo). In addition, increased numbers of severe asthma exacerbations were noted in the pivotal trials submitted to the FDA for formoterol approval, particularly in the higher dose formoterol arms of the trials (Mann et al. 2003). Thus the FDA determined that a Black Box warning was warranted on all preparations containing a LABA.
- The Expert Panel recommends that the established, beneficial effects of LABA for the great majority of patients whose asthma is not well controlled with ICS alone should be weighed against the increased risk for severe exacerbations, although uncommon, associated with the daily use of LABAs.
- Therefore, the Expert Panel has modified its previous recommendation (EPR—Update 2002) and has now concluded that, for patients who have asthma not sufficiently controlled with ICS alone, the option to increase the ICS dose should be given equal weight to the option of the addition of a LABA to ICS.
- Daily use of LABA generally should not exceed 100 mcg salmeterol or 24 mcg formoterol.
- It is not currently recommended that LABA be used for treatment of acute symptoms or exacerbations.
- LABAs are not to be used as monotherapy for long-term control. Patients should be instructed not to stop ICS therapy while taking salmeterol or formoterol even though their symptoms may significantly improve.

General Safety. LABAs induce sustained relaxation of airway smooth muscle that allows twice-daily administration. The two LABAs currently available for the treatment of asthma are salmeterol and formoterol. They have slightly different properties in that salmeterol is a partial agonist and formoterol is a full agonist, but the only clinically relevant difference is that formoterol has a more rapid onset of bronchodilation (similar to albuterol) (Kips and Pauwels 2001). Both are highly selective beta$_2$-adrenergic receptor agonists that produce clinically relevant cardiovascular effects (tachycardia, QTc interval prolongation, and hypokalemia) at doses approximately 4–5 times those recommended (Guhan et al. 2000; Ostrom 2003;

Palmqvist et al. 1999). Other dose-dependent sympathomimetic effects include tremor and hyperglycemia. Because the LABAs are devoid of any clinically apparent anti-inflammatory activity (Currie et al. 2003; Lazarus et al. 2001), they should not be used as monotherapy for long-term control of persistent asthma. Discontinuation of ICS therapy following initiation of LABA results in an increase in asthma exacerbations (Lemanske et al. 2001). Of greatest concern have been the reports of an increased risk of severe asthma exacerbations, both life-threatening and fatal, associated with regular LABA use (Mann et al. 2003; Nelson et al. 2006) that has resulted in a Black Box Warning label for products in the United States containing either salmeterol or formoterol.

Early recognition of the potential dangers of LABAs followed a large, randomized, prospective postmarketing study in approximately 25,000 patients in the United Kingdom. The study reported an increased (although not statistically significant) number of deaths in patients treated with salmeterol (42 mcg/day) versus albuterol (180 mcg four times/day) added to usual asthma therapy (12 of 16,787 patients taking salmeterol versus 2 of 8,393 patients on albuterol) (Castle et al. 1993). However, an observational, prescription-event monitoring program in the United Kingdom evaluating 15,407 patients taking salmeterol found no evidence that salmeterol contributed to the death of any of the patients (Mann et al. 1996). Similarly, a retrospective review of a large, health insurance claims database in the United States, comparing a cohort of 2,708 patients receiving salmeterol to 3,825 recipients of sustained release theophylline, found no increase in ED visits, hospitalizations, or ICU admissions among those receiving salmeterol during the year following initiation of therapy (Lanes et al. 1998).

Due to the concerns generated by the initial United Kingdom study, a large, randomized, placebo-controlled, 28-week trial of salmeterol versus placebo added to usual care in adults who had asthma was performed to assess the safety of salmeterol (Nelson et al. 2006). The goal was to enroll approximately 60,000 patients, and the primary outcome variable was combined respiratory-related deaths or respiratory-related, life-threatening experiences; secondary end points included all-cause deaths, asthma-related deaths, and combined asthma-related deaths or life-threatening experiences. A planned interim analysis of more than 26,000 patients found no increase in the primary outcome but did find an increased risk of asthma-related deaths and combined asthma-related death or life-threatening experiences in the total population. Although the study was not designed to assess subgroups, a subgroup analysis reported that African Americans, who were 18 percent of the total population, experienced a significant increased risk for the primary end point as well as combined asthma-related death or life-threatening experiences. In addition, an analysis of serious asthma exacerbations in the pivotal trials submitted to the FDA for marketing approval of formoterol revealed an increased number of these events in patients receiving formoterol, particularly at the higher dose of 48 mcg daily that exceeds current labeling (Chowdhury 2005; Mann et al. 2003). A followup analysis of the same data reiterated the potential risks (Salpeter et al. 2006). The data from the Salmeterol Multicenter Asthma Research Trial (SMART), Chowdhury, and Mann and colleagues prompted the FDA to convene a meeting of the Pulmonary and Allergy Drugs Advisory Committee (www.fda.gov/cder/drug/advisory/LABA.htm) (FDA 2005). This group, in conjunction with the FDA, determined that these data represented a serious safety concern for the use of LABAs but that the significant benefit provided by these agents to a large number of patients, particularly in conjunction with ICS therapy, warranted continued use of LABA as adjunctive therapy for patients who have asthma that is not well controlled with ICS alone.

A meta-analysis of trials, performed for the EPR—Update 2002, reported greater benefit in measures of asthma control with the addition of a LABA compared to doubling the dose of ICS

(EPR—Update 2002). A Cochrane Library systematic review of 85 RCTs (60 studies with salmeterol and 25 studies with formoterol) comparing LABA with a placebo in chronic asthma (Walters et al. 2003) reported a decrease in severe asthma exacerbations (defined as requiring intervention other than as-needed SABA) associated with LABA use. Additional meta-analyses showed that the addition of LABA compared to increasing the ICS dose improved lung function and symptom control (Ni et al. 2005), reduced exacerbations (Masoli et al. 2005), and did not increase serious asthma exacerbations or participant withdrawals due to worsening asthma. A recent case-control study of 532 asthma patients who died from asthma did not find a positive association between LABA use and death (Anderson et al. 2005). A more recent large, postmarketing study (2,085 patients) of adding formoterol, either 24 mcg or 12 mcg twice daily, to usual care (65 percent receiving concomitant anti-inflammatory therapy) failed to detect an increase risk of serious asthma exacerbations (Wolfe et al. 2006).

A mechanism for a direct effect of LABAs in producing exacerbations has not been established. The primary hypotheses for LABAs' increasing the risk of severe, life-threatening asthma exacerbations include: (1) a direct adverse effect of LABA on bronchial smooth muscle, resulting in more severe obstruction following any bronchoconstrictive stimulus, or (2) maintenance of lung function in the face of worsening underlying inflammation, leading either to a catastrophic increase in obstruction or to patients' delaying seeking appropriate medical attention for a severe exacerbation. Clinical trials clearly demonstrate that, in patients who have persistent asthma, discontinuation of ICS after starting LABA results in increased markers of inflammation and increased risk of exacerbations (Lazarus et al. 2001; Lemanske et al. 2001; Mcivor et al. 1998). In patients who have mild asthma, the increase in exacerbations occurs despite benefits in measures of daily asthma control such as symptoms, as-needed use of SABA, and PEFs (Lazarus et al. 2001). Unlike regular use of SABA, the regular daily administration of LABA has not produced an increase in bronchial hyperresponsiveness (Cheung et al. 1992; Lazarus et al. 2001; Simons 1997; Van Schayck et al. 2002; Walters et al. 2003).

Genetic studies assessing the role of the polymorphism at codon 16 of the $beta_2$-adrenergic receptor gene have produced inconclusive results. A cross-over study by Taylor and coworkers (2000) reported that, during 24 weeks of treatment with placebo, albuterol, and salmeterol, the number of major exacerbations was significantly increased for homozygous Arg-16 subjects (only 17 subjects) during albuterol treatment compared with placebo but not during salmeterol treatment. In addition, researchers found no adverse effect of salmeterol on morning peak flow in the homozygote Arg-16 subjects compared with placebo or compared to homozygous Gly-16 subjects. More recently, Wechsler and colleagues (2006) reported that homozygote Arg-16 subjects (n = 8) who were taking salmeterol and an ICS had lower FEV_1, increased symptom scores, and increased use of SABA compared with Gly/Gly subjects (n = 22) taking the same combination therapy. On the other hand, Bleecker (2006) reported that, in a study of patients receiving LABA and ICS (N = 183), there were no differences in clinical response between Arg/Arg or Gly/Gly genotypes.

Studies assessing the qualitative nature of exacerbations have shown no difference in the rapidity of onset or severity of obstruction, reporting of symptoms, or use of SABA whether patients who had asthma were receiving LABA or not (Matz et al. 2001; Tattersfield et al. 1999). However, the patients in these studies were all receiving ICS as well as LABA. No studies have specifically addressed whether patients who take LABA delay seeking medical attention for deterioration of asthma, but this effect would be difficult to assess.

What ameliorative role, if any, the concomitant administration of ICS has on the potential for severe asthma exacerbations associated with LABA use has not been studied adequately. In a meta-analysis, the addition of LABA to ICS produced a significant reduction in severe exacerbations, but only a borderline significant decrease occurred in studies of patients who were not receiving ICS (Walters et al. 2003). In large clinical trials of at least 1 year duration, with severe exacerbations as a primary end point, LABA added to low- to medium-dose ICS significantly reduced the number of severe exacerbations in patients who had moderate asthma (O'Byrne et al. 2001; Pauwels et al. 1997) and reduced the number of patients who withdrew from the study because of an excessive number of exacerbations (Tattersfield et al. 1999). These results have been confirmed in a recent meta-analysis (Masoli et al. 2005). Although the study was not designed to assess subgroups or to assess concomitant medication use during the trial, no increase in the primary outcome of asthma deaths or life-threatening experiences was seen in association with salmeterol in the 12,265 patients who self-reported taking ICS at baseline in the SMART trial; however, this finding should not be considered conclusive (Nelson et al. 2006).

On the other hand, there did not appear to be a protective effect of ICS in the number of serious exacerbations reported in the formoterol pivotal trials. Although not statistically significant, an increased number of exacerbations were observed in the formoterol group (Chowdhury 2005). Thus, while the data do not necessarily support an increased risk of severe or serious exacerbations in patients who are taking LABA and are receiving concomitant ICS, data are also insufficient to establish definitively that ICS therapy completely obviates the risk. Further research is urgently needed to clarify this issue.

Methylxanthines

The Expert Panel recommends that sustained-release theophylline is an alternative but not preferred treatment for mild persistent asthma (Step 2 care) (Evidence A); it may also be used as alternative but not preferred adjunctive therapy with ICS (Evidence B).
Theophylline, the principally used methylxanthine, provides mild or moderate bronchodilation in persons who have asthma. Theophylline is a nonselective phosphodiesterase inhibitor; as such, it has exhibited mild anti-inflammatory activity according to some but not all studies (Jaffar et al. 1996; Kidney et al. 1995; Page et al. 1998).

Theophylline produces minimal to no effect on airway reactivity and significantly less control of asthma than low-dose ICS does (Dahl et al. 2002; Reed et al. 1998). The addition of theophylline to ICS produces a small improvement in lung function similar to doubling the dose of ICS (Evans et al. 1997; Lim et al. 2000; Suessmuth et al. 2003). In a 24-week randomized, placebo-controlled trial in patients who had poorly controlled asthma, the addition of theophylline or montelukast led to small improvement in lung function but did not improve episodes of poor asthma control, symptoms, or quality of life (American Lung Association Asthma Clinical Research Centers 2007). Thus, the main use of theophylline is as adjunctive therapy to ICS. Sustained-release theophylline may be considered as a nonpreferred alternative long-term preventive therapy when issues arise concerning cost or a patient's aversion to inhaled medication. Monitoring serum concentrations of theophylline is essential to ensure that toxic concentrations are avoided. For sustained-release theophyllines, the serum concentration is obtained in the middle of the dosing interval, at least 3–5 days after initiation of theophylline and then at least 2 days after initiation of any factor known to affect theophylline clearance significantly. If patients experience signs and symptoms of toxicity (e.g., severe headache, tachycardia, nausea and vomiting), theophylline should be discontinued and a serum concentration obtained.

Tiotropium Bromide

Tiotropium bromide is a new, long-acting inhaled anticholinergic indicated once daily for COPD; this drug has not been studied in the long-term management of asthma (Gross 2004), and it has not received FDA-approved labeling for use in treating asthma. Ipratropium bromide, a short-acting anticholinergic, also has not demonstrated effectiveness in long-term management of asthma (Kerstjens et al. 1992).

QUICK-RELIEF MEDICATIONS

Quick-relief medications are used to provide prompt relief of bronchoconstriction and its accompanying acute symptoms such as cough, chest tightness, and wheezing. These medications include SABAs and anticholinergics (ipratropium bromide). Although the onset of action is slow (>4 hours), systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses.

Anticholinergics

The Expert Panel concludes that ipratropium bromide, administered in multiple doses along with SABA in moderate or severe asthma exacerbations in the ED, provides additive benefit (Evidence B). Patients who have more severe obstruction of airways appear to benefit the most (Rodrigo and Castro-Rodriguez 2005). Ipratropium bromide has been used, with some success, as a quick-relief medication to avoid use of as-needed albuterol in clinical research trials in patients who have mild asthma (Israel et al. 2004). It has not been compared adequately to SABAs, however, nor does it have FDA-approved labeling for use in treatment of asthma.

Inhaled Short-Acting Beta$_2$-Agonists

The Expert Panel recommends that SABAs are the drug of choice for treating acute asthma symptoms and exacerbations and for preventing EIB (Evidence A). The SABAs (albuterol, levalbuterol, pirbuterol, etc.) relax airway smooth muscle and cause a prompt (within 3–5 minutes) increase in airflow. All synthetic beta$_2$-agonists exist chemically as racemic mixtures; however, the therapeutic activity primarily resides in the (R)-enantiomers and not the (S)-enantiomers. Due to the stereoselectivity of biological systems, the (R)-enantiomers are more active than the (S)-enantiomers. In vitro studies have suggested a possible deleterious effect of the (S)-enantiomer of albuterol on airway smooth muscle responsiveness and other airway cells (Berger 2003; Waldeck 1999). Therefore, a product containing only the active enantiomer of albuterol (levalbuterol) was developed and approved for clinical use. Some clinical studies suggested an improved efficacy of levalbuterol over racemic albuterol (Carl et al. 2003; Nelson et al. 1998) when administered in equal (R)-albuterol doses; however, other trials have failed to detect any advantage of levalbuterol over racemic albuterol (Cockcroft and Swystun 1997; Lotvall et al. 2001; Qureshi et al. 2005). (See also Evidence Table 16, Bronchodilators: Levalbuterol.) Concerns about the safety of SABAs are discussed below.

Formoterol, a LABA, has an onset of action similar to the SABAs (within 5 minutes) due to its lower lipophilicity than salmeterol (onset at 15 minutes) (Grembiale et al. 2002; Kips and Pauwels 2001). In acute bronchospasm induced by methacholine or exercise, formoterol improves FEV_1 as rapidly as inhaled albuterol or terbutaline (Hermansen et al. 2006; Politiek et al. 1999). In a large, 12-week comparison trial in patients receiving ICS therapy, formoterol was

as effective as terbutaline when used by outpatients as a quick-relief medication; fewer patients in the group that used formoterol experienced severe asthma exacerbations (Tattersfield et al. 2001). Initial studies of formoterol delivered by DPI showed rapid improvement in lung function in patients who presented in the ED with acute exacerbation (Bateman et al. 2006; Boonsawat et al. 2003). The onset of action and efficacy is comparable when formoterol is administered with budesonide in combination inhalers (Balanag et al. 2006; Bateman et al. 2006). This result has led numerous investigators to assess the efficacy of the combination inhaler for adjustable therapy in conjunction with standard administration (see discussion in the section above on "Inhaled Corticosteroids, Variability in Response and Adjustable Dose Therapy.") Although the Expert Panel is not currently recommending the use of formoterol as therapy for acute exacerbations, nor is formoterol approved for this indication, this area of research clearly warrants further investigation.

Safety of Inhaled Short-Acting Beta$_2$-Agonists

KEY POINTS: SAFETY OF INHALED SHORT-ACTING BETA$_2$-AGONISTS

- SABAs are the most effective medication for relieving acute bronchospasm (Evidence A).
- Increasing use of SABA treatment or using SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control of asthma and the need for initiating or intensifying anti-inflammatory therapy (Evidence C).
- Regularly scheduled, daily, chronic use of SABA is not recommended (Evidence A).

The Expert Panel recommends the use of SABA as the most effective medication for relieving acute bronchoconstriction; SABAs have few negative cardiovascular effects (Evidence A).

The Expert Panel does not recommend regularly scheduled, daily, long-term use of SABA (Evidence A).

SABAs are the mainstay of treatment for acute symptoms of bronchospasm. This is true both in routine outpatient management of persons who have asthma and for their treatment in the clinic or ED. The main SABAs in use today (i.e., albuterol, levalbuterol, and pirbuterol) are effective agonists and have few negative cardiovascular effects. In contrast, in the past, two SABAs (isoprenaline and fenoterol) which were less selective or used at higher doses have been associated with severe and fatal attacks of asthma. In addition, regular use of fenoterol produced a significant diminution in control of asthma and in objective measurements of pulmonary function (Sears et al. 1990). Regularly scheduled use of albuterol in patients who have mild or moderate asthma, compared to use of albuterol on an as-needed basis, resulted in no significant differences between groups in levels of asthma control. The regularly scheduled use of albuterol produced neither demonstrable benefits nor harmful effects (Dennis et al. 2000; Drazen et al. 1996). On the basis of these and other studies (Cockcroft et al. 1993; Ernst et al. 1993; Mullen et al. 1993; O'Connor et al. 1992; Suissa et al. 1994; Van Schayck et al. 1991), the regularly scheduled daily use of SABA is not recommended.

The frequency of SABA use can be clinically useful as a barometer of disease activity, because increasing use of SABA has been associated with increased risk for death or near death in patients who have asthma (Spitzer et al. 1992). Use of more than one SABA canister every 1–2 months is also associated with an increased risk of an acute exacerbation that requires an ED visit or hospitalization (Crystal-Peters et al. 2002; Lieu et al. 1998; Schatz et al. 2005). Thus, the use of more than one SABA canister (e.g., albuterol, 200 puffs per canister), predominantly for quick-relief treatment during a 1-month period, most likely indicates overreliance on this drug and suggests inadequate control of asthma (Spitzer et al. 1992).

Over the last few years, further studies have identified problems with chronic use of albuterol, especially when used without ICS (Eisner et al. 2001; Lemaitre et al. 2002). The possibility that regular albuterol use may be deleterious in some patients who have asthma was supported by studies that showed an increased risk of exacerbations in subjects who had elevated markers of inflammation as well as in those not taking ICS (Wraight et al. 2003, 2004).

Several different mechanisms have been proposed for the adverse effects of regular use of SABA. Evidence has been reported for increased expression of CxCL8 (Gordon et al. 2003) and increased response to allergen challenge (Swystun et al. 2000) and exercise (Hancox et al. 2002). In addition, decreases in lung function after stopping chronic use have been reported with regular use of SABAs (Hancox et al. 2000; Israel et al. 2000; Van Schayck et al. 2002). It is not possible to state with confidence which of these mechanisms is responsible for the increased exacerbation rate seen in large-scale observational studies.

Sequencing of the beta$_2$-agonist receptor gene has made it possible to identify polymorphisms, some of which may be relevant to the function of the receptor. Two studies have shown that subjects who are homozygous for arginine at position 16 (Arg/Arg 16) are more likely than patients who are homozygous for glycine (Gly/Gly 16) to experience decline in lung function when taking regularly scheduled daily albuterol treatment (Israel et al. 2000, 2004), although, as noted in "Component 1: Measures of Asthma Assessment and Monitoring," the clinical significance of the difference in lung function has not been established. In addition, a retrospective genetic analysis reported that patients who have Arg/Arg 16 and regularly received albuterol experienced increased exacerbations compared to patients who had Arg/Gly and Gly/Gly (Taylor et al. 2000). Due to the complex genetic nature of the beta$_2$-agonist receptor and its response, the current findings are not definitive in identifying the functional variant responsible for this adverse effect or the number of individuals in whom this effect may occur. The current data leave little doubt, however, that regularly scheduled administration of SABA can result in deleterious effects on lung function and asthma control in a subset of patients who have asthma. Although the mechanism of this effect is not clear, its association with polymorphisms of the beta$_2$-receptor is becoming more clear.

Systemic Corticosteroids

The Expert Panel recommends the use of oral systemic corticosteroids in moderate or severe exacerbations (Evidence A).

The Expert Panel recommends that multiple courses of oral systemic corticosteroids, especially more than three courses per year, should prompt a reevaluation of the asthma management plan for a patient (Evidence C). The risk of adverse effects from systemic corticosteroids depends on dose and duration. Systemic corticosteroids can speed resolution of airflow obstruction and reduce the rate of relapse (Rowe et al. 2001a, b; Rowe et al. 2004; Scarfone et al. 1993; Smith et al. 2003). Common adverse effects of systemic corticosteroids

include the potential for growth suppression, osteoporosis, cataracts, myopathy, adrenal suppression, increased appetite with weight gain, and development of cushingoid habitus consisting of moon facies, buffalo hump, central obesity with wasting of extremities, atrophy of the skin with the development of striae, and hirsutism. Psychologic disturbances—from increased emotional lability to frank psychosis—can occur, as well as hypertension, peptic ulcer disease, atherosclerosis, aseptic necrosis of bone, and diabetes mellitus. High-dose systemic corticosteroids can be immunosuppressive; if such treatment is used, appropriate steps should be taken to monitor and prevent infection (Spahn et al. 2003).

In regard to risk of adverse effects related to short courses of systemic corticosteroids, little information is available, and available studies used different products at varying doses. One epidemiologic study suggests that children, 4–17 years of age, who require more than four courses of oral corticosteroids (average duration 6.4 days) as treatment for underlying disease have an increased risk of fracture (van Staa et al. 2003). Another study concluded that multiple short courses of oral corticosteroids (median four courses in the preceding year) in the treatment of asthma in children 2–17 years of age were not associated with any lasting effect on bone metabolism, bone mineralization, or adrenal function (Ducharme et al. 2003). In another study, children who received four or more bursts of oral corticosteroids for acute asthma exacerbations in the previous year demonstrated a subnormal response of the HPA axis to hypoglycemic stress or ACTH (Dolan et al. 1987).

ROUTE OF ADMINISTRATION

Medications for asthma can be administered by either inhaled or systemic routes. Systemic routes are oral (ingested) or parenteral (subcutaneous, intramuscular, or intravenous). The major advantages of delivering drugs directly into the lungs via inhalation are that higher concentrations can be delivered more effectively to the airways and that systemic side effects are lessened (Newhouse and Dolovich 1986). Some drugs are therapeutically active in asthma only when inhaled (e.g., most ICS preparations, cromolyn, salmeterol).

Inhaled medications, or aerosols, are available in a variety of devices that differ in technique required and quantity of drug delivered to the lung. See figure 3–24 for a summary of issues to consider for different devices including inhalers, spacers, and nebulizers. Whatever device is selected, patients should be instructed in its use, and their technique should be checked regularly.

Alternatives to CFC-Propelled MDIs

Many inhaled medications currently used for asthma are available in MDIs. Historically, MDI technology has utilized chlorofluorocarbons (CFCs) as propellants. CFCs usually constitute 95 percent or more of the formulation emitted from an MDI. CFCs are metabolically stable, and even the portion of an actuation that is systemically absorbed is quickly excreted unchanged via exhalation. CFCs have been found to deplete stratospheric ozone, however, and have been banned internationally. Although a temporary medical exemption has been granted, it is expected that MDIs with CFC propellant will be phased out completely. For example, albuterol CFC will be phased out by the end of 2008. Alternatives include MDIs with other propellants (nonchlorinated propellants such as HFA 134a do not have ozone-depleting properties); multidose, breath-activated DPIs; and other handheld devices with convenience and delivery characteristics similar to current MDIs. MDIs with HFA 134a have been approved for use with albuterol, levalbuterol, beclomethasone dipropionate, and fluticasone propionate. Additional non-CFC products and delivery systems are expected in the future. Albuterol MDIs with HFA

propellant deliver comparable doses to the lung and produce comparable efficacy and safety as albuterol CFC-MDIs (Lumry et al. 2001; Ramsdell et al. 1999; Shapiro et al. 2000a,b). Beclomethasone dipropionate with HFA propellant delivers a significantly greater dose to the lungs than its respective CFC-MDIs, however, resulting in lower recommended doses (figures 4–4a, b, c; 4–8a, b, c) (Busse et al. 1999; Leach et al. 1998; Richards et al. 2001), whereas fluticasone propionate with HFA propellant delivers slightly less drug to the lungs than the CFC-MDI but dosage recommendations are unchanged. During the phaseout of CFC products, clinicians will need to be informed of the alternatives and assist their patients in the transition to non-CFC products.

Spacers and Valved Holding Chambers

"Spacer" is a generic term that refers to simple open tubes that are placed on the mouthpiece of an MDI to extend it away from the mouth of the patient. Spacers have consisted of manufactured and homemade devices such as plastic bottles, corrugated ventilation tubing, toilet tissue cores, etc. Spacers have also been integrated with the MDI (triamcinolone acetonide, flunisolide HFA).

VHCs are manufactured devices (Aerochamber, Optichamber, Prochamber, Vortex) that have one-way valves that do not allow the patient to exhale into the device. Thus, patients—either very young children or infants or those who for some other reason are unable to cooperate—can breathe normally and have someone else actuate the device without loss of the actuated dose and obviating the need for coordinating actuation and inhalation.

Both spacers and VHCs are intended to retain large particles emitted from the MDI so they do not deposit in the oropharynx and thereby lead to a higher proportion of small, respirable particles being inhaled. They perform this function to various degrees, however, depending upon their size and shape as well as the formulation of the MDI (drug, propellant, and/or excipients). Thus, a spacer or VHC can increase lung delivery of a drug from one MDI and decrease lung delivery from another (Ahrens et al. 1995; Dolovich 2000). In addition, in vitro and in vivo studies comparing various spacers and VHCs with the same MDI have demonstrated a two- to six-fold variation in the respirable dose emitted from the devices and two- to five-fold difference in systemic availability of the drug (Asmus et al. 2004; Liang et al. 2002).

VHCs are preferred over spacers because the vast majority of controlled clinical trials demonstrating safety and efficacy of drugs administered by MDIs that do not have integrated spacers and use an add-on device have been performed with VHCs (Dolovich et al. 2005). However, due to the significant variation found between the performance of specific VHCs and MDIs, it may be preferable to use the same combination of MDI and VHC reported in the individual drug study to achieve comparable results. No specific combination of MDI and VHC currently has been specifically approved by the FDA for use together.

Complementary and Alternative Medicine

KEY POINTS: COMPLEMENTARY AND ALTERNATIVE MEDICINE

- It is recommended that the clinician ask patients about all medications and treatments they are using for asthma and advise the patients that complementary and alternative medicines and treatments are not a substitute for the clinician's recommendations for asthma treatment (Evidence D).
- Evidence is insufficient to recommend or not recommend most complementary and alternative medicines or treatments.
- Acupuncture is not recommended for the treatment of asthma (Evidence B).
- Patients who use herbal treatments for asthma should be cautioned that there is the potential for harmful ingredients in herbal treatments and for interactions with recommended asthma medications (Evidence D).

Alternative healing methods are not substitutes for recommended asthma management strategies (i.e., pharmacologic therapy, environmental control measures, or patient education). Although alternative healing methods may be popular, clinical trials that adequately address safety and efficacy are limited, and their scientific basis has not been established.

The most widely known complementary and alternative medicine methods are acupuncture, homeopathy, herbal medicine, and Ayurvedic medicine (which includes transcendental meditation, herbs, and yoga).

Because complementary and alternative medicine is reported to be used by as much as one-third of the U.S. population (Eisenberg et al. 1993), it is important to inquire about all the medications and interventions a patient uses and advise the patient accordingly (See "Component 2: Education for a Partnership in Asthma Care.").

ACUPUNCTURE

The Expert Panel does not recommend the use of acupuncture for the treatment of asthma (Evidence B). Acupuncture involves the superficial insertion of thin needles along acupuncture points or acupoints on the body. (Acupressure is an alternative method of stimulating the same acupoints.) Two Cochrane database systematic reviews (Linde et al. 2000; McCarney et al. 2004) of 7 and 11 randomized trials (with 174 and 324 participants, respectively) using real acupuncture and sham acupuncture to treat asthma or asthma-like symptoms found no statistically significant or clinically relevant effects for acupuncture compared to sham acupuncture. Both reviews concluded that adequate evidence to make recommendations about the value of acupuncture in asthma treatment is lacking. A meta-analysis of 11 RCTs published in the period 1970–2000, comparing real acupuncture with placebo acupuncture, found no evidence of an effect of acupuncture in reducing asthma symptoms (Martin et al. 2002).

CHIROPRACTIC THERAPY

The Expert Panel concludes that there is insufficient evidence to recommend the use of chiropractic or related techniques in the treatment of asthma.

Chiropractic therapy and other forms of spinal or bodily manipulation or massage have been reported anecdotally to benefit patients who have asthma. Systematic reviews of chiropractic techniques in asthma (Balon and Mior 2004) and related therapies, such as the Alexander technique (Dennis 2000), found few randomized, controlled studies. Those studies, where available, showed mixed results, with perhaps some benefit in symptoms or health-related quality-of-life measures but no definitive improvement on more objective measures of asthma outcomes.

HOMEOPATHY AND HERBAL MEDICINE

The Expert Panel concludes that there is insufficient evidence to support effectiveness of homeopathy and that more clinical trial and observational data are necessary.

The Expert Panel concludes that there is insufficient evidence to recommend herbal products for treating asthma. Furthermore, because herbal products are not standardized, one must be aware that some may have harmful ingredients and that some may interact with other pharmaceutical products that the patient may be taking (Evidence D).

Homeopathy deals with the use of diluted substances which cause symptoms in the undiluted form. A systematic review of homeopathy for asthma included six RCTs. The trials were of variable quality and used different homeopathic treatments, which limit the ability to reliably assess the possible role of homeopathy in asthma (McCarney et al. 2004).

A variety of herbal products have been used alone and as adjunctive therapy for asthma with positive results in small trials that have not been duplicated (Gupta et al. 1998; Khayyal et al. 2003; Lee et al. 2004; Urata et al. 2002). The National Center for Complementary and Alternative Medicine of the National Institutes of Health encourages the development of well-designed clinical trials to assess with clarity the role of herbal products.

BREATHING TECHNIQUES

The Expert Panel concludes there is insufficient evidence to suggest that breathing techniques provide clinical benefit to patients who have asthma. Controlled studies have been conducted with breathing exercises (Holloway and Ram 2004), inspiratory muscle training (Ram et al. 2003; Weiner et al. 2002), and Buteyko breathing (Cooper et al. 2003) (raising blood PCO_2 through hypoventilation). A systematic review of breathing exercises identified seven studies meeting inclusion criteria (Holloway and Ram 2004). Treatment interventions and outcome measurements varied greatly in these studies. Thus, although there was a suggestion of improvement in such outcomes as SABA use, quality of life, and exacerbations in persons who have asthma, no reliable conclusions could be drawn regarding the use of breathing exercises for treatment of asthma in clinical practice (Holloway and Ram 2004). Inspiratory muscle training has also been examined in a systematic review (Ram et al. 2003). In three studies in which the maximum inspiratory pressure (PI_{max}) was reported, it was significantly improved compared to controls. In one study, increased PI_{max} in women was accompanied by decreased perception of dyspnea and decreased SABA use (Weiner et al. 2002). A recent

randomized, double-blind, controlled study of 57 patients assessed the impact of two different breathing techniques on the use of SABA, controlling for the advice given to patients regarding the use of either breathing technique before using SABA. A marked reduction in SABA use was observed with both breathing techniques, but no significant changes occurred in the quality of life or in any physiological markers. This study suggests that, in mild persistent asthma, using breathing techniques before using SABA might curb overuse of SABA, and that the process of practicing breathing techniques may be more important than the type of breathing technique used (Slader et al. 2006). Larger studies are needed to confirm study findings.

RELAXATION TECHNIQUES

The Expert Panel concludes that, despite some encouraging data from small studies, further positive data from randomized, controlled studies will be necessary before relaxation techniques can be recommended in the treatment of asthma. Recent controlled studies have been conducted to investigate whether relaxation techniques, including biofeedback and hypotherapy, may be beneficial in asthma. Preliminary data suggest that relaxation techniques may help improve not only symptoms (which in studies appeared to improve nonspecifically) but also lung function (Lehrer et al. 2004; Loew et al. 2001). Due to limitations of size and clearly prespecified hypotheses, these studies would need further confirmation. A systematic review of RCTs of relaxation techniques (Huntley et al. 2002) concluded that there was a lack of data from well-conducted studies of relaxation therapies to recommend them in the treatment of asthma. This review did find some evidence, however, that muscle relaxation techniques in particular may lead to improvements in lung function.

YOGA

There is a paucity of well-controlled studies on the effects of yoga on asthma outcomes. A recent, well-controlled pilot study of one type of yoga (Iyengar) showed no significant effects on physiologic or health-related quality-of-life measures (Sabina et al. 2005).

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Corticosteroids (Glucocorticoids) ***Inhaled (ICS):*** Beclomethasone dipropionate Budesonide Flunisolide Fluticasone propionate Mometasone furoate Triamcinolone acetonide	*Indications* ■ Long-term prevention of symptoms; suppression, control, and reversal of inflammation. ■ Reduce need for oral corticosteroid. *Mechanisms* ■ **Anti-inflammatory.** Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. ■ Reverse beta$_2$-receptor downregulation. Inhibit microvascular leakage.	■ Cough, dysphonia, oral thrush (candidiasis). ■ In high doses (see figures 4-4b and 4–8b), systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising) (Barnes and Pedersen 1993; Kamada et al. 1996). In low-to-medium doses, suppression of growth velocity has been observed in children, but this effect may be transient, and the clinical significance has not been established (CAMP 2000; Guilbert et al. 2006).	■ Spacer/holding chamber devices with nonbreath-activated MDIs and mouth washing after inhalation decrease local side effects. ■ Preparations are not absolutely interchangeable on a mcg or per puff basis (see figures 4–4b and 4–8b for estimated clinical comparability). New delivery devices may provide greater delivery to airways; this change may affect dose. ■ The risks of uncontrolled asthma should be weighed against the limited risks of ICS therapy. The potential but small risk of adverse events is well balanced by their efficacy. (See text.) ■ "Adjustable dose" approach to treatment may enable reduction in cumulative dose of ICS treatment over time without sacrificing maintenance of asthma control. ■ Dexamethasone is not included as an ICS for long-term control because it is highly absorbed and has long-term suppressive side effects.
Systemic: Methylprednisolone Prednisolone Prednisone	*Indications* ■ For short-term (3–10 days) "burst": to gain prompt control of inadequately controlled persistent asthma. ■ For long-term prevention of symptoms in severe persistent asthma: suppression, control, and reversal of inflammation. *Mechanisms* ■ Same as inhaled.	■ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. ■ Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness, and—in rare instances—impaired immune function. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and *Strongyloides.*	■ Use at lowest effective dose. For long-term use, alternate-day a.m. dosing produces the least toxicity. If daily doses are required, one study shows improved efficacy with no increase in adrenal suppression when administered at 3 p.m. rather than in the morning (Beam et al. 1992).

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS (CONTINUED)

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Cromolyn Sodium and Nedocromil	*Indications* ■ Long-term prevention of symptoms in mild persistent asthma; may modify inflammation. ■ Preventive treatment prior to exposure to exercise or known allergen. *Mechanisms* ■ **Anti-inflammatory.** Blocks *early* and late reaction to allergen. Interferes with chloride channel function. Stabilizes mast cell membranes and inhibits activation and release of mediators from eosinophils and epithelial cells. ■ Inhibits acute response to exercise, cold dry air, and SO_2.	■ Cough and irritation. ■ 15–20 percent of patients complain of an unpleasant taste from nedocromil.	■ Therapeutic response to cromolyn and nedocromil often occurs within 2 weeks, but a 4- to 6-week trial may be needed to determine maximum benefit. ■ Dose of cromolyn by MDI (1 mg/puff) may be inadequate to affect airway hyperresponsiveness. Nebulizer delivery (20 mg/ampule) may be preferred for some patients. ■ Safety is the primary advantage of these agents.
Immunomodulators			
Omalizumab (Anti-IgE) For subcutaneous use	*Indications* ■ Long-term control and prevention of symptoms in adults (≥12 years old) who have moderate or severe persistent allergic asthma inadequately controlled with ICS. *Mechanisms* ■ Binds to circulating IgE, preventing it from binding to the high-affinity (FcεRI) receptors on basophils and mast cells. ■ Decreases mast cell mediator release from allergen exposure. ■ Decreases the number of FcεRIs in basophils and submucosal cells.	■ Pain and bruising of injection sites has been reported in 5–20 percent of patients. ■ Anaphylaxis has been reported in 0.2 percent of treated patients. ■ Malignant neoplasms were reported in 0.5 percent of patients compared to 0.2 percent receiving placebo; relationship to drug is unclear.	■ Monitor patients following injection. Be prepared and equipped to identify and treat anaphylaxis that may occur. ■ The dose is administered either every 2 or 4 weeks and is dependent on the patient's body weight and IgE level before therapy. ■ A maximum of 150 mg can be administered in one injection. ■ Needs to be stored under refrigeration at 2–8 °C. ■ Whether patients will develop significant antibody titers to the drug with long-term administration is unknown.

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS (CONTINUED)

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Leukotriene Receptor Antagonists (LTRAs)	*Mechanisms* ■ **Leukotriene receptor antagonist;** selective competitive inhibitor of $CysLT_1$ receptor.		■ May attenuate EIB in some patients, but less effective than ICS therapy (Vidal et al. 2001). ■ Do not use LTRA + LABA as a substitute for ICS + LABA.
Montelukast tablets and granules	*Indications* ■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥1 year of age. May also be used with ICS as combination therapy in moderate persistent asthma.	■ No specific adverse effects have been identified. ■ Rare cases of Churg-Strauss have occurred, but the association is unclear.	■ A flat dose-response curve, without further benefit, if dose is increased above those recommended.
Zafirlukast tablets	■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥7 years of age. May also be used with ICS as combination therapy in moderate persistent asthma.	■ Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation.	■ Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ Zafirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. INRs should be monitored during coadministration. ■ Patients should be warned to discontinue use if they experience signs and symptoms of liver dysfunction (right upper quadrant pain, pruritis, lethargy, jaundice, nausea), and patients' ALTs should be monitored.
5-Lipoxygenase Inhibitor	*Mechanisms* ■ Inhibits the production of leukotrienes from arachidonic acid, both LTB_4 and the cysteinyl leukotrienes.		
Zileuton tablets	*Indications* ■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age. ■ May be used with ICS as combination therapy in moderate persistent asthma in patients ≥12 years of age.	■ Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia.	■ Zileuton is microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly. ■ Monitor hepatic enzymes (ALT).

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS (CONTINUED)

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Long-Acting Beta$_2$-Agonists (LABA) *Inhaled LABA:* Formoterol Salmeterol	*Indications* ■ Long-term prevention of symptoms, added to ICS ■ Prevention of EIB. ■ *Not to be used to treat acute symptoms or exacerbations.* *Mechanisms* ■ **Bronchodilation.** Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP, producing functional antagonism of bronchoconstriction. ■ Compared to SABA, salmeterol (but not formoterol) has slower onset of action (15–30 minutes). Both salmeterol and formoterol have longer duration (>12 hours) compared to SABA.	■ Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose. ■ A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established. ■ Potential risk of uncommon, severe, life-threatening or fatal exacerbation; see text for additional discussion regarding safety of LABAs.	■ Not to be used to treat acute symptoms or exacerbations. ■ Should not be used as monotherapy for long-term control of asthma or as anti-inflammatory therapy. ■ May provide more effective symptom control when added to standard doses of ICS compared to increasing the ICS dosage. ■ Clinical significance of potentially developing tolerance is uncertain, because studies show symptom control and bronchodilation are maintained. ■ Decreased duration of protection against EIB may occur with regular use.
Oral: Albuterol, sustained-release			■ Inhaled route is preferred because LABAs are longer acting and have fewer side effects than oral sustained-release agents. Oral agents have not been adequately studied as adjunctive therapy with ICS.
Methylxanthines Theophylline, sustained-release tablets and capsules	*Indications* ■ Long-term control and prevention of symptoms in mild persistent asthma or as adjunctive with ICS, in moderate or persistent asthma. *Mechanisms* ■ **Bronchodilation.** Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism. ■ May affect eosinophilic infiltration into bronchial mucosa as well as decreases T-lymphocyte numbers in epithelium. ■ Increases diaphragm contractility and mucociliary clearance.	■ Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia. ■ Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males who have prostatism.	■ Maintain steady-state serum concentrations between 5 and 15 mcg/mL. Routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by numerous factors which can produce significant changes in steady-state serum theophylline concentrations. ■ Patients should be told to discontinue if they experience toxicity. ■ Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of SABA. Serum concentration monitoring is mandatory.

Key: anti-IgE, anti-immunoglobulin E, EIB, exercise-induced bronchospasm; INR, International Normalized Ratio; LABA, long-acting beta$_2$-agonist; MDI, metered-dose inhaler; SABA, inhaled short-acting beta$_2$-agonist

FIGURE 3–23. QUICK-RELIEF MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Short-Acting Beta$_2$-Agonists (SABA) *Inhaled SABA:* Albuterol Levalbuterol Pirbuterol	*Indications* ■ Relief of acute symptoms; quick-relief medication. ■ Preventive treatment for EIB prior to exercise. *Mechanisms* ■ **Bronchodilation.** Binds to the beta$_2$-adrenergic receptor, producing smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction.	■ Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia. Inhaled route, in general, causes few systemic adverse effects. Patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.	■ Drugs of choice for acute bronchospasm. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. The less beta$_2$-selective agents (isoproterenol, metaproterenol, isoetharine, and epinephrine) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses. Oral systemic beta$_2$-agonists are not recommended. ■ For patients who have intermittent asthma, regularly scheduled daily use neither harms nor benefits asthma control (Drazen et al. 1996). Regularly scheduled daily use is not recommended. ■ Regular use >2 days/week for symptom control (not prevention of EIB), increasing use, or lack of expected effect indicates inadequate asthma control. ■ For patients frequently using SABA, anti-inflammatory medication should be initiated or intensified. ■ Levalbuterol at one-half the mcg dose produces clinically comparable bronchodilation and systemic side effects as racemic albuterol.

FIGURE 3–23. QUICK-RELIEF MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Anticholinergics Ipratropium bromide	*Indications* ■ Relief of acute bronchospasm (See Therapeutic Issues column.). *Mechanisms* ■ **Bronchodilation.** Competitive inhibition of muscarinic cholinergic receptors. ■ Reduces intrinsic vagal tone of the airways. May block reflex bronchoconstriction secondary to irritants or to reflux esophagitis. ■ May decrease mucous gland secretion.	■ Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes. If used in the ED, produces less cardiac stimulation than SABAs.	■ Reverses only cholinergically mediated bronchospasm; does not modify reaction to antigen. Does not block EIB. ■ Multiple doses of ipratropium in the ED provide additive effects to SABA. ■ May be alternative for patients who do not tolerate SABA. ■ Treatment of choice for bronchospasm due to beta-blocker medication. ■ Has not proven to be efficacious as long-term control therapy for asthma.
Corticosteroids *Systemic:* Methylprednisolone Prednisolone Prednisone	*Indications* ■ For moderate or severe exacerbations to prevent progression of exacerbation, reverse inflammation, speed recovery, and reduce rate of relapse. *Mechanisms* ■ **Anti-inflammatory.** See figure 3–22.	■ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, facial flushing, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and *Strongyloides.*	■ Short-term therapy should continue until patient's symptoms resolve. This usually requires 3–10 days but may require longer. — Action may begin within an hour. ■ There is no evidence that tapering the dose following improvement is useful in preventing a relapse in asthma exacerbations. ■ Other systemic corticosteroids such as hydrocortisone and dexamethasone given in equipotent daily doses are likely to be as effective as prednisolone.

Key: ED, emergency department; EIB, exercise-induced bronchospasm

FIGURE 3–24. AEROSOL DELIVERY DEVICES

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Metered-dose inhaler (MDI) Beta$_2$-agonists Corticosteroids Cromolyn sodium Anticholinergics	≥5 years old (<5 with spacer or valved holding chamber (VHC) mask)	Actuation during a slow (30 L/min or 3–5 seconds) deep inhalation, followed by 10-second breathhold. Under laboratory conditions, open-mouth technique (holding MDI 2 inches away from open mouth) enhances delivery to the lung. This technique, however, has not been shown to enhance clinical benefit consistently compared to closed-mouth technique (inserting MDI mouthpiece between lips and teeth).	Slow inhalation and coordination of actuation during inhalation may be difficult, particularly in young children and elderly. Patients may incorrectly stop inhalation at actuation. Deposition of 50–80 percent of actuated dose in oropharynx. Mouth washing and spitting is effective in reducing the amount of drug swallowed and absorbed systemically (Selroos and Halme 1991). Lung delivery under ideal conditions varies significantly between MDIs due to differences in formulation (suspension versus solution), propellant (chlorofluorocarbon (CFC) versus hydrofluoralkane (HFA)), and valve design (Dolovich 2000). For example, inhaled corticosteroid (ICS) delivery varies from 5–50 percent (Kelly 2003).
Breath-actuated MDI Beta$_2$-agonist	≥5 years old	Tight seal around mouthpiece and slightly more rapid inhalation than standard MDI (see above) followed by 10-second breathhold.	May be particularly useful for patients unable to coordinate inhalation and actuation. May also be useful for elderly patients (Newman et al. 1991). Patients may incorrectly stop inhalation at actuation. Cannot be used with currently available spacer/valved-holding chamber (VHC) devices.
Dry powder inhaler (DPI) Beta$_2$-agonists Corticosteroids Anticholinergics	≥4 years old	Rapid (60 L/min or 1–2 seconds), deep inhalation. Minimally effective inspiratory flow is device dependent. Most children <4 years of age may not generate sufficient inspiratory flow to activate the inhaler.	Dose is lost if patient exhales through device after actuating. Delivery may be greater or lesser than MDI, depending on device and technique. Delivery is more flow dependent in devices with highest internal resistance. Rapid inhalation promotes greater deposition in larger central airways (Dolovich 2000). Mouth washing and spitting is effective in reducing amount of drug swallowed and absorbed (Selroos and Halme 1991).

FIGURE 3–24. AEROSOL DELIVERY DEVICES (CONTINUED)

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Spacer or valved holding chamber (VHC)	≥4 years old <4 years old VHC with face mask	Slow (30 L/min or 3–5 seconds) deep inhalation, followed by 10-second breathhold immediately following actuation. Actuate only once into spacer/VHC per inhalation (O'Callaghan et al. 1994). If face mask is used, it should have a tight fit and allow 3–5 inhalations per actuation (Amirav and Newhouse 2001; Everard et al. 1992). Rinse plastic VHCs once a month with low concentration of liquid household dishwashing detergent (1:5,000 or 1–2 drops per cup of water) and let drip dry (Pierart et al. 1999; Wildhaber et al. 2000).	Indicated for patients who have difficulty performing adequate MDI technique. May be bulky. Simple tubes do not obviate coordinating actuation and inhalation. The VHCs are preferred. Face mask allows MDIs to be used with small children. However, use of a face mask reduces delivery to lungs by 50 percent (Wildhaber et al. 1999). The VHC improves lung delivery and response in patients who have poor MDI technique. The effect of a spacer or VHC on output from an MDI depends on both the MDI and device type; thus data from one combination should not be extrapolated to all others (Ahrens et al. 1995; Dolovich 2000). Spacers and/or VHCs decrease oropharyngeal deposition and thus decrease risk of topical side effects (e.g., thrush) (Salzman and Pyszczynski 1988; Toogood et al. 1984). Spacers will also reduce the potential systemic availability of ICSs with higher oral absorption (Brown et al. 1990; Selroos and Halme 1991). However, spacer/VHCs may increase systemic availability of ICSs that are poorly absorbed orally by enhancing delivery to lungs (Dempsey et al. 1999; Kelly 2003). No clinical data are available on use of spacers or VHCs with ultrafine-particle-generated HFA MDIs. Use antistatic VHCs or rinse plastic nonantistatic VHCs with dilute household detergents to enhance delivery to lungs and efficacy (Lipworth et al. 2002; Pierart et al. 1999; Wildhaber et al. 2000). This effect is less pronounced for albuterol MDIs with HFA propellant than for albuterol MDIs with CFC propellant (Chuffart et al. 2001). As effective as nebulizer for delivering SABAs and anticholinergics in mild to moderate exacerbations; data in severe exacerbations are limited.

FIGURE 3–24. AEROSOL DELIVERY DEVICES (CONTINUED)

Device/Drugs	Population	Optimal Technique*	Therapeutic Issues
Nebulizer Beta$_2$-agonists Corticosteroids Cromolyn sodium Anticholinergics	Patients of any age who cannot use MDI with VHC and face mask.	Slow tidal breathing with occasional deep breaths. Tightly fitting face mask for those unable to use mouthpiece. Using the "blow by" technique (i.e., holding the mask or open tube near the infant's nose and mouth) is not appropriate.	Less dependent on patient's coordination and cooperation. Delivery method of choice for cromolyn sodium in young children. May be expensive; time consuming; bulky; output is dependent on device and operating parameters (fill volume, driving gas flow); internebulizer and intranebulizer output variances are significant (Dolovich 2000). Use of a face mask reduces delivery to lungs by 50 percent (Wildhaber et al. 1999). Nebulizers are as effective as MDIs plus VHCs for delivering bronchodilators in the ED for mild to moderate exacerbations; data in severe exacerbations are limited. Choice of delivery system is dependent on resources, availability, and clinical judgment of the clinician caring for the patient (Cates et al. 2002; Dolovich et al. 2005). Potential for bacterial infections if not cleaned properly.

Key: ED, emergency department; SABAs, inhaled short-acting beta$_2$-agonists
*See figures in "Component 2: Education for a Partnership in Asthma Care" for description of MDI and DPI techniques.

References

Aalbers R, Backer V, Kava TT, Omenaas ER, Sandstrom T, Jorup C, Welte T. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Opin* 2004;20(2):225–40.

Aaron SD, Dales RE, Pham B. Management of steroid-dependent asthma with methotrexate: a meta-analysis of randomized clinical trials. *Respir Med* 1998;92(8):1059–65.

Adams RJ, Fuhlbrigge A, Finkelstein JA, Lozano P, Livingston JM, Weiss KB, Weiss ST. Impact of inhaled antiinflammatory therapy on hospitalization and emergency department visits for children with asthma. *Pediatrics* 2001;107(4):706–11.

Ahrens R, Lux C, Bahl T, Han SH. Choosing the metered-dose inhaler spacer or holding chamber that matches the patient's need: evidence that the specific drug being delivered is an important consideration. *J Allergy Clin Immunol* 1995;96(2):288–94.

Alton EW, Norris AA. Chloride transport and the actions of nedocromil sodium and cromolyn sodium in asthma. *J Allergy Clin Immunol* 1996;98(5 Pt 2):S102–S105, discussion S105–106.

American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for the use of live attenuated varicella vaccine. *Pediatrics* 1995;95(5):791–6. Erratum in: *Pediatrics* 1995;96(1 Pt 1): preceding 151, following 171.

American Lung Association Asthma Clinical Research Centers. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. *Am J Respir Crit Care Med* 2007;175(3):235–42. Epub September 2006.

Amirav I, Newhouse MT. Aerosol therapy with valved holding chambers in young children: importance of the facemask seal. *Pediatrics* 2001;108(2):389–94.

Anderson HR, Ayres JG, Sturdy PM, Bland JM, Butland BK, Peckitt C, Taylor JC, Victor CR. Bronchodilator treatment and deaths from asthma: case-control study. *BMJ* 2005;330(7483):117. Epub December 2004.

Asmus MJ, Liang J, Coowanitwong I, Hochhaus G. In vitro performance characteristics of valved holding chamber and spacer devices with a fluticasone metered-dose inhaler. *Pharmacotherapy* 2004;24(2):159–66.

Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy* 2004;59(7):701–8.

Balanag VM, Yunus F, Yang PC, Jorup C. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. *Pulm Pharmacol Ther* 2006;19(2):139–47. Epub July 2005.

Balon JW, Mior SA. Chiropractic care in asthma and allergy. *Ann Allergy Asthma Immunol* 2004;93(2 Suppl 1):S55–S60.

Barnes NC, Marone G, Di Maria GU, Visser S, Utama I, Payne SL. A comparison of fluticasone propionate, 1 mg daily, with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma. International Study Group. *Eur Respir J* 1993;6(6):877–85.

Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. Report of a workshop held in Eze, France, October 1992. *Am Rev Respir Dis* 1993;148(4 Pt 2):S1–S26.

Bateman ED, Bantje TA, Joao GM, Toumbis MG, Huber RM, Naya I, Eliraz A. Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone propionate alone in patients with moderate persistent asthma. *Am J Respir Med* 2003;2(3):275–81.

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004;170(8):836–44.

Bateman ED, Fairall L, Lombardi DM, English R. Budesonide/formoterol and formoterol provide similar rapid relief in patients with acute asthma showing refractoriness to salbutamol. *Respir Res* 2006;7:13.

Beam WR, Weiner DE, Martin RJ. Timing of prednisone and alterations of airways inflammation in nocturnal asthma. *Am Rev Respir Dis* 1992;146(6):1524–30.

Berger W, Gupta N, McAlary M, Fowler-Taylor A. Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic asthma. *Ann Allergy Asthma Immunol* 2003;91(2):182–8.

Berger WE. Levalbuterol: pharmacologic properties and use in the treatment of pediatric and adult asthma. *Ann Allergy Asthma Immunol* 2003;90(6):583–591, quiz 591–2. 659.

Bernstein IL, Bernstein DI, Dubb JW, Faiferman I, Wallin B. A placebo-controlled multicenter study of auranofin in the treatment of patients with corticosteroid-dependent asthma. Auranofin Multicenter Drug Trial. *J Allergy Clin Immunol* 1996;98(2):317–24.

Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006;130(6):1733–43.

Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, Tozzi CA, Polos P. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;171(4):315–22. Epub November 2004.

Bleecker ER, Welch MJ, Weinstein SF, Kalberg C, Johnson M, Edwards L, Rickard KA. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. *J Allergy Clin Immunol* 2000;105(6 Pt 1):1123–9.

Bleecker ER, Yancey SW, Baitinger LA, Edwards LD, Klotsman M, Anderson WH, Dorinsky PM. Salmeterol response is not affected by beta$_2$-adrenergic receptor genotype in subjects with persistent asthma. *J Allergy Clin Immunol* 2006;118(4):809–16.

Boonsawat W, Charoenratanakul S, Pothirat C, Sawanyawisuth K, Seearamroongruang T, Bengtsson T, Brander R, Selroos O. Formoterol (OXIS) Turbuhaler as a rescue therapy compared with salbutamol pMDI plus spacer in patients with acute severe asthma. *Respir Med* 2003;97(9):1067–74.

Booth H, Richmond I, Ward C, Gardiner PV, Harkawat R, Walters EH. Effect of high dose inhaled fluticasone propionate on airway inflammation in asthma. *Am J Respir Crit Care Med* 1995;152(1):45–52.

Borish LC, Nelson HS, Corren J, Bensch G, Busse WW, Whitmore JB, Agosti JM; IL-4R Asthma Study Group. Efficacy of soluble IL-4 receptor for the treatment of adults with asthma. *J Allergy Clin Immunol* 2001;107(6):963–70.

Borish LC, Nelson HS, Lanz MJ, Claussen L, Whitmore JB, Agosti JM, Garrison L. Interleukin-4 receptor in moderate atopic asthma. A phase I/II randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 1999;160(6):1816–23.

Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, Chinchilli VM, Craig TJ, DiMango EA, Deykin A, et al.; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352(15):1519–28.

Bousquet J, Ben Joseph R, Messonnier M, Alemao E, Gould AL. A meta-analysis of the dose-response relationship of inhaled corticosteroids in adolescents and adults with mild to moderate persistent asthma. *Clin Ther* 2002;24(1):1–20.

Brown PH, Blundell G, Greening AP, Crompton GK. Do large volume spacer devices reduce the systemic effects of high dose inhaled corticosteroids? *Thorax* 1990;45(10):736–9.

Bryan SA, O'Connor BJ, Matti S, Leckie MJ, Kanabar V, Khan J, Warrington SJ, Renzetti L, Rames A, Bock JA, et al. Effects of recombinant human interleukin-12 on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356(9248):2149–53.

Buhl R, Creemers JP, Vondra V, Martelli NA, Naya IP, Ekstrom T. Once-daily budesonide/formoterol in a single inhaler in adults with moderate persistent asthma. *Respir Med* 2003;97(4):323–30.

Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001a;108(2):184–90.

Busse W, Raphael GD, Galant S, Kalberg C, Goode-Sellers S, Srebro S, Edwards L, Rickard K; Fluticasone Proprionate Clinical Research Study Group. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol* 2001b;107(3):461–8.

Busse W, Wolfe J, Storms W, Srebro S, Edwards L, Johnson M, Bowers BW, Rogenes PR, Rickard K. Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. *J Fam Pract* 2001c;50(7):595–602.

Busse WW. What role for inhaled steroids in chronic asthma? *Chest* 1993;104(5):1565–71.

Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, Donnell D, Hannon S, Colice GL. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999;104(6):1215–22.

Campbell IA, Douglas JG, Francis RM, Prescott RJ, Reid DM; Research Committee of the British Thoracic Society. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. *Thorax* 2004;59(9):761–8.

Capewell S, Reynolds S, Shuttleworth D, Edwards C, Finlay AY. Purpura and dermal thinning associated with high dose inhaled corticosteroids. *BMJ* 1990;300(6739):1548–51.

Carl JC, Myers TR, Kirchner HL, Kercsmar CM. Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. *J Pediatr* 2003;143(6):731–6.

Casale TB, Nelson HS, Kemp J, Parasuraman B, Uryniak T, Liljas B. Budesonide Turbuhaler delivered once daily improves health-related quality of life and maintains improvements with a stepped-down dose in adults with mild to moderate asthma. *Ann Allergy Asthma Immunol* 2003;90(3):323–30.

Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306(6884):1034–7.

Cates CJ, Rowe BH, Bara A. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2002;(2):CD000052.

Centers for Disease Control and Prevention. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1994;43(RR-1):1–38.

Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002;57(3):226–30.

Chan MT, Leung DY, Szefler SJ, Spahn JD. Difficult-to-control asthma: clinical characteristics of steroid-insensitive asthma. *J Allergy Clin Immunol* 1998;101(5):594–601.

Chanez P, Karlstrom R, Godard P. High or standard initial dose of budesonide to control mild-to-moderate asthma? *Eur Respir J* 2001;17(5):856–62.

Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003;168(11):1308–11.

Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting beta$_2$-adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992;327(17):1198–203.

Childhood Asthma Management Program Research Group (CAMP). Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054–63.

Chowdhury BA. June 15, 2005. Letter to members of the Pulmonary-Allergy Drugs Advisory Committee. Available at: www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4148B_03_01-FDA-Dir-Memo.pdf.

Chuffart AA, Sennhauser FH, Wildhaber JH; Swiss Paediatric Respiratory Physiology Research Group. Factors affecting the efficiency of aerosol therapy with pressurised metered-dose inhalers through plastic spacers. *Swiss Med Wkly* 2001;131(1–2):14–8.

Clark B. General pharmacology, pharmacokinetics, and toxicology of nedocromil sodium. *J Allergy Clin Immunol* 1993;92(1 Pt 2):200–2.

Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;342(8875):833–7.

Cockcroft DW, Swystun VA. Effect of single doses of S-salbutamol, R-salbutamol, racemic salbutamol, and placebo on the airway response to methacholine. *Thorax* 1997;52(10):845–8.

Cooper S, Oborne J, Newton S, Harrison V, Thompson CJ, Lewis S, Tattersfield A. Effect of two breathing exercises (Buteyko and pranayama) in asthma: a randomised controlled trial. *Thorax* 2003;58(8):674–9.

Creticos P, Burk J, Smith L, Comp R, Norman P, Findlay S. The use of twice daily nedocromil sodium in the treatment of asthma. *J Allergy Clin Immunol* 1995;95(4):829–36.

Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002;109(1):57–62.

Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337(1):8–14.

Currie GP, Bates CE, Lee DK, Jackson CM, Lipworth BJ. Effects of fluticasone plus salmeterol versus twice the dose of fluticasone in asthmatic patients. *Eur J Clin Pharmacol* 2003;59(1):11–5. Epub March 2003.

Dahl R, Larsen BB, Venge P. Effect of long-term treatment with inhaled budesonide or theophylline on lung function, airway reactivity and asthma symptoms. *Respir Med* 2002;96(6):432–8.

Dahl R, Lundback B, Malo JL, Mazza JA, Nieminen MM, Saarelainen P, Barnacle H. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. International Study Group. *Chest* 1993;104(5):1352–8.

Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, Mastalerz L, Pinis G, Swanson LJ, Boodhoo TI, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1187–94.

Dahlen B, Zetterstrom O, Bjorck T, Dahlen SE. The leukotriene-antagonist ICI-204,219 inhibits the early airway reaction to cumulative bronchial challenge with allergen in atopic asthmatics. *Eur Respir J* 1994;7(2):324–31.

Davies H, Olson L, Gibson P. Methotrexate as a steroid sparing agent for asthma in adults. *Cochrane Database Syst Rev* 2000;(2):CD000391.

de Benedictis FM, Tuteri G, Pazzelli P, Bertotto A, Bruni L, Vaccaro R. Cromolyn versus nedocromil: duration of action in exercise-induced asthma in children. *J Allergy Clin Immunol* 1995;96(4):510–4.

Dempsey OJ, Wilson AM, Coutie WJ, Lipworth BJ. Evaluation of the effect of a large volume spacer on the systemic bioactivity of fluticasone propionate metered-dose inhaler. *Chest* 1999;116(4):935–40.

Dennis J. Alexander technique for chronic asthma. *Cochrane Database Syst Rev* 2000;(2):CD000995.

Dennis SM, Sharp SJ, Vickers MR, Frost CD, Crompton GK, Barnes PJ, Lee TH. Regular inhaled salbutamol and asthma control: the TRUST randomised trial. Therapy Working Group of the National Asthma Task Force and the MRC General Practice Research Framework. *Lancet* 2000;355(9216):1675–9.

Deykin A, Lazarus SC, Fahy JV, Wechsler ME, Boushey HA, Chinchilli VM, Craig TJ, DiMango E, Kraft M, Leone F, et al.; Asthma Clinical Research Network, National Heart, Lung, and Blood Institute/NIH. Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. *J Allergy Clin Immunol* 2005;115(4):720–7.

Dixon CM, Barnes PJ. Bradykinin-induced bronchoconstriction: inhibition by nedocromil sodium and sodium cromoglycate. *Br J Clin Pharmacol* 1989;27(6):831–6.

Djukanovic R, Wilson JW, Britten KM, Wilson SJ, Walls AF, Roche WR, Howarth PH, Holgate ST. Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. *Am Rev Respir Dis* 1992;145(3):669–74.

Djukanovic R, Wilson SJ, Kraft M, Jarjour NN, Steel M, Chung KF, Bao W, Fowler-Taylor A, Matthews J, Busse WW, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004;170(6):583–93. Epub June 2004.

Dolan LM, Kesarwala HH, Holroyde JC, Fischer TJ. Short-term, high-dose, systemic steroids in children with asthma: the effect on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol* 1987;80(1):81–7.

Dolovich MA. Influence of inspiratory flow rate, particle size, and airway caliber on aerosolized drug delivery to the lung. *Respir Care* 2000;45(6):597–608.

Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, Smaldone GC, Guyatt G; American College of Chest Physicians; American College of Asthma, Allergy, and Immunology. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest* 2005;127(1):335–71.

Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997;277(11):887–91.

Drazen JM, Israel E, Boushey HA, Chinchilli VM, Fahy JV, Fish JE, Lazarus SC, Lemanske RF, Martin RJ, Peters SP, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. *N Engl J Med* 1996;335(12):841–7.

Ducharme FM, Chabot G, Polychronakos C, Glorieux F, Mazer B. Safety profile of frequent short courses of oral glucocorticoids in acute pediatric asthma: impact on bone metabolism, bone density, and adrenal function. *Pediatrics* 2003;111(2):376–83.

Duddridge M, Ward C, Hendrick DJ, Walters EH. Changes in bronchoalveolar lavage inflammatory cells in asthmatic patients treated with high dose inhaled beclomethasone dipropionate. *Eur Respir J* 1993;6(4):489–97.

Eady RP. The pharmacology of nedocromil sodium. *Eur J Respir Dis Suppl* 1986;147:112–119. Review.

Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med* 1993;328(4):246–52.

Eisner MD, Lieu TA, Chi F, Capra AM, Mendoza GR, Selby JV, Blanc PD. Beta agonists, inhaled steroids, and the risk of intensive care unit admission for asthma. *Eur Respir J* 2001;17(2):233–40.

EPR—2. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD, U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

EPR—Update 2002. Expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics 2002 (EPR—Update 2002). NIH Publication No. 02-5074. Bethesda, MD, U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003.

Ernst P, Habbick B, Suissa S, Hemmelgarn B, Cockcroft D, Buist AS, Horwitz RI, McNutt M, Spitzer WO. Is the association between inhaled beta-agonist use and life-threatening asthma because of confounding by severity? *Am Rev Respir Dis* 1993;148(1):75–9.

Evans DJ, Cullinan P, Geddes DM. Cyclosporin as an oral corticosteroid sparing agent in stable asthma. *Cochrane Database Syst Rev* 2001;(2):CD002993.

Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997;337(20):1412–8.

Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. *Arch Dis Child* 1992;67(5):580–5.

Fabbri L, Burge PS, Croonenborgh L, Warlies F, Weeke B, Ciaccia A, Parker C. Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. International Study Group. *Thorax* 1993;48(8):817–23.

Federico MJ, Covar RA, Brown EE, Leung DY, Spahn JD. Racial differences in T-lymphocyte response to glucocorticoids. *Chest* 2005;127(2):571–8.

Fish JE, Peters SP, Chambers CV, McGeady SJ, Epstein KR, Boushey HA, Cherniack RM, Chinchilli VM, Drazen JM, Fahy JV, et al. An evaluation of colchicine as an alternative to inhaled corticosteriods in moderate asthma. National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. *Am J Respir Crit Care Med* 1997;156(4 Pt 1):1165–71.

FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004;59(7):550–6.

Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003;167(2):199–204. Epub October 2002.

Food and Drug Administration (FDA). 2003. Advisory Panel. Available at: www.fda.gov/ohrms/dockets/ac/03/slides/20.

Food and Drug Administration (FDA). 2005. Public health advisory: Serevent diskus, Advair diskus, and Foradil (long acting beta agonists). Available at: http://www.fda.gov/cder/drug/advisory/LABA.htm.

Food and Drug Administration (FDA). 2007. FDA alert: Omalizumab (marketed as Xolair) information 2/2007. Available at: http://www.fda.gov/cder/drug/infopage/omalizumab/default.htm.

Foresi A, Morelli MC, Catena E. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group. *Chest* 2000;117(2):440–6.

Fost DA, Leung DY, Martin RJ, Brown EE, Szefler SJ, Spahn JD. Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. *J Allergy Clin Immunol* 1999;103(6):1031–5.

Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA* 1997;277(9):722–7.

Garbe E, Suissa S, LeLorier J. Association of inhaled corticosteroid use with cataract extraction in elderly patients. *JAMA* 1998;280(6):539–43. Erratum in: *JAMA* 1998;280(21):1830.

Garcia-Garcia ML, Wahn U, Gilles L, Swern A, Tozzi CA, Polos P. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatrics* 2005;116(2):360–9.

Gauvreau GM, Inman MD, Kelly M, Watson RM, Dorman SC, O'Byrne PM. Increased levels of airway neutrophils reduce the inhibitory effects of inhaled glucocorticosteroids on allergen-induced airway eosinophils. *Can Respir J* 2002;9(1):26–32.

Gonzalez JP, Brogden RN. Nedocromil sodium. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of reversible obstructive airways disease. *Drugs* 1987;34(5):560–77. Review.

Gordon JR, Swystun VA, Li F, Zhang X, Davis BE, Hull P, Cockcroft DW. Regular salbutamol use increases CXCL8 responses in asthma: relationship to the eosinophil response. *Eur Respir J* 2003;22(1):118–26.

Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002;57(10):875–9.

Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X, Ducharme FM. Combination of inhaled long-acting beta$_2$-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane Database Syst Rev* 2005;(4):CD005533.

Grembiale RD, Pelaia G, Naty S, Vatrella A, Tranfa CM, Marsico SA. Comparison of the bronchodilating effects of inhaled formoterol, salmeterol and salbutamol in asthmatic patients. *Pulm Pharmacol Ther* 2002;15(5):463–6.

Gross NJ. Tiotropium bromide. *Chest* 2004;126(6):1946–53. Review.

Guhan AR, Cooper S, Oborne J, Lewis S, Bennett J, Tattersfield AE. Systemic effects of formoterol and salmeterol: a dose-response comparison in healthy subjects. *Thorax* 2000;55(8):650–6.

Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, Bacharier LB, Lemanske RF Jr, Strunk RC, Allen DB, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354(19):1985–97.

Gupta I, Gupta V, Parihar A, Gupta S, Ludtke R, Safayhi H, Ammon HP. Effects of *Boswellia serrata* gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. *Eur J Med Res* 1998;3(11):511–4.

Gustafsson P, Tsanakas J, Gold M, Primhak R, Radford M, Gillies E. Comparison of the efficacy and safety of inhaled fluticasone propionate 200 micrograms/day with inhaled beclomethasone dipropionate 400 micrograms/day in mild and moderate asthma. *Arch Dis Child* 1993;69(2):206–11.

Haahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, Nikander K, Persson T, Reinikainen K, Selroos O, et al. Comparison of a beta$_2$-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325(6):388–92.

Hancox RJ, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, Taylor DR. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. *Respir Med* 2000;94(8):767–71.

Hancox RJ, Subbarao P, Kamada D, Watson RM, Hargreave FE, Inman MD. Beta$_2$-agonist tolerance and exercise-induced bronchospasm. *Am J Respir Crit Care Med* 2002;165(8):1068–70.

Harrison TW, Oborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. *Lancet* 2004;363(9405):271–5.

Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *BMJ* 2003;326(7399):1115.

Henderson WR Jr. The role of leukotrienes in inflammation. *Ann Intern Med* 1994;121(9):684–97. Review.

Hermansen MN, Nielsen KG, Buchvald F, Jespersen JJ, Bengtsson T, Bisgaard H. Acute relief of exercise-induced bronchoconstriction by inhaled formoterol in children with persistent asthma. *Chest* 2006;129(5):1203–9.

Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, Bousquet J, Kerstjens HA, Fox H, Thirlwell J, et al.; Omalizumab 011 International Study Group. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;34(4):632–8.

Holloway E, Ram FS. Breathing exercises for asthma. *Cochrane Database Syst Rev* 2004;(1):CD001277.

Holt S, Suder A, Weatherall M, Cheng S, Shirtcliffe P, Beasley R. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001;323(7307):253–6.

Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, Beeh KM, Ramos S, Canonica GW, Hedgecock S, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60(3):309–16.

Huntley A, White AR, Ernst E. Relaxation therapies for asthma: a systematic review. *Thorax* 2002;57(2):127–31.

Ind PW, Haughney J, Price D, Rosen JP, Kennelly J. Adjustable and fixed dosing with budesonide/ formoterol via a single inhaler in asthma patients: the ASSURE study. *Respir Med* 2004;98(5):464–75.

Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 1994;105(6):1722–7.

Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med* 2001;345(13):941–7.

Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, Deykin A, Fagan JK, Fahy JV, Fish J, et al.; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004;364(9444):1505–12.

Israel E, Cohn J, Dubé L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. Zileuton Clinical Trial Group. *JAMA* 1996;275(12):931–6.

Israel E, Drazen JM, Liggett SB, Boushey HA, Cherniack RM, Chinchilli VM, Cooper DM, Fahy JV, Fish JE, Ford JG, et al. The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med* 2000;162(1):75–80.

Israel E, Fischer AR, Rosenberg MA, Lilly CM, Callery JC, Shapiro J, Cohn J, Rubin P, Drazen JM. The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. *Am Rev Respir Dis* 1993;148(6 Pt 1):1447–51.

Jaffar ZH, Sullivan P, Page C, Costello J. Low-dose theophylline modulates T-lymphocyte activation in allergen-challenged asthmatics. *Eur Respir J* 1996;9(3):456–62.

Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson SA. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. A quantitative light and electron microscopic study. *Am Rev Respir Dis* 1992;145(4 Pt 1):890–9.

Jenkins CR, Thien FC, Wheatley JR, Reddel HK. Traditional and patient-centred outcomes with three classes of asthma medication. *Eur Respir J* 2005;26(1):36–44.

Jick SS, Vasilakis-Scaramozza C, Maier WC. The risk of cataract among users of inhaled steroids. *Epidemiology* 2001;12(2):229–34.

Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB. The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med* 2006;354(15):1589–600.

Jonasson G, Carlsen KH, Jonasson C, Mowinckel P. Low-dose inhaled budesonide once or twice daily for 27 months in children with mild asthma. *Allergy* 2000;55(8):740–8.

Jones AH, Langdon CG, Lee PS, Lingham SA, Nankani JP, Follows RM, Tollemar U, Richardson PD. Pulmicort Turbohaler once daily as initial prophylactic therapy for asthma. *Respir Med* 1994;88(4):293–9.

Juniper EF, Kline PA, Morris MM, Hargreave FE. Airway constriction by isocapnic hyperventilation of cold, dry air: comparison of magnitude and duration of protection by nedocromil sodium and sodium cromoglycate. *Clin Allergy* 1987;17(6):523–8.

Kamada AK, Szefler SJ, Martin RJ, Boushey HA, Chinchilli VM, Drazen JM, Fish JE, Israel E, Lazarus SC, Lemanske RF. Issues in the use of inhaled glucocorticoids. The Asthma Clinical Research Network. *Am J Respir Crit Care Med* 1996;153(6 Pt 1):1739–48. Review.

Kasayama S, Fujita M, Goya K, Yamamoto H, Fujita K, Morimoto Y, Kawase I, Miyatake A. Effects of alendronate on bone mineral density and bone metabolic markers in postmenopausal asthmatic women treated with inhaled corticosteroids. *Metabolism* 2005;54(1):85–90.

Kasper WJ, Howe PM. Fatal varicella after a single course of corticosteroids. *Pediatr Infect Dis J* 1990;9(10):729–32.

Kelly HW. Pharmaceutical characteristics that influence the clinical efficacy of inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2003;91(4):326–334, quiz 334–5, 404.

Kemp JP, Berkowitz RB, Miller SD, Murray JJ, Nolop K, Harrison JE. Mometasone furoate administered once daily is as effective as twice-daily administration for treatment of mild-to-moderate persistent asthma. *J Allergy Clin Immunol* 2000;106(3):485–92.

Kerrebijn KF, Van Essen-Zandvliet EE, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. *J Allergy Clin Immunol* 1987;79(4):653–9.

Kerstjens HA, Brand PL, Hughes MD, Robinson NJ, Postma DS, Sluiter HJ, Bleecker ER, Dekhuijzen PN, de Jong PM, Mengelers HJ, et al. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. Dutch Chronic Non-Specific Lung Disease Study Group. *N Engl J Med* 1992;327(20):1413–9.

Khan LN, Kon OM, Macfarlane AJ, Meng Q, Ying S, Barnes NC, Kay AB. Attenuation of the allergen-induced late asthmatic reaction by cyclosporin A is associated with inhibition of bronchial eosinophils, interleukin-5, granulocyte macrophage colony-stimulating factor, and eotaxin. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1377–82.

Khayyal MT, el-Ghazaly MA, el-Khatib AS, Hatem AM, de Vries PJ, el-Shafei S, Khattab MM. A clinical pharmacological study of the potential beneficial effects of a propolis food product as an adjuvant in asthmatic patients. *Fundam Clin Pharmacol* 2003;17(1):93–102.

Kidney J, Dominguez M, Taylor PM, Rose M, Chung KF, Barnes PJ. Immunomodulation by theophylline in asthma. Demonstration by withdrawal of therapy. *Am J Respir Crit Care Med* 1995;151(6):1907–14.

Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, Danzig M, Cuss F, Pauwels RA. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med* 2003;167(12):1655–9. Epub March 2003.

Kips JC, Pauwels RA. Long-acting inhaled beta(2)-agonist therapy in asthma. *Am J Respir Crit Care Med* 2001;164(6):923–32.

Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, Glovsky M, Stiehm R, Stocks J, Rosenberg L, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. *Clin Immunol* 1999;91(2):126–33.

Konig P. Evidence for benefits of early intervention with non-steroidal drugs in asthma. *Pediatr Pulmonol Suppl* 1997;15:34–9.

Kostadima E, Tsiodras S, Alexopoulos EI, Kaditis AG, Mavrou I, Georgatou N, Papamichalopoulos A. Clarithromycin reduces the severity of bronchial hyperresponsiveness in patients with asthma. *Eur Respir J* 2004;23(5):714–7.

Kraft M, Cassell GH, Pak J, Martin RJ. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in asthma: effect of clarithromycin. *Chest* 2002;121(6):1782–8.

Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a beta$_2$-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. *J Allergy Clin Immunol* 1992;90(1):32–42.

Laitinen LA, Laitinen A, Heino M, Haahtela T. Eosinophilic airway inflammation during exacerbation of asthma and its treatment with inhaled corticosteroid. *Am Rev Respir Dis* 1991;143(2):423–7.

Landwehr LP, Jeppson JD, Katlan MG, Esterl B, McCormick D, Hamilos DL, Gelfand EW. Benefits of high-dose i.v. immunoglobulin in patients with severe steroid-dependent asthma. *Chest* 1998;114(5):1349–56.

Lanes SF, Lanza LL, Wentworth CE III. Risk of emergency care, hospitalization, and ICU stays for acute asthma among recipients of salmeterol. *Am J Respir Crit Care Med* 1998;158(3):857–61.

Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol* 2003;91(2):154–9.

Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I, Zhang J, Reiss TF. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. *Am J Respir Crit Care Med* 1999;160(6):1862–8.

Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, Kraft M, Fish JE, Peters SP, Craig T, et al.; Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Long-acting beta$_2$-agonist monotherapy vs. continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285(20):2583–93.

Lazarus SC, Lee T, Kemp JP, Wenzel S, Dube LM, Ochs RF, Carpentier PJ, Lancaster JF. Safety and clinical efficacy of zileuton in patients with chronic asthma. *Am J Manag Care* 1998;4(6):841–8.

Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998;12(6):1346–53.

Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, Mathur AK, Cowley HC, Chung KF, Djukanovic R, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356(9248):2144–8.

Lee DK, Haggart K, Robb FM, Lipworth BJ. Butterbur, a herbal remedy, confers complementary anti-inflammatory activity in asthmatic patients receiving inhaled corticosteroids. *Clin Exp Allergy* 2004;34(1):110–4.

Lehrer PM, Vaschillo E, Vaschillo B, Lu SE, Scardella A, Siddique M, Habib RH. Biofeedback treatment for asthma. *Chest* 2004;126(2):352–61.

Lemaitre RN, Siscovick DS, Psaty BM, Pearce RM, Raghunathan TE, Whitsel EA, Weinmann SA, Anderson GD, Lin D. Inhaled beta$_2$-adrenergic receptor agonists and primary cardiac arrest. *Am J Med* 2002;113(9):711–6.

Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, Drazen JM, Chinchilli VM, Craig T, Fish JE, et al.; Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *JAMA* 2001;285(20):2594–603.

Leone FT, Fish JE, Szefler SJ, West SL. Systematic review of the evidence regarding potential complications of inhaled corticosteroid use in asthma: collaboration of American College of Chest Physicians, American Academy of Allergy, Asthma, and Immunology, and American College of Allergy, Asthma, and Immunology. *Chest* 2003;124(6):2329–40.

Leung DY, Bloom JW. Update on glucocorticoid action and resistance. *J Allergy Clin Immunol* 2003;111(1):3–22; quiz 23.

Leuppi JD, Salzberg M, Meyer L, Bucher SE, Nief M, Brutsche MH, Tamm M. An individualized, adjustable maintenance regimen of budesonide/formoterol provides effective asthma symptom control at a lower overall dose than fixed dosing. *Swiss Med Wkly* 2003;133(21–22):302–9.

Levy J, Zalkinder I, Kuperman O, Skibin A, Apte R, Bearman JE, Mielke PW Jr, Tal A. Effect of prolonged use of inhaled steroids on the cellular immunity of children with asthma. *J Allergy Clin Immunol* 1995;95(4):806–12.

Liang J, Asmus MJ, Hochhaus G, Chesrown S, Hendeles L. Differences in inhaled fluticasone bioavailability between holding chambers in children with asthma. *Pharmacotherapy* 2002;22(8):947–53.

Lieu TA, Quesenberry CP, Sorel ME, Mendoza GR, Leong AB. Computer-based models to identify high-risk children with asthma. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1173–80.

Lim S, Jatakanon A, Gordon D, Macdonald C, Chung KF, Barnes PJ. Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax* 2000;55(10):837–41.

Lin H, Boesel KM, Griffith DT, Prussin C, Foster B, Romero FA, Townley R, Casale TB. Omalizumab rapidly decreases nasal allergic response and FcepsilonRI on basophils. *J Allergy Clin Immunol* 2004;113(2):297–302.

Linde K, Jobst K, Panton J. Acupuncture for chronic asthma. *Cochrane Database Syst Rev* 2000;(2):CD000008.

Lipworth BJ, Lee DK, Anhoj J, Bisgaard H. Effect of plastic spacer handling on salbutamol lung deposition in asthmatic children. *Br J Clin Pharmacol* 2002;54(5):544–7.

Loew TH, Tritt K, Siegfried W, Bohmann H, Martus P, Hahn EG. Efficacy of 'functional relaxation' in comparison to terbutaline and a 'placebo relaxation' method in patients with acute asthma. A randomized, prospective, placebo-controlled, crossover experimental investigation. *Psychother Psychosom* 2001;70(3):151–7.

Lotvall J, Palmqvist M, Arvidsson P, Maloney A, Ventresca GP, Ward J. The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients. *J Allergy Clin Immunol* 2001;108(5):726–31.

Lumry W, Noveck R, Weinstein S, Barnhart F, VanderMeer A, Murray A, Reisner C. Switching from Ventolin CFC to Ventolin HFA is well tolerated and effective in patients with asthma. *Ann Allergy Asthma Immunol* 2001;86(3):297–303.

Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest* 2003;124(1):70–4.

Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996;49(2):247–50.

Martin J, Donaldson AN, Villarroel R, Parmar MK, Ernst E, Higginson IJ. Efficacy of acupuncture in asthma: systematic review and meta-analysis of published data from 11 randomised controlled trials. *Eur Respir J* 2002;20(4):846–52.

Masoli M, Weatherall M, Holt S, Beasley R. Clinical dose-response relationship of fluticasone propionate in adults with asthma. *Thorax* 2004a;59(1):16–20.

Masoli M, Weatherall M, Holt S, Beasley R. Systematic review of the dose-response relation of inhaled fluticasone propionate. *Arch Dis Child* 2004b;89(10):902–7.

Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005;60(9):730–34.

Mastalerz L, Gawlewicz-Mroczka A, Nizankowska E, Cmiel A, Szczeklik A. Protection against exercise-induced bronchoconstriction by montelukast in aspirin-sensitive and aspirin-tolerant patients with asthma. *Clin Exp Allergy* 2002;32(9):1360–5.

Matz J, Emmett A, Rickard K, Kalberg C. Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: an analysis of asthma exacerbations. *J Allergy Clin Immunol* 2001;107(5):783–9.

Mazer BD, Gelfand EW. An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma. *J Allergy Clin Immunol* 1991;87(5):976–83.

McCarney RW, Brinkhaus B, Lasserson TJ, Linde K. Acupuncture for chronic asthma. *Cochrane Database Syst Rev* 2004;(1):CD000008.

McGill KA, Joseph B, Busse WW. Corticosteroids in the treatment of asthma. Practical recommendations. *Clin Immunother* 1995;4:16–48.

Mcivor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. *Am J Respir Crit Care Med* 1998;158(3):924–30.

Meltzer SS, Hasday JD, Cohn J, Bleecker ER. Inhibition of exercise-induced bronchospasm by zileuton: a 5-lipoxygenase inhibitor. *Am J Respir Crit Care Med* 1996;153(3):931–5.

Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, Taylor AF, Rohane P. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001;108(2):E36.

Mitchell P, Cumming RG, Mackey DA. Inhaled corticosteroids, family history, and risk of glaucoma. *Ophthalmology* 1999;106(12):2301–6.

Moraes TJ, Selvadurai H. Management of exercise-induced bronchospasm in children: the role of leukotriene antagonists. *Treat Respir Med* 2004;3(1):9–15. Review.

Mullen M, Mullen B, Carey M. The association between beta-agonist use and death from asthma. A meta-analytic integration of case-control studies. *JAMA* 1993;270(15):1842–5.

Nayak AS, Banov C, Corren J, Feinstein BK, Floreani A, Friedman BF, Goldsobel A, Gottschlich GM, Hannaway PJ, Lampl KL, et al. Once-daily mometasone furoate dry powder inhaler in the treatment of patients with persistent asthma. *Ann Allergy Asthma Immunol* 2000;84(4):417–24.

Nelson HS, Bensch G, Pleskow WW, DiSantostefano R, DeGraw S, Reasner DS, Rollins TE, Rubin PD. Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. *J Allergy Clin Immunol* 1998;102(6 Pt 1):943–52.

Nelson HS, Hamilos DL, Corsello PR, Levesque NV, Buchmeier AD, Bucher BL. A double-blind study of troleandomycin and methylprednisolone in asthmatic subjects who require daily corticosteroids. *Am Rev Respir Dis* 1993;147(2):398–404.

Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129(1):15–26. Erratum in: *Chest* 2006;129(5):1393.

Newhouse MT, Dolovich MB. Control of asthma by aerosols. *N Engl J Med* 1986;315(14):870–4. Review.

Newman KB, Mason UG, Buchmeier A, Schmaling KB, Corsello P, Nelson HS. Failure of colchicine to reduce inhaled triamcinolone dose in patients with asthma. *J Allergy Clin Immunol* 1997;99(2):176–8.

Newman SP, Weisz AW, Talaee N, Clarke SW. Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax* 1991;46(10):712–6.

Ni CM, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, Ducharme FM. Long-acting beta$_2$-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. *Cochrane Database Syst Rev* 2005;(4):CD005535.

Niggemann B, Leupold W, Schuster A, Schuster R, Berg A, Grubl A, Hardt H, Eibl MM, Wahn U. Prospective, double-blind, placebo-controlled, multicentre study on the effect of high-dose, intravenous immunoglobulin in children and adolescents with severe bronchial asthma. *Clin Exp Allergy* 1998;28(2):205–10.

Noonan M, Chervinsky P, Busse WW, Weisberg SC, Pinnas J, de Boisblanc BP, Boltansky H, Pearlman D, Repsher L, Kellerman D. Fluticasone propionate reduces oral prednisone use while it improves asthma control and quality of life. *Am J Respir Crit Care Med* 1995;152(5 Pt 1):1467–73.

Noonan M, Karpel JP, Bensch GW, Ramsdell JW, Webb DR, Nolop KB, Lutsky BN. Comparison of once-daily to twice-daily treatment with mometasone furoate dry powder inhaler. *Ann Allergy Asthma Immunol* 2001;86(1):36–43.

Novembre E, Frongia GF, Veneruso G, Vierucci A. Inhibition of exercise-induced-asthma (EIA) by nedocromil sodium and sodium cromoglycate in children. *Pediatr Allergy Immunol* 1994;5(2):107–10.

O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, Tattersfield A. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164(8 Pt 1):1392–7.

O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekstrom T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171(2):129–36. Epub October 2004.

O'Callaghan C, Cant M, Robertson C. Delivery of beclomethasone dipropionate from a spacer device: what dose is available for inhalation? *Thorax* 1994;49(10):961–4.

O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled beta$_2$-agonists in asthma. *N Engl J Med* 1992;327(17):1204–8.

Ostrom NK. Tolerability of short-term, high-dose formoterol in healthy volunteers and patients with asthma. *Clin Ther* 2003;25(11):2635–46.

Ostrom NK, Decotiis BA, Lincourt WR, Edwards LD, Hanson KM, Carranza Rosenzweig JR, Crim C. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. *J Pediatr* 2005;147(2):213–20.

Page CP, Cotter T, Kilfeather S, Sullivan P, Spina D, Costello JF. Effect of chronic theophylline treatment on the methacholine dose-response curve in allergic asthmatic subjects. *Eur Respir J* 1998;12(1):24–9.

Palmqvist M, Ibsen T, Mellen A, Lotvall J. Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients. *Am J Respir Crit Care Med* 1999;160(1):244–9.

Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;337(20):1405–11. Erratum in: *N Engl J Med* 1998;338(2):139.

Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, O'Byrne PM. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361(9363):1071–6.

Pearlman DS, Lampl KL, Dowling PJ Jr, Miller CJ, Bonuccelli CM. Effectiveness and tolerability of zafirlukast for the treatment of asthma in children. *Clin Ther* 2000;22(6):732–747.

Petty TL, Rollins DR, Christopher K, Good JT, Oakley R. Cromolyn sodium is effective in adult chronic asthmatics. *Am Rev Respir Dis* 1989;139(3):694–701.

Pierart F, Wildhaber JH, Vrancken I, Devadason SG, Le Souef PN. Washing plastic spacers in household detergent reduces electrostatic charge and greatly improves delivery. *Eur Respir J* 1999;13(3):673–8.

Pincus DJ, Szefler SJ, Ackerson LM, Martin RJ. Chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J Allergy Clin Immunol* 1995;95(6):1172–8.

Politiek MJ, Boorsma M, Aalbers R. Comparison of formoterol, salbutamol and salmeterol in methacholine-induced severe bronchoconstriction. *Eur Respir J* 1999;13(5):988–92.

Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: an evidence-based approach. *Med J Aust* 2003;178(5):223–5.

Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG, Konstantopoulos S, Rojas R, van Noord JA, Pons M, et al.; Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) International Study Group. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;58(3):211–6.

Qureshi F, Zaritsky A, Welch C, Meadows T, Burke BL. Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. *Ann Emerg Med* 2005;46(1):29–36.

Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368(9537):744–53.

Rafferty P, Tucker LG, Frame MH, Fergusson RJ, Biggs BA, Crompton GK. Comparison of budesonide and beclomethasone dipropionate in patients with severe chronic asthma: assessment of relative prednisolone-sparing effects. *Br J Dis Chest* 1985;79(3):244–50.

Ram FS, Cates CJ, Ducharme FM. Long-acting beta$_2$-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev* 2005;(1):CD003137.

Ram FS, Wellington SR, Barnes NC. Inspiratory muscle training for asthma. *Cochrane Database Syst Rev* 2003;(4):CD003792.

Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respir Med* 1994;88(5):363–8.

Ramsdell JW, Klinger NM, Ekholm BP, Colice GL. Safety of long-term treatment with HFA albuterol. *Chest* 1999;115(4):945–51.

Reddel HK, Barnes DJ. Pharmacological strategies for self-management of asthma exacerbations. *Eur Respir J* 2006;28(1):182–99.

Reddel HK, Jenkins CR, Marks GB, Ware SI, Xuan W, Salome CM, Badcock CA, Woolcock AJ. Optimal asthma control, starting with high doses of inhaled budesonide. *Eur Respir J* 2000;16(2):226–35.

Reed CE, Offord KP, Nelson HS, Li JT, Tinkelman DG. Aerosol beclomethasone dipropionate spray compared with theophylline as primary treatment for chronic mild-to-moderate asthma. The American Academy of Allergy, Asthma and Immunology Beclomethasone Dipropionate-Theophylline Study Group. *J Allergy Clin Immunol* 1998;101(1 Pt 1):14–23.

Richards J, Hirst P, Pitcairn G, Mahashabde S, Abramowitz W, Nolting A, Newman SP. Deposition and pharmacokinetics of flunisolide delivered from pressurized inhalers containing non-CFC and CFC propellants. *J Aerosol Med* 2001;14(2):197–208.

Rinehart JJ, Sagone AL, Balcerzak SP, Ackerman GA, LoBuglio AF. Effects of corticosteroid therapy on human monocyte function. *N Engl J Med* 1975;292(5):236–41.

Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet* 2001;357(9273):2007–11.

Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005;60(9):740–6. Epub July 2005. Erratum in: *Thorax* 2006;61(3):274 and *Thorax* 2006;61(5):458.

Roux C, Kolta S, Desfougeres JL, Minini P, Bidat E. Long-term safety of fluticasone propionate and nedocromil sodium on bone in children with asthma. *Pediatrics* 2003;111(6 Pt 1):e706–713.

Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA Jr. Corticosteroid therapy for acute asthma. *Respir Med* 2004;98(4):275–84.

Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2001a;(1):CD002178.

Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev* 2001b;(1):CD000195.

Sabina AB, Williams AL, Wall HK, Bansal S, Chupp G, Katz DL. Yoga intervention for adults with mild-to-moderate asthma: a pilot study. *Ann Allergy Asthma Immunol* 2005;94(5):543–8.

Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med* 2006;144(12):904–12.

Salzman GA, Pyszczynski DR. Oropharyngeal candidiasis in patients treated with beclomethasone dipropionate delivered by metered-dose inhaler alone and with Aerochamber. *J Allergy Clin Immunol* 1988;81(2):424–8.

Scarfone RJ, Fuchs SM, Nager AL, Shane SA. Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. *Pediatrics* 1993;92(4):513–8.

Schatz M, Nakahiro R, Crawford W, Mendoza G, Mosen D, Stibolt TB. Asthma quality-of-care markers using administrative data. *Chest* 2005;128(4):1968–73.

Sears MR, Taylor DR, Print CG, Lake DC, Li QQ, Flannery EM, Yates DM, Lucas MK, Herbison GP. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336(8728):1391–6.

Selroos O, Halme M. Effect of a volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler. *Thorax* 1991;46(12):891–4.

Shapiro G, Bronsky E, Murray A, Barnhart F, VanderMeer A, Reisner C. Clinical comparability of ventolin formulated with hydrofluoroalkane or conventional chlorofluorocarbon propellants in children with asthma. *Arch Pediatr Adolesc Med* 2000a;154(12):1219–25.

Shapiro GS, Klinger NM, Ekholm BP, Colice GL. Comparable bronchodilation with hydrofluoroalkane-134a (HFA) albuterol and chlorofluorocarbons-11/12 (CFC) albuterol in children with asthma. *J Asthma* 2000b;37(8):667–75.

Shaw NJ, Edmunds AT. Inhaled beclomethasone and oral candidiasis. *Arch Dis Child* 1986;61(8):788–90.

Silk HJ, Guay-Woodford L, Perez-Atayde AR, Geha RS, Broff MD. Fatal varicella in steroid-dependent asthma. *J Allergy Clin Immunol* 1988;81(1):47–51.

Simons FE. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. *N Engl J Med* 1997;337(23):1659–65.

Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997;99(5):655–9.

Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, Laessig W, Schuster A, Perez-Frias J, Sekerel BE, et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001;138(5):694–8.

Slader CA, Reddel HK, Spencer LM, Belousova EG, Armour CL, Bosnic-Anticevich SZ, Thien FC, Jenkins CR. Double blind randomised controlled trial of two different breathing techniques in the management of asthma. *Thorax* 2006;61(8):651–6. Epub March 2006.

Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352(21):2163–73. Epub May 2005.

Smith M, Iqbal S, Elliott TM, Everard M, Rowe BH. Corticosteroids for hospitalised children with acute asthma. *Cochrane Database Syst Rev* 2003;(1):CD002886.

Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della Cioppa G. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18(2):254–61.

Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1043–51.

Sorkness CA, Lemanske RF, Jr., Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, Strunk RC, Szefler SJ, Zeiger RS, Bacharier LB, et al.; for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: The Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007;119(1):64–72. Epub November 2006.

Spahn JD, Covar R, Szefer SJ. Glucocorticoids: B. Clinical science. In: Adkinson NJ, Bochner BS, Busse WW, Holgate ST, Simons FER, Yunginger JW, eds. *Middleton's Allergy Principles and Practice.* 6th ed. Philadelphia: Mosby, 2003. pp. 887–913.

Spahn JD, Fost DA, Covar R, Martin RJ, Brown EE, Szefler SJ, Leung DY. Clarithromycin potentiates glucocorticoid responsiveness in patients with asthma: results of a pilot study. *Ann Allergy Asthma Immunol* 2001;87(6):501–5.

Spahn JD, Leung DY, Chan MT, Szefler SJ, Gelfand EW. Mechanisms of glucocorticoid reduction in asthmatic subjects treated with intravenous immunoglobulin. *J Allergy Clin Immunol* 1999;103(3 Pt 1):421–6.

Spector SL, Smith LJ, Glass M. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D4 receptor antagonist, in subjects with bronchial asthma. ACCOLATE Asthma Trialists Group. *Am J Respir Crit Care Med* 1994;150(3):618–23.

Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, Boivin JF, McNutt M, Buist AS, Rebuck AS. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326(8):501–6.

Suessmuth S, Freihorst J, Gappa M. Low-dose theophylline in childhood asthma: a placebo-controlled, double-blind study. *Pediatr Allergy Immunol* 2003;14(5):394–400.

Suissa S, Baltzan M, Kremer R, Ernst P. Inhaled and nasal corticosteroid use and the risk of fracture. *Am J Respir Crit Care Med* 2004;169(1):83–8.

Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343(5):332–6.

Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockroft D, Blais L, McNutt M, Buist AS, Spitzer WO. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;149(3 Pt 1):604–10.

Swystun VA, Gordon JR, Davis EB, Zhang X, Cockcroft DW. Mast cell tryptase release and asthmatic responses to allergen increase with regular use of salbutamol. *J Allergy Clin Immunol* 2000;106(1 Pt 1):57–64.

Szefler SJ, Eigen H. Budesonide inhalation suspension: a nebulized corticosteroid for persistent asthma. *J Allergy Clin Immunol* 2002;109(4):730–42.

Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, Craig TJ, Dolovich M, Drazen JM, Fagan JK, et al.; Asthma Clinical Research Network of the National Heart Lung, and Blood Institute. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;109(3):410–8.

Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, Zeiger RS, Larsen G, Spahn JD, Bacharier LB, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115(2):233–42.

Tasche MJ, Uijen JH, Bernsen RM, de Jongste JC, van der Wouden JC. Inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma: a systematic review. *Thorax* 2000;55(11):913–20.

Tattersfield AE, Lofdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, Ekstrom T. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001;357(9252):257–61.

Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM, Lofdahl CG, Pauwels RA, Ullman A. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med* 1999;160(2):594–9.

Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term beta agonist use: influence of beta(2) adrenoceptor polymorphism. *Thorax* 2000;55(9):762–7.

Taylor IK, O'Shaughnessy KM, Fuller RW, Dollery CT. Effect of cysteinyl-leukotriene receptor antagonist ICI 204.219 on allergen-induced bronchoconstriction and airway hyperreactivity in atopic subjects. *Lancet* 1991;337(8743):690–4.

Thoonen BP, Schermer TR, Van Den Boom G, Molema J, Folgering H, Akkermans RP, Grol R, Van Weel C, Van Schayck CP. Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial. *Thorax* 2003;58(1):30–6.

Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92(1):64–77.

Toogood JH, Jennings B, Baskerville J, Anderson J, Johansson SA. Dosing regimen of budesonide and occurrence of oropharyngeal complications. *Eur J Respir Dis* 1984;65(1):35–44.

Toogood JH, Jennings B, Greenway RW, Chuang L. Candidiasis and dysphonia complicating beclomethasone treatment of asthma. *J Allergy Clin Immunol* 1980;65(2):145–53.

Turpeinen M, Sorva R, Juntunen-Backman K. Changes in carbohydrate and lipid metabolism in children with asthma inhaling budesonide. *J Allergy Clin Immunol* 1991;88(3 Pt 1):384–9.

Urata Y, Yoshida S, Irie Y, Tanigawa T, Amayasu H, Nakabayashi M, Akahori K. Treatment of asthma patients with herbal medicine TJ-96: a randomized controlled trial. *Respir Med* 2002;96(6):469–74.

van der Wouden JC, Tasche MJ, Bernsen RM, Uijen JH, de Jongste JC, Ducharme FM. Inhaled sodium cromoglycate for asthma in children. *Cochrane Database Syst Rev* 2003;(3):CD002173.

Van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta$_2$-agonists on lung function, airway responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-specific Lung Disease Study Group. *Am Rev Respir Dis* 1992;146(3):547–54.

Van Schayck CP, Cloosterman SG, Bijl-Hofland ID, van den Hoogen H, Folgering HT, Van Weel C. Is the increase in bronchial responsiveness or FEV_1 shortly after cessation of $beta_2$-agonists reflecting a real deterioration of the disease in allergic asthmatic patients? A comparison between short-acting and long-acting $beta_2$-agonists. *Respir Med* 2002;96(3):155–62.

Van Schayck CP, Dompeling E, van Herwaarden CL, Folgering H, Verbeek AL, van der Hoogen HJ, Van Weel C. Bronchodilator treatment in moderate asthma or chronic bronchitis: continuous or on demand? A randomised controlled study. *BMJ* 1991;303(6815):1426–31.

van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res* 2003;18(5):913–8.

Vaquerizo MJ, Casan P, Castillo J, Perpina M, Sanchis J, Sobradillo V, Valencia A, Verea H, Viejo JL, Villasante C, et al.; CASIOPEA (Capacidad de Singulair Oral en la Prevencion de Exacerbaciones Asmaticas) Study Group. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* 2003;58(3):204–10. Erratum in: *Thorax* 2003;58(4):370.

Vidal C, Fernandez-Ovide E, Pineiro J, Nunez R, Gonzalez-Quintela A. Comparison of montelukast versus budesonide in the treatment of exercise-induced bronchoconstriction. *Ann Allergy Asthma Immunol* 2001;86(6):655–658.

Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, Fox H, Surrey K. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004;59(7):709–17.

Waldeck B. Enantiomers of bronchodilating $beta_2$-adrenoceptor agonists: is there a cause for concern? *J Allergy Clin Immunol* 1999;103(5 Pt 1):742–8. Review.

Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti-IgE for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2004;(3):CD003559.

Walters EH, Walters JA, Gibson MD. Inhaled long acting beta agonists for stable chronic asthma. *Cochrane Database Syst Rev* 2003;(4):CD001385.

Wechsler ME, Lehman E, Lazarus SC, Lemanske RF Jr, Boushey HA, Deykin A, Fahy JV, Sorkness CA, Chinchilli VM, Craig TJ, et al.; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Beta-adrenergic receptor polymorphisms and response to salmeterol. *Am J Respir Crit Care Med* 2006;173(5):519–26. Epub December 2005.

Weiner P, Magadle R, Massarwa F, Beckerman M, Berar-Yanay N. Influence of gender and inspiratory muscle training on the perception of dyspnea in patients with asthma. *Chest* 2002;122(1):197–201.

Wildhaber JH, Dore ND, Wilson JM, Devadason SG, LeSouef PN. Inhalation therapy in asthma: nebulizer or pressurized metered-dose inhaler with holding chamber? In vivo comparison of lung deposition in children. *J Pediatr* 1999;135(1):28–33.

Wildhaber JH, Waterer GW, Hall GL, Summers QA. Reducing electrostatic charge on spacer devices and bronchodilator response. *Br J Clin Pharmacol* 2000;50(3):277–80.

Wolfe J, LaForce C, Friedman B, Sokol W, Till D, Della Cioppa G, van As A. Formoterol, 24 microg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12 microg bid, with and without extra doses taken on demand, and placebo. *Chest* 2006;129(1):27–38.

Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R, Cawte S, Green DJ, Pringle M, Tattersfield AE. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000;355(9213):1399–403.

Wraight JM, Hancox RJ, Herbison GP, Cowan JO, Flannery EM, Taylor DR. Bronchodilator tolerance: the impact of increasing bronchoconstriction. *Eur Respir J* 2003;21(5):810–5.

Wraight JM, Smith AD, Cowan JO, Flannery EM, Herbison GP, Taylor DR. Adverse effects of short-acting beta-agonists: potential impact when anti-inflammatory therapy is inadequate. *Respirology* 2004;9(2):215–21.

Zeiger RS, Bird SR, Kaplan MS, Schatz M, Pearlman DS, Orav EJ, Hustad CM, Edelman JM. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. *Am J Med* 2005;118(6):649–57.

Zeiger RS, Szefler SJ, Phillips BR, Schatz M, Martinez FD, Chinchilli VM, Lemanske RF Jr, Strunk RC, Larsen G, Spahn JD, et al.; Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *J Allergy Clin Immunol* 2006;117(1):45–52.

SECTION 4, MANAGING ASTHMA LONG TERM: OVERVIEW

KEY POINTS: MANAGING ASTHMA LONG TERM

- The goal for therapy is to control asthma by (Evidence A):
  - Reducing impairment
    - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion)
    - Require infrequent use (≤2 days a week) of inhaled short-acting beta$_2$-agonist (SABA) for quick relief of symptoms (not including prevention of exercise-induced bronchospasm (EIB))
    - Maintain (near) normal pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients' and families' expectations of and satisfaction with asthma care
  - Reducing risk
    - Prevent recurrent exacerbations of asthma and minimize the need for emergency department (ED) visits or hospitalizations
    - Prevent progressive loss of lung function; for children, prevent reduced lung growth
    - Provide optimal pharmacotherapy with minimal or no adverse effects
- A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma in both the impairment and risk domains (Evidence A):
  - The type, amount, and scheduling of medication is dictated by asthma *severity for initiating* therapy and the level of asthma *control for adjusting* therapy (Evidence A).
  - Step-down therapy is essential to identify the minimum medication necessary to maintain control (Evidence D).
- Monitoring and followup is essential (Evidence B).
  - When initiating therapy, monitor at 2- to 6-week intervals to ensure that asthma control is achieved (Evidence D).
  - Regular followup contacts at 1- to 6-month intervals, depending on level of control, are recommended to ensure that control is maintained and the appropriate adjustments in therapy are made: step up if necessary or step down if possible. Consider 3-month intervals if a step down in therapy is anticipated (Evidence D).

- Because asthma is a chronic inflammatory disorder of the airway, persistent asthma is most effectively controlled with daily long-term control medication directed toward suppression of airway inflammation (Evidence A).
- Therapeutic strategies should be considered in concert with clinician-patient partnership strategies; education of patients is essential for achieving optimal pharmacologic therapy (Evidence A).
- At each step, patients should be advised to avoid or control allergens (Evidence A), irritants, or comorbid conditions that make the patient's asthma worse (Evidence B).
- A written asthma action plan detailing for the individual patient the daily management (medications and environmental control strategies) and how to recognize and handle worsening asthma is recommended for all patients; it is particularly recommended for patients who have moderate or severe asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B). The written asthma action plan can be either symptom or peak-flow based; evidence shows similar benefits for each (Evidence B).
- Referral to an asthma specialist for consultation or comanagement of the patient is recommended if there are difficulties achieving or maintaining control of asthma; if additional education is needed to improve adherence; if the patient requires step 4 care or higher (step 3 care or higher for children 0–4 years of age); or if the patient has had an exacerbation requiring hospitalization. Consider referral if a patient requires step 3 care (step 2 care for children 0–4 years of age) or if additional testing for the role of allergy is indicated (Evidence D).

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- Recommendations for managing asthma in children 0–4 and 5–11 years of age are presented separately from recommendations for managing asthma in youths ≧12 years of age and adults.
- Treatment decisions for *initiating* long-term control therapy are based on classifying severity (considering both the impairment and risk domains) and selecting a corresponding step for treatment. Recommendations on when to initiate therapy in children 0–4 years of age have been revised.
- Treatment decisions for *adjusting* therapy and maintaining control are based on assessing the level of asthma control (considering both the impairment and risk domains).
- The distinction between the domains of impairment and risk for assessing asthma control and guiding decisions for therapy emphasizes the need to consider separately asthma's effects on quality of life and functional capacity on an ongoing basis (i.e., in the present) and the risks it presents for adverse events in the future, such as exacerbations and progressive reduction in lung growth or lung function. These domains of asthma may respond differentially to treatment.

- Stepwise approach to managing asthma has been expanded to include six steps of care to simplify the actions within each step. For example, previous guidelines had several progressive actions within step 3, whereas the current guidelines separate the actions into different steps.
- Treatment options within the steps have been revised, especially:
  - For patients not well controlled on low-dose inhaled corticosteroid (ICS), increasing the dose of ICSs to medium dose is recommended before adding adjunctive therapy in the 0–4 years age group; for other age groups (children 5–11 years of age and youths ≥12 years of age and adults), increasing the dose of ICS to medium dose or adding adjunctive therapy to a low dose of ICS are considered as equal options.
  - Evidence for the selection of adjunctive therapy is limited in children under 12 years of age; recommendations vary according to the assessment of impairment or risk.
  - Steps 5–6 for youths ≥12 years of age and adults include consideration of omalizumab.
- Managing special situations has been expanded to include racial and ethnic disparities.

Introduction

The literature searches and results for all four components of asthma management (See section 3.) provided the foundation for the update of this section: "Managing Asthma Long Term." The Expert Panel's recommendations for managing asthma long term integrate the four components of therapy into a stepwise therapeutic approach for managing asthma long term, in which medications are increased as necessary and decreased if possible to achieve and maintain control of asthma. The general stepwise approach is applicable to all patients who have asthma. Adaptations are required, however, to tailor the approach to the needs of different patient groups. For example, it is important to consider the age of the patient, because the course of the disease may change over time, and the relevance of different assessment measures and potential short- and long-term impact of medications may be age related. Thus, the Expert Panel's recommendations are presented for three different age groups: children 0–4 years of age, children 5–11 years of age, and youths ≥12 years of age and adults, based on the following considerations:

- Evidence available demonstrating safety and efficacy for many medications is age dependent (e.g., many clinical trials have enrolled patients ≥12 years of age only, and it is unknown if these results are applicable to children 5–11 years of age; furthermore, few trial data are available for children <5 years of age).
- Issues related to drug delivery are often age dependent (e.g., the ability of a child and/or their caregivers to use nebulizers versus metered dose inhalers (MDIs) versus dry powder inhaler (DPI) devices).
- Approval of medications by the U.S. Food and Drug Administration (FDA) is based on age.
- Lung function measurements, used to classify asthma severity (impairment domain) and control (risk domain), are usually not possible in children <5 years of age, and

interpretations of these tests may require special considerations for children 5–11 years of age.

- The characterization of various wheezing phenotypes is frequently age dependent, with different patterns among children 0–4 years of age compared to children 5–11 years of age or children 12 years of age or older and adults (e.g., severe episodes of virus-induced wheezing (risk domain) with periods of no symptoms in between episodes (impairment domain) are most frequently seen in preschool children).

Furthermore, situations arise which require special consideration of therapeutic options within the stepwise care: EIB, surgery, pregnancy, and racial and ethnic disparity.

This section, “Managing Asthma Long Term,” will present recommendations for each group separately: managing asthma long term in children (ages 0–4 years and 5–11 years), managing asthma long term in youths ≥12 years of age and adults, and managing special situations in asthma.

SECTION 4, MANAGING ASTHMA LONG TERM IN CHILDREN 0–4 YEARS OF AGE AND 5–11 YEARS OF AGE

Diagnosis and Prognosis of Asthma in Children

Long-term management decisions begin with diagnosis and an appreciation for factors that may influence the prognosis for asthma in children.

DIAGNOSIS OF ASTHMA

0–4 Years of Age: **The Expert Panel recommends that essential elements in the evaluation include the history, symptoms, physical examination, and assessment of quality of life, as discussed in "Component 1: Measures of Asthma Assessment and Monitoring." A therapeutic trial with medications listed in figure 4–1a will also aid in the diagnosis.**

Several studies show that as many as 50–80 percent of children who have asthma develop symptoms before their fifth birthdays. Diagnosis can be difficult in this age group and has important implications. On the one hand, asthma in early childhood is frequently underdiagnosed (receiving such inappropriate labels as chronic bronchitis, wheezy bronchitis, reactive airway disease (RAD), recurrent pneumonia, gastroesophageal reflux, and recurrent upper respiratory tract infections). Therefore, many infants and young children do not receive adequate therapy. On the other hand, not all wheeze and cough are caused by asthma, and caution is needed to avoid giving infants and young children inappropriate prolonged asthma therapy. Episodic or chronic wheeze, cough, and breathlessness also may be seen in other, less common, conditions, including cystic fibrosis, vascular ring, tracheomalacia, primary immunodeficiency, congenital heart disease, parasitic disease, and foreign-body aspiration.

Diagnosis is complicated by the difficulty in obtaining objective measurements of lung function in this age group.

5–11 Years of Age: **The Expert Panel recommends that the diagnosis in children 5 years of age and older should follow the same procedures recommended in "Component 1: Measures of Asthma Assessment and Monitoring."**

PROGNOSIS OF ASTHMA

Although asthma clearly has been demonstrated to be associated with airway inflammation and structural changes in adult patients, the age when these changes begin in asthma has not yet been defined precisely. Elevations in both inflammatory cells and mediators have been demonstrated in bronchoalveolar lavage specimens obtained from preschool children who have recurrent wheezing (Krawiec et al. 2001). Recently, endobronchial biopsy specimens from infants who have wheezing and documented airflow obstruction that was both reversible and nonreversible following the administration of bronchodilator were compared to four other groups of subjects: infants who had wheezing without airflow obstruction, school-aged children who had difficult-to-control asthma, and both school-aged children and adults who did not have asthma (Saglani et al. 2005). In the infants who had wheezing, regardless of bronchodilator reversibility or atopic status, the characteristic histopathologic features of thickening of the laminar reticularis and eosinophil inflammation were absent. Taken together, these data indicate that the airway inflammatory responses and structural changes that are characteristic of

asthma develop during the preschool years and may follow, and not precede, the physiologic changes associated with asthma.

Among children 5 years of age and younger, the most common cause of asthma symptoms is viral respiratory infection. At present, the relative contributions of airway inflammation, bronchial smooth muscle abnormalities, or other structural factors in producing wheeze with acute viral upper respiratory infections are unknown. Two general patterns of illness appear in infants and children who have wheezing with acute viral upper respiratory infections: a remission of symptoms in the preschool years and persistence of asthma throughout childhood. No absolute markers are available to predict the prognosis of an individual child; however, an asthma predictive index has been developed that identifies risk factors for developing persistent asthma. Children under 3 years of age who had four or more episodes of wheezing in the past year that lasted more than 1 day and affected sleep are significantly likely to have persistent asthma after the age of 5 years if they also have either (1) one of the following: parental history of asthma, a physician diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens, OR (2) two of the following: evidence of sensitization to foods, ≥4 percent peripheral blood eosinophilia, or wheezing apart from colds (See section 2, "Definition and Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma.").

PREVENTION OF ASTHMA PROGRESSION

The Expert Panel concludes that evidence to date does not support the previously hypothesized contention that early intervention with an ICS, either continuously (CAMP 2000; Guilbert et al. 2006) or intermittently (Bisgaard and Szefler 2006), may alter the underlying severity or progression of the disease. ICSs should be used to control asthma symptoms and to improve the child's quality of life, but their use should not be initiated or prolonged for the purpose of changing the natural history of the disease (i.e., the underlying severity or progression of asthma) (Evidence A).

Although a preliminary, retrospective study suggested that appropriate control of childhood asthma may prevent more serious asthma or irreversible obstruction in later years (Agertoft and Pedersen 1994), these observations were not verified in a more recent long-term randomized controlled trial (RCT) in children 5–12 years of age (CAMP 2000) (Evidence A). The best available evidence does not support the assumption that children 5–12 years of age who have mild or moderate persistent asthma, on average, have a progressive decline in lung function. A followup analysis from the Childhood Asthma Management Program (CAMP) study indicates, however, that a subset of participants in both treatment and placebo groups experienced progressive reductions in lung growth compared to predicted measures (Covar et al. 2004). Further studies are needed to assess this risk fully.

Observational prospective data from other large groups of children suggest that the timing of the CAMP intervention was too late, as most loss of lung function in early childhood asthma appears to occur during the first 3–5 years of life (Martinez et al. 1995; Morgan et al. 2005). A recent study enrolled children 2–3 years of age who were at high risk of developing persistent asthma and compared ICS therapy to placebo. The study demonstrated that this intervention clearly reduced symptom burden and the frequency of exacerbations while the ICS was administered daily for 2 years, but this therapy did not prevent the reappearance of persistent symptoms in the year of followup after discontinuing therapy (Guilbert et al. 2006).

MONITORING ASTHMA PROGRESSION

The Expert Panel recommends that the following measures be monitored over the course of children's followup visits, especially in those children who have moderate or severe persistent asthma (require Step 3 care or higher), to assess both impairment and risk domains for the development of progressive disease: course of medications, including increasing use of SABAs and escalation of long-term control medications; episodes of severe exacerbations requiring systemic corticosteroids, urgent care visits, or hospitalizations; pulmonary function measures including prebronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) and FEV_1 (percent predicted) and postbronchodilator FEV_1 (percent predicted) (Evidence B). If these measures so indicate, therapy should be stepped up to ensure adequate asthma control. See box 4–1 for a sample patient record for monitoring asthma progression in children.

BOX 4–1. SAMPLE RECORD FOR MONITORING THE RISK DOMAIN IN CHILDREN: RISK OF ASTHMA PROGRESSION (INCREASED EXACERBATIONS OR NEED FOR DAILY MEDICATION, OR LOSS OF LUNG FUNCTION), AND POTENTIAL ADVERSE EFFECTS OF CORTICOSTEROID THERAPY

Patient name:

Date					
Long-term control medication					
ICS daily dose*					
LTRA					
LABA					
Theophylline					
Other					
Significant exacerbations					
Exacerbations (number/month)					
Oral systemic corticosteroids (number/year)*					
Hospitalization (number/year)					
Pulmonary function					
Prebronchodilator FEV_1/FVC					
Prebronchodilator FEV_1 percent predicted					
Postbronchodilator FEV_1 percent predicted					
Percent bronchodilator reversibility					
Potential risk of adverse corticosteroid effects (as indicated by corticosteroid dose and duration of treatment)					
Height, cm					
Percentile Plots of growth velocity					

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; LTRA, leukotriene receptor antagonist

*Consider ophthalmologic exam and bone density measurement in children using high doses of ICS or multiple courses of oral corticosteroids.

Although there is no indication that treatment alters the progression of asthma severity in children, asthma is highly variable over time (see sections on "Natural History" and "Pathophysiology"), and treatment may have to be adjusted accordingly.

Treatment: Principles of Stepwise Therapy in Children

The Expert Panel recommends that the goal of asthma therapy is to maintain long-term control of asthma with the least amount of medication and hence minimal risk for adverse effects. Control of asthma may be viewed in the context of two domains—impairment and risk—and within these domains, defined as follows (Evidence A).

- **Reducing impairment**
  - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion)
  - Require infrequent use (≤2 days a week) of SABA for quick relief of symptoms (not including prevention of EIB)
  - Maintain (near) normal pulmonary function
  - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
  - Meet patients' and families' expectations of and satisfaction with asthma care
- **Reducing risk**
  - Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations
  - Prevent progressive loss of lung function; for children, prevent reduced lung growth
  - Provide optimal pharmacotherapy with minimal or no adverse effects

The Expert Panel recommends that the stepwise approach to therapy, in which the dose and number of medications and frequency of administration are increased as necessary (Evidence B, extrapolated from studies in older children and adults) and decreased when possible (Evidence D), is used to achieve and maintain this control.

The distinction between assessing impairment and risk to make treatment decisions draws attention to the multifaceted nature of asthma and the need to consider all manifestations of the disease. Assessing both domains emphasizes the need to consider separately asthma's effects on quality of life and functional capacity on an ongoing basis (i.e., at present) and the risks asthma presents for adverse events in the future, such as exacerbations or progressive reduction in lung growth. These domains may respond differentially to treatment. For example, a large study of children who had asthma revealed that 30 percent of the low-dose ICS treatment group, whose levels of impairment (symptoms, SABA use, lung function) improved, remained at risk of exacerbations requiring oral systemic corticosteroids (CAMP 2000).

The steps of care for managing asthma to achieve and maintain this control are presented in figures 4–1a and 4–1b. Deciding which step of care is appropriate for a patient depends on whether long-term control therapy is being initiated for the first time or whether therapy is being adjusted (i.e., stepped up to regain control or stepped down, for patients who have maintained control for a sufficient length of time, to determine the minimal amount of medication required to maintain control and/or reduce the risk of side effects). The classification of asthma severity, which considers the severity of both impairment and risk domains, provides a guide for initiating therapy for patients who are not currently taking long-term control medications. (See figures 4–2a and 4–2b for children 0–4 years of age and 5–11 years of age, respectively.) Once therapy is selected, or if the patient is already taking long-term control medication, the patient's response to therapy will guide decisions about adjusting therapy based on the level of control achieved in both the impairment and risk domains (figure 4–3a for children 0–4 years of age and figure 4–3b for children 5–11 years of age).

ACHIEVING CONTROL OF ASTHMA

Selecting Initial Therapy

0–4 Years of Age: Initiating Long-Term Control Therapy. **The Expert Panel concludes that initiating daily long-term control therapy:**

- **Is recommended for reducing impairment and risk of exacerbations in infants and young children who had four or more episodes of wheezing in the past year that lasted more than 1 day and affected sleep AND who have risk factors for developing persistent asthma: either (1) one of the following: parental history of asthma, a physician diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens OR (2) two of the following: evidence of sensitization to foods, ≥4 percent peripheral blood eosinophilia, or wheezing apart from colds (Evidence A).**

- **Should be considered for reducing impairment in infants and young children who consistently require symptomatic treatment more than 2 days per week for a period of more than 4 weeks (Evidence D).**

- **Should be considered for reducing risk in infants and young children who have a second asthma exacerbation requiring systemic corticosteroids within 6 months (Evidence D).** Recognition of these children and treatment with daily low-dose ICS therapy can significantly reduce overall symptom burden and the frequency of exacerbations, even though such treatment will not alter the underlying severity of asthma in later childhood (Guilbert et al. 2006).

- **May be considered for use only during periods of previously documented risk for a child (Evidence D). If daily long-term control therapy is discontinued after the season of increased risk, written asthma action plans indicating specific signs of worsening asthma and actions to take should be reviewed with the caregivers, and a clinic contact should be scheduled 2–6 weeks after discontinuation of therapy to ascertain whether adequate control is maintained satisfactorily (Evidence D).** Because of seasonal variations in exacerbations among children, such as during the seasons of increased upper respiratory infections (Johnston et al. 2006), it is possible, although not yet evaluated systematically, that some of the children described above may require daily therapy only during previously documented periods of increased risk of exacerbations for that individual.

5–11 Years of Age: Initiating Long-Term Control Therapy. **The Expert Panel recommends daily long-term control therapy for children who have persistent asthma (Evidence A).** In deciding when to initiate daily long-term control therapy, the clinician must weigh the possible long-term effects of inadequately controlled asthma versus the possible adverse effects of medications given over prolonged periods. Long-term studies in children 5–12 years of age at the time of enrollment conclude that ICSs improve health outcomes for children who have mild or moderate persistent asthma, and that the potential albeit small risk of delayed growth from the use of ICSs is well balanced by their effectiveness (Evidence A) (CAMP 2000). Furthermore, available long-term data indicate that most children treated with recommended doses of ICSs achieve their predicted adult heights (Agertoft and Pedersen 2000). It is noted that the long-term prospective studies on growth involved budesonide, and retrospective analyses included studies on beclomethasone, but the results have been generalized to include all ICS preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies on numerous preparations suggest that the effect of ICSs on growth is a drug-class effect.

Adjusting Therapy

The Expert Panel recommends that, if a child is already taking long-term control medication, treatment decisions are based on the level of asthma control that has been achieved: therapy should be stepped up if necessary to achieve control (Evidence B—extrapolated from studies in youths and adults) (See figures 4–3a and 4–3b.). After identifying the patient's treatment step, based on the patient's or parents' report of what medications the patient is currently taking, classify the level of control by measuring *impairment* based on symptoms, SABA use, and lung function (in children 5–11 years of age) and *risk* based on previous exacerbations and potential side effects. In general, the assessment leads to the following sequence of actions.

- **Address the *impairment* domain.** Consider factors related to the different age groups.
  - ***0–4 years of age:*** The level of impairment generally is judged on the most severe symptom. The risk domain is usually more strongly associated with asthma morbidity than the impairment domain, because children are often symptom free between exacerbations.
  - ***5–11 years of age:*** The level of impairment generally is judged on the most severe measure among symptom report, asthma control score (using validated tools if available), and pulmonary function measures. For patients at step 3 or higher care, if office spirometry is feasible and suggests poorer control than does the assessment of impairment based on other measures, consider fixed airway obstruction as the explanation and reassess the other measures of impairment. If fixed airway obstruction does not appear to be the explanation, consider a step up in therapy, because low FEV_1 is a predictor of risk for exacerbations in children. (See "Component 1: Measures of Asthma Assessment and Monitoring.")
  - **The Expert Panel recommends the following actions if control of the impairment domain is not achieved and maintained at any step of care:**
    - **Patient adherence and technique in using medications correctly should be assessed and addressed as appropriate (Evidence C).** See

"Component 2: Education for a Partnership in Asthma Care" for discussion on assessing adherence. Key questions to ask the child and parent include:

- Which medicines is your child currently taking? How often?
- Who is responsible for administering the child's medicine?
- Please show me how the child takes the medicine.
- How many times a week does the child miss taking the medication?
- What problems have you/your child had taking the medicine (cost, time, lack of perceived need)?
- What concerns do you have about your asthma medicines?

♦ **Other factors that diminish control of asthma impairment should be addressed as possible reasons for poor response to therapy and targets for intervention (Evidence C).** These factors include the presence of a coexisting condition (e.g., sinusitis), a new or increased exposure to allergens or irritants, or psychosocial problems. In some cases, alternative diagnoses, such as vocal cord dysfunction (VCD), should be considered.

♦ **If patient adherence, inhaler technique, and environmental control measures are adequate, and asthma is not well controlled, a step up in treatment may be needed (Evidence B—extrapolated).** For patients who have asthma that is not well controlled, in general step up one treatment step. For patients who have *very poor* asthma control, consider increasing treatment by two steps, a course of oral corticosteroids, or both (Evidence D).

■ **Address the *risk* domain.**

— **The Expert Panel recommends the following actions if control of the risk of exacerbations is not achieved or maintained (Evidence D):**

♦ ***0–4 years of age:*** If there is a history of one or more exacerbations, review adherence to medications and control of environmental exposures, review the patient's written asthma action plan to confirm that it includes oral prednisone for patients who have histories of severe exacerbations, and consider stepping up therapy to the next level (Evidence D).

♦ ***5–11 years of age:*** If the history of exacerbations suggests poorer control than does the assessment of impairment, the following actions are recommended: reassess the impairment domain, review adherence to medications and control of environmental exposures, review the patient's written asthma action plan to confirm that it includes oral prednisone for patients who have a history of severe exacerbations, and consider a step up in therapy, especially for children who have reduced lung function (Fuhlbrigge et al. 2001, 2006).

— **Address the *risk* domain with regard to side effects.**

The Expert Panel recommends consideration of alternative and/or adjunctive therapies within the step of care the patient is receiving if the patient experiences troublesome or debilitating side effects. In addition, confirm efforts to control environmental exposures (Evidence D).

- **Consider referral to an asthma specialist. The Expert Panel *recommends* referral to an asthma specialist for consultation or comanagement of the patient if (Evidence D):**

  — **There are difficulties achieving or maintaining control of asthma.**

  — **A child 0–4 years of age requires step 3 care or higher (step 4 care or higher for children 5–11 years of age) to achieve and maintain control or if additional education is indicated to improve the patients' management skills or adherence. Referral may be *considered* if a child 0–4 years of age requires step 2 care or a child 5–11 years of age requires step 3 care.**

  — **The patient has had an exacerbation requiring hospitalization.**

  — **Immunotherapy or other immunomodulators are considered, or additional tests are indicated, to determine the role of allergy.**

MAINTAINING CONTROL OF ASTHMA

The Expert Panel recommends that regular followup contact is essential (Evidence B). Contact at 1- to 6-month intervals is recommended, depending on the level of control; consider a 3-month interval if a step down in therapy is anticipated (Evidence D). Clinicians need to assess whether control of asthma has been maintained and whether a step up or down in therapy is appropriate. Clinicians also need to monitor and review the written asthma action plan, which includes the medications, and the patient's self-management behaviors for daily management and handling worsening asthma (e.g., inhaler and peak flow monitoring techniques, actions to control factors that aggravate his or her asthma) (See "Component 2: Education for a Partnership in Asthma Care," figures 3–11 and 3–15, respectively.).

The Expert Panel recommends that once well-controlled asthma is achieved and maintained for at least 3 months, a reduction in pharmacologic therapy—a step down—can be considered helpful to identify the minimum therapy for maintaining well-controlled asthma (Evidence D). The opinion of the Expert Panel is that the dose of ICS may be reduced about 25–50 percent every 3 months to the lowest dose possible required to maintain control (Evidence D). Reduction in therapy should be gradual, because asthma control can deteriorate at a highly variable rate and intensity. The patient should be instructed to contact the clinician if and when asthma worsens. Guidelines for the rate of reduction and intervals for evaluation have not been validated, and clinical judgment of the individual patient's response to therapy is important. Patients may relapse when the ICS is completely discontinued (CAMP 2000; Guilbert et al. 2006; Waalkens et al. 1993); however, giving daily therapy only during periods of documented risk for a child (e.g., seasons of viral respiratory infections) may be considered (Evidence D).

KEY POINTS: INHALED CORTICOSTEROIDS IN CHILDREN

- ICSs are the preferred therapy for initiating long-term control therapy in children of all ages (Evidence A).
- ICSs, especially at low doses and even for extended periods of time, are generally safe (Evidence A).
- The potential for the adverse effect of low- to medium-dose ICS on linear growth is usually limited to a small reduction in growth velocity, approximately 1 cm in the first year of treatment, that is generally not progressive over time (Evidence A). Children receiving ICS should be monitored, by using a stadiometer, for changes in growth (Evidence D).
- The potential risks of ICSs are well balanced by their benefits.
- High doses of ICS administered for prolonged periods of time (for example, more than 1 year), particularly in combination with frequent courses of systemic corticosteroid therapy, may be associated with adverse growth effects and risk of posterior subcapsular cataracts or reduced bone density. Age-appropriate dietary intake of calcium and vitamin D should be reviewed with the child's caregivers (Evidence D). Slit-lamp eye exam and bone densitometry should be considered (Evidence D).
- See also section 3, component 4—Medications.

KEY POINTS: MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE

- Diagnosing asthma in infants is often difficult. Underdiagnosis and undertreatment are key problems in this age group. However, not all wheeze and cough are caused by asthma, and caution is needed to avoid giving inappropriate prolonged asthma therapy (EPR—2 1997). Thus, a diagnostic trial of asthma medications may be helpful.
- Treatment for young children, especially infants, who have asthma has not been studied adequately. Most recommendations for treatment are based on limited data and extrapolations from studies in older children and adults.
- The initiation of long-term control therapy:
  - Is recommended for reducing impairment and risk of exacerbations in infants and young children who had four or more episodes of wheezing in the past year that lasted more than 1 day and affected sleep AND who have either (1) one of the following: a parental history of asthma, a physician's diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens OR (2) two of the following: evidence of sensitization to foods, ≥4 percent peripheral blood eosinophilia, or wheezing apart from colds (Evidence A).

— Should be considered for reducing impairment in infants and young children who consistently require symptomatic treatment more than 2 days per week for a period of more than 4 weeks (Evidence D).

— Should be considered for reducing risk in infants and young children who have two exacerbations requiring systemic corticosteroids within 6 months (Evidence D).

— May be considered for use only during periods, or seasons, of previously documented risk for a child (Evidence D).

- When initiating daily long-term control therapy, daily ICS is the preferred treatment (Evidence A). Alternative treatment options (listed here in alphabetical order) include cromolyn (Evidence B—extrapolated from studies in older children) or leukotriene receptor antagonist (LTRA) (montelukast). The initial choice of long-term control medication includes consideration of treatment effectiveness, the domain of particular relevance for the individual patient (impairment, risk, or both), the patient's history of previous response to therapies, the ability of the patient and family to use the medication correctly, and anticipated patient and family adherence to the treatment regimen (Evidence D).

- Response to therapy should be carefully monitored. If there is a clear and positive response for at least 3 months, a careful step down in therapy should be attempted to identify the lowest dose required to maintain control. If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, the therapy should be discontinued and alternative therapies or diagnoses should be considered (Evidence D).

- Administration of an ICS early in the course of the disease will not alter the underlying progression of the disease (Evidence A). ICSs should be used to control symptoms, prevent exacerbations, and improve the child's quality of life, but their use should not be initiated or prolonged for the purpose of changing the progression or underlying severity of the disease.

The following recommendations for different steps of pharmacologic therapy to gain and maintain asthma control are intended to be general guidelines for making therapeutic decisions. They are not intended to be prescriptions for individual treatment. Specific therapy should be tailored to the needs and circumstances of individual patients. Pharmacologic therapy must be accompanied at every step by measures to control those environmental factors and comorbid conditions that can impede asthma control and by patient education (See section 3, "Component 2: Education for a Partnership in Asthma Care" and "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma.").

Treatment: Pharmacologic Issues for Children 0–4 Years of Age

The Expert Panel recommends that treatment of young children is often in the form of a therapeutic trial; therefore, it is essential to monitor the child's response to therapy. If there is no clear response within 4–6 weeks, the therapy should be discontinued and alternative therapies or alternative diagnoses considered (Evidence D). If there is a clear and positive response for at least 3 months, a step down in therapy should be undertaken to the lowest possible doses of medication required to maintain asthma control (Evidence D).

Treatment for young children, especially infants, has not been studied adequately. Recommendations are based on expert opinion, limited data, and extrapolations from studies in older children and adults (Baker et al. 1999; Kemp et al. 1999).

FDA APPROVAL

The following long-term control medications are approved by the FDA for young children:

- ICS budesonide nebulizer solution (approved for children 1–8 years of age)
- ICS fluticasone DPI (approved for children 4 years of age and older)
- Long-acting inhaled beta$_2$-agonist (LABA) salmeterol DPI and combination product (salmeterol + fluticasone) DPI (approved for children 4 years of age and older)
- LTRA montelukast, based on safety data rather than efficacy data, in a 4 mg chewable tablet (approved for children 2–6 years of age) and in 4 mg granules (approved down to 1 year of age)
- Cromolyn nebulizer (approved for children ≥2 years of age)

DELIVERY DEVICES

Several delivery devices are available for infants and young children. The dose received may vary considerably among devices and age groups. (See "Component 4: Medications," figure 3–24, for a summary of therapeutic issues regarding aerosol delivery devices.) In general, children less than 4 years of age will have less difficulty with an MDI plus valved holding chamber (VHC) with a face mask or a nebulizer with a face mask. The child's caregivers must be instructed in the proper use of nebulizers, appropriate size of face masks, and how to use VHCs with and without face masks for medication delivery to be effective and efficient. Using the "blow by" technique, holding the mask or open tube near the infant's nose and mouth, is not appropriate. For younger children, nebulizer therapy is an option for administering budesonide and cromolyn. Children between 3 and 5 years old may begin therapy with an MDI and spacer or VHC alone, but if the desired therapeutic effects are not achieved, they may require a nebulizer or an MDI plus spacer or VHC and face mask.

Treatment: Pharmacologic Steps for Children 0–4 Years of Age

Figure 4–1a presents treatment options within the stepwise approach to therapy. Selection of the step of care for a patient depends on whether long-term control therapy is being initiated for the first time or therapy is being adjusted. Classifying severity in patients not currently taking long-term control medication will guide decisions for initiating therapy (See figure 4–2a.). Assessing the level of asthma control in patients taking long-term control medication will guide decisions for adjusting therapy (See figure 4–3a.). Figures 4–4a, b, and c list usual dosages of asthma medications.

INTERMITTENT ASTHMA

Step 1 Care, Children 0–4 Years of Age

The Expert Panel recommends the following treatment for intermittent asthma:

- **SABA taken as needed to treat symptoms is usually sufficient therapy for intermittent asthma (EPR—2 1997).** If effective in relieving symptoms, intermittent use of SABA can continue on an as-needed basis. Increasing use, however, may indicate more severe or inadequately controlled asthma and thus a need to step up therapy.

- **The Expert Panel recommends the following actions for managing exacerbations due to viral respiratory infections, which are especially common in children (EPR—2 1997). These exacerbations may be intermittent yet severe.**

  — If the symptoms are mild, SABA (every 4–6 hours for 24 hours, longer with a physician consult) may be sufficient to control symptoms and improve lung function. If this therapy needs to be repeated more frequently than every 6 weeks, consider a step up in long-term care.

  — If the viral respiratory infection provokes a moderate-to-severe exacerbation, a short course of oral systemic corticosteroids should be considered (1 mg/kg/day prednisone or equivalent for 3–10 days).

  — For those patients who have a history of severe exacerbations with viral respiratory infections, consider initiating oral systemic corticosteroids at the first sign of the infection.

- **The Expert Panel recommends that a detailed written asthma action plan be developed for those patients who have intermittent asthma and a history of severe exacerbations (Evidence B)** (See "Component 2: Education for a Partnership in Asthma Care."). Intermittent asthma—infrequent exacerbations separated by periods of no symptoms and normal pulmonary function—is often mild. Some patients, however, who have intermittent asthma experience sudden, severe, and life-threatening exacerbations. It is essential to treat these exacerbations accordingly. The patient's written asthma action plan should include indicators of worsening asthma (specific symptoms) as well as specific recommendations for using SABAs, early administering of oral systemic corticosteroids, and seeking medical care.

  Furthermore, periodic monitoring (See "Component 1: Measures of Asthma Assessment and Monitoring.") of the patient is appropriate to evaluate whether the patient's asthma is indeed intermittent. The occurrence of two or more severe exacerbations within 6 months without symptoms in between them is an example of a child's having minimal or intermittent impairment, but a persistent, high risk of exacerbation. In the opinion of the Expert Panel, this child should be considered to have persistent asthma (See figure 4–2a.). Such children can benefit from daily long-term control therapy (Bisgaard et al. 2004, 2005).

PERSISTENT ASTHMA

The Expert Panel recommends the following therapy for persistent asthma:

- **Daily long-term control medication at step 2 or above is recommended for children who had four or more wheezing episodes in 1 year and risk factors for persistent asthma (Evidence A). Consider daily therapy for children who have a second exacerbation requiring oral systemic corticosteroids in 6 months or children who consistently require symptomatic treatment >2 days a week for > 4 weeks (Evidence D).**

- **Quick-relief medication must be available. SABA should be taken as needed to relieve symptoms (EPR—2 1997).** The intensity of treatment will depend on the severity of the exacerbation (See section 5, "Managing Exacerbations of Asthma."). Use of SABA more than 2 days a week for symptom control (not prevention of EIB), or increasing use, indicates the need for additional long-term control therapy.

- **To gain more rapid control of asthma, a course of oral systemic corticosteroids may be necessary for the patient who has an exacerbation at the time long-term control therapy is started or in patients who have moderate or severe asthma with frequent interference with sleep or normal activity (EPR—2 1997).**

- **Close monitoring of the child's response to therapy is recommended (EPR—2 1997); treatment recommendations are based on limited data in this age group, and thus treatment is often in the form of a therapeutic trial. If no clear response occurs within 4–6 weeks and medication technique and adherence are satisfactory, the treatment should be discontinued and a change in therapy or alternative diagnoses should be considered. If there is a clear and positive response for at least 3 months, a step down in therapy should be undertaken to the lowest possible doses of medication required to maintain asthma control (Evidence D).**

- **Giving daily therapy only during specific periods of previously documented risk for a child may be considered (Evidence D).** Although this approach is not yet evaluated, it is possible that children who have specifically defined periods of increased risk for symptoms and exacerbations (e.g., during the seasons in which viral respiratory infections are common) may require daily long-term control therapy only during this historically documented period of risk. If long-term control therapy is discontinued, then written action plans for recognizing and handling signs of worsening asthma should be reviewed with the caregivers, and followup appointments 2–6 weeks later should be conducted to ensure that asthma control is maintained.

Step 2 Care, Children 0–4 Years of Age

- **Preferred treatment for step 2 care is daily ICS at a low dose (Evidence A based on studies of individual drug efficacy in this age group; comparator trials are not available).**

- **Alternative, but not preferred, treatments include (listed in alphabetical order) cromolyn (Evidence B—extrapolated from studies in older children) and montelukast (Evidence A). If an alternative treatment is selected and adequate asthma control is**

not achieved and maintained in 4–6 weeks, then discontinue that treatment and use the preferred medication before stepping up therapy.

- **Theophylline is not recommended as alternative treatment (EPR—2 1997)** because of its erratic metabolism during viral infections and febrile illness in children less than 5 years of age and the need to closely monitor and control serum concentrations.

At present, few studies of medications have been conducted in children younger than 3 years of age. ICSs have been shown to be effective in long-term clinical studies with infants and young children (Bisgaard et al. 2004; Guilbert et al. 2006). In contrast, cromolyn has demonstrated inconsistent symptom control in children younger than 5 years of age (Tasche et al. 2000). Montelukast has shown some effectiveness in children 2–5 years of age (Knorr et al. 2001) and, in young children who have a history of exacerbations, can reduce symptoms associated with exacerbations and the amount of ICSs used during exacerbations, although montelukast was not shown to reduce requirements for oral systemic corticosteroid to control exacerbations (Bisgaard et al. 2005).

Therefore, it is the opinion of the Expert Panel that low-dose ICS is the preferred daily long-term control therapy for infants and young children who have never before been treated with long-term control therapy. This medication should be prescribed in the form of a therapeutic trial, and response should be monitored carefully. Treatment should be stopped if a clear beneficial effect is not obvious within 4–6 weeks and the patient/family medication technique and adherence are satisfactory. If a clear and positive response exists for at least 3 months (and given the high rates of spontaneous remission of symptoms in this age group), the need for ICS therapy should be reevaluated. A step down to intermittent therapy, as needed for symptoms, may then be considered (Evidence D). If long-term control therapy is discontinued, then written asthma action plans for recognizing and handling signs of worsening asthma should be reviewed with the caregivers, and followup appointments should be conducted 2–6 weeks later to ensure that asthma control is maintained.

A trial of montelukast in children 2 years of age or older can be considered in situations in which inhaled medication delivery is suboptimal due to poor technique or adherence.

Step 3 Care, Children 0–4 Years of Age

- **Medium-dose ICS is the preferred step 3 treatment (Evidence D). The Expert Panel recommends increasing the dose of ICS, for children 0–4 years of age whose asthma is not well controlled on low doses of ICS, to ensure that an adequate dose is delivered (due to the inherent difficulty and variability of delivering aerosols) before adding adjunctive therapy (Evidence D).**

Only a few data are available to address step 3 care in children from 0 to 4 years of age in regard to the various options that have been studied in older children and adults (See the section on “Managing Asthma Long Term—Youths ≥12 Years of Age and Adults.”). The pivotal trials for budesonide nebulizer solution included children 6 months to 8 years of age and failed to detect a significant dose-dependent effect, from doses ranging from 0.25 mg twice daily to 1.0 mg twice daily, on either impairment or risk domains (Szefler and Eigen 2002). In children <5 years of age, ICS clearly reduced risk and impairment compared to placebo (Bisgaard 1999; Roorda et al. 2001; Szefler and Eigen 2002). One trial in 237 children 1–4 years of age suggested a dose-dependent decrease in exacerbations (risk domain), some symptoms, and as-needed albuterol use (impairment domain) from fluticasone propionate 100 mcg/day and

200 mcg/day by MDI plus VHC (Bisgaard 1999), although the 100 mcg/day did not lower exacerbations differently from placebo. Some trials comparing budesonide nebulizer solution 0.25 mg twice daily to 1.0 mg daily in infants 5–40 months old have shown improved symptom control with the higher dose; other trials show no difference (Szefler and Eigen 2002).

Few data are available on the addition of LABA in step 3 care in this age group. The only data are those involving 4 year olds who have asthma that is not well controlled on low-dose ICS; there are no data for children under 4 years of age. The LABA DPI preparation (either alone or as a combination product) currently available and approved for use in the United States has a delivery system that is difficult to administer correctly to the majority of children less than 4 years of age. Data from studies and clinical experience are needed to determine how conveniently the newly released LABA hydrofluoroalkane (HFA) preparation can be delivered to this age group. FDA approval for the combination of LABA and ICS in children 4–11 years of age is based primarily on safety data and extrapolation of efficacy data from adolescents and adults (Malone et al. 2005; Van den Berg et al. 2000). Two studies in children 4–11 years of age whose asthma was not completely controlled on ICS have demonstrated that the addition of LABA improved lung function and symptom control compared to placebo (Russell et al. 1995; Zimmerman et al. 2004). To date, studies have not shown a reduction in significant asthma exacerbations with the addition of LABA to ICS (Bisgaard 2003) in young children. Although 4-year-old children were included in these study populations, the small numbers enrolled preclude any accurate extrapolation from these findings to the larger population of children 0–4 years of age. No other studies have evaluated adjunctive therapies in this 0–4 years of age group.

In summary, few studies in this age group are available, and they have mixed findings. Some data show improvement in both the impairment and risk domains with increasing the dose of ICS in children 1–4 years of age. Data from studies including only small numbers of 4-year-old children show improvement in the impairment domain with the use of ICS plus LABA, but no studies show improvement in the risk domain with combination therapy.

Step 4 Care, Children 0–4 Years of Age

- **Medium-dose ICS AND either (listed in alphabetical order) LABA or montelukast is the preferred treatment for step 4 (Evidence D). Theophylline is not recommended as add-on therapy (EPR—2 1997).**

No data were found on add-on therapy in children 0–4 years of age whose asthma is not well controlled on medium-dose ICS. In the opinion of the Expert Panel, and extrapolating from studies in older children and adults, adding a noncorticosteroid long-term control medication to the medium dose of ICS may be considered before increasing the dose of ICS to high dose, to avoid the potential risk of side effects with high doses of medication. The LABA DPI preparation is difficult to administer correctly to the majority of children less than 4 years of age; studies are needed to determine if the recently released LABA HFA will be convenient to administer in this age group. Montelukast (an LTRA) in combination with lower doses of an ICS can be considered for add-on therapy in these children.

Theophylline is not recommended as add-on therapy due to the erratic metabolism of theophylline during viral infections and febrile illness (See figure 4–4a.), which are common in this age group, and the need for careful monitoring of serum concentration levels.

Step 5 Care, Children 0–4 Years of Age

- **High-dose ICS AND either LABA or montelukast is the preferred treatment (Evidence D).**

Step 6 Care, Children 0–4 Years of Age

- **High-dose ICS AND either LABA or montelukast AND oral systemic corticosteroids may be given for step 6 (Evidence D).**

Before oral systemic corticosteroids are given for prolonged periods as a long-term control medication, consider a 2-week course of oral systemic corticosteroids to confirm clinical reversibility and the possibility of an effective response to therapy or, in 4-year-old children, consider high-dose ICS in combination with both an LTRA and a LABA.

For patients who require long-term oral systemic corticosteroids:

- Use the lowest possible dose (single dose daily or on alternative days).
- Monitor patients closely for corticosteroid adverse effects (See component 4—Medications.).
- When control of asthma symptoms is achieved, make persistent attempts to reduce oral systemic corticosteroids. High doses of ICS are preferable because they have fewer side effects than oral systemic corticosteroids.
- Recommend consultation with an asthma specialist.

KEY POINTS: MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE

- Classification of severity, considering the new dimensions of both the impairment and risk domains, should guide decisions for initiating therapy in children not currently taking long-term control medications (EPR—2 1997).
- Assessment of asthma control, considering both the impairment and risk domains, should guide decisions for adjusting therapy—either stepping up (Evidence A) or stepping down (Evidence D).
- When initiating daily long-term control therapy for persistent asthma, daily ICS is the preferred treatment (Evidence A); alternative treatment options include cromolyn, LTRA, and theophylline (Evidence B). The choice of medication includes consideration of treatment effectiveness, the domain of particular relevance to the individual patient (impairment, risk, or both), the individual patient's history of previous response to therapies, the ability of the patient and family to use the medication correctly, and anticipated patient and family adherence with the treatment regime and cost (Evidence D).

- Administration of ICS early in the course of the disease will not alter the underlying progression of the disease. ICSs should be used to control symptoms, prevent exacerbations, and improve the child's quality of life, but their use should not be initiated or prolonged for the purpose of changing the progression or underlying severity of the disease (Evidence A).
- Children should be directly involved as much as possible in establishing goals for therapy and developing their written asthma action plans.
- Active participation in physical activities, exercise, and sports should be promoted (EPR—2 1997). Treatment immediately before vigorous activity or exercise usually prevents EIB. If symptoms occur during usual play activities, a step up in treatment is warranted (EPR—2 1997).
- A written asthma action plan should be prepared for the student's school, extended care, or camp, including the clinician's recommendation regarding self-administration of medication. Either encourage parents to take a copy to the child's school or obtain parental permission and send a copy to the school nurse or designee (Evidence C).

The following recommendations for pharmacologic therapy to gain and maintain asthma control (See figures 4–1b, 4–3b, 4–4a, b, and c.) are intended to be general guidelines for making therapeutic decisions. They are not intended to be prescriptions for individual treatment or to replace clinical judgment. Specific therapy should be tailored to the need and circumstances of individual patients. Pharmacologic therapy must be accompanied at every step by patient education and measures to control those environmental factors and comorbid conditions that can impede asthma control.

Treatment: Special Issues for Children 5–11 Years of Age

PHARMACOLOGIC ISSUES

The Expert Panel recommends that, when initiating daily long-term control therapy for mild or moderate persistent asthma, the choice of medication includes consideration of treatment effectiveness, the domain of particular relevance to the patient's asthma (impairment, risk, or both), the individual patient's history of previous response to therapies, the ability of the patient and family to use the medication correctly, anticipated patient and family adherence to the treatment regimen, and cost (Evidence D).

The Expert Panel recommends that children ≥10 years of age (and younger children as appropriate) be directly involved in developing their written asthma action plans (EPR—2 1997). Children entering puberty may experience more difficulties than younger children in adhering to a written asthma action plan because they may fail to recognize the danger of poorly controlled asthma (Strunk et al. 1985), they may not accept having a chronic illness, or they may view the plan as infringing upon their emerging independence and adulthood. In teaching these children the same asthma self-management techniques expected of adults, the clinician should address developmental issues, such as building a positive self-image and confidence, increasing personal responsibility, and gaining problem-solving skills. To accomplish this, it is often helpful to see the child initially without parents present and to involve

the child directly in setting goals for therapy, choosing the appropriate treatment, and reviewing the effectiveness of the written asthma action plan at repeated visits. The parents can be brought in at the end of the visit to review the plan together and to emphasize the parents' important role in supporting the child's efforts.

SCHOOL ISSUES

The Expert Panel recommends that the clinician prepare a written asthma action plan for the student's school or childcare setting. Either encourage parents to take a copy to the child's school or obtain parental permission and send a copy to the school nurse or designee (Evidence C). The written asthma action plan should include the following information (See "Component 2: Education for a Partnership in Asthma Care," figure 3–16.): instructions for handling exacerbations (including the clinician's recommendation regarding self-administration of medication); recommendations for long-term control medications and prevention of EIB, if appropriate; and identification of those factors that make the student's asthma worse, so the school may help the student avoid exposure. Nonrandomized studies and observational studies have demonstrated the usefulness of written asthma action plans and peak flow monitoring in schools (Barbot et al. 2006; Borgmeyer et al. 2005; Byrne et al. 2006; Erickson et al. 2006).

It is preferable to schedule daily, long-term medications so that they are not taken at school, even if this results in unequal dosing intervals throughout the day. In school districts that have more comprehensive school nurse coverage, however, children who would benefit from close supervision to promote adherence may be given medications at school. In this way, daily medication can be administered, and patient education can be supplemented most days of the week.

Students who have asthma often require medication during school to treat acute symptoms or to prevent EIB that may develop during physical education class, school recess, or organized sports. Reliable, prompt access to medication is essential, but it may be difficult because of school rules that preclude the child from carrying medications. The NAEPP and several member organizations have adopted resolutions that endorse allowing students to carry and self-administer medications when the physician and parent consider this appropriate. Many State governments have passed legislation that allows self-administration of asthma medication in schools. It may be helpful for some children to have a compressor-driven nebulizer and medication available at the school. See also "Component 2: Education for a Partnership in Asthma Care," for a discussion of school-based asthma programs that promote effective management of asthma in the school setting.

SPORTS AND EXERCISE ISSUES

The Expert Panel recommends that physical activity at play or in organized sports is an essential part of a child's life, and full participation in physical activities should be encouraged (EPR—2 1997). Many children who have asthma experience cough, wheeze, or excessive fatigue when they exercise. Treatment immediately before vigorous activity or exercise usually prevents EIB. If symptoms occur during usual play activities, a step up in long-term therapy is warranted. Poor endurance or EIB can be an indication of poorly controlled persistent asthma; appropriate use of long-term control medication can reduce EIB (See the section on "Managing Special Situations in Asthma—Exercise-Induced Bronchospasm."). Activity should be limited or curtailed only as a last resort.

Treatment: Pharmacologic Steps for Children 5–11 Years of Age

Figure 4–1b presents treatment options within the stepwise approach to therapy. Selection of the step of care for a patient depends on whether long-term control therapy is being initiated for the first time or whether therapy is being adjusted. Classifying severity in patients not currently taking long-term control medication is a guide for initiating therapy (See figure 4–2b.); assessing the level of asthma control in patients taking long-term control medication will guide decisions for adjusting therapy (See figure 4–3b.). Figures 4–4a, b, and c list usual dosages of asthma medications. Note that the recommendations in stepwise therapy are meant to assist, not replace, the clinical decisionmaking required to meet the individual patient's needs.

INTERMITTENT ASTHMA

Step 1 Care, Children 5–11 Years of Age

The Expert Panel recommends the following therapy for intermittent asthma (step 1 care):

- **SABA, taken as needed to treat symptoms, is usually sufficient therapy for intermittent asthma.**

  If a child requires increasing amounts of as-needed SABA, this may indicate more severe or poorly controlled asthma and thus the need to step up therapy (See figures 4–1b and 4–2b.).

- **Manage moderate or severe exacerbations due to viral respiratory infections, especially common in children, with a short course of oral systemic corticosteroids. Consider initiating systemic corticosteroids at the first sign of infection in children who have a history of severe exacerbations with viral respiratory infections (Evidence D).**

- **Provide a detailed written asthma action plan for those patients who have intermittent asthma and a history of severe exacerbations (Evidence B).** Intermittent asthma—infrequent exacerbations separated by periods of no symptoms and normal pulmonary function—is often mild. However, some patients who have intermittent asthma experience sudden, severe, and life-threatening exacerbations, and it is essential to treat these exacerbations accordingly. The patient's written asthma action plan should include indicators of worsening asthma (specific symptoms and peak expiratory flow (PEF) measurement), specific recommendations for using SABA, early administration of systemic corticosteroids, and seeking medical care. Recommendations regarding avoidance or control of allergies, irritants, or comorbid conditions that affect the child's asthma should also be included. Periodic monitoring is important to evaluate whether the patient's asthma is indeed intermittent. The occurrence of more than two exacerbations a year that require oral systemic corticosteroids, without symptoms between them, is an example of a child's having minimal or intermittent impairment, but a persistent risk of exacerbation. In the opinion of the Expert Panel, this child should be considered to have persistent asthma (See figure 4–2b.).

PERSISTENT ASTHMA

The Expert Panel recommends the following therapy for persistent asthma:

- **Use daily long-term control medication. The most effective long-term control medications are those with anti-inflammatory effects, that is, those that diminish chronic airway inflammation and airway hyperresponsiveness (Evidence A).**

- **Quick-relief medication must be available. SABA, taken as needed to relieve symptoms, is recommended (Evidence A).** The intensity of treatment will depend on the severity of the exacerbation (See section 5 on "Managing Exacerbations of Asthma."). Increasing use of SABA or use more than 2 days week for symptom control (not prevention of EIB) indicates the need to step up therapy.

- **To gain more rapid control of asthma, consider a course of oral systemic corticosteroids for the patient who has an exacerbation at the time long-term control therapy is started or in patients who have moderate or severe asthma with frequent interference with sleep or normal activity (EPR—2 1997).**

- **Giving daily therapy only during specific periods of previously documented risk for a child may be considered (Evidence D).** Although this approach is not yet evaluated, it is possible that children who have specifically defined periods of increased risk for symptoms and exacerbations (e.g., during the seasons in which viral respiratory infections are common) may require daily long-term control therapy only during this historically documented period of risk. If long-term control therapy is discontinued, then written action plans for recognizing and handling signs of worsening asthma should be reviewed with the caregivers, and followup appointments 2–6 weeks later should be conducted to ensure that asthma control is maintained.

- **Consider treating patients who had two or more exacerbations requiring oral systemic corticosteroids in the past year the same as patients who have persistent asthma, even in the absence of an impairment level consistent with persistent asthma (Evidence D).**

Step 2 Care, Children 5–11 Years of Age

- **Daily low-dose ICS is the preferred step 2 treatment (Evidence A).** High-quality evidence demonstrates the effectiveness of ICS as initial therapy for children who have persistent asthma (See "Component 4: Medications."). This approach is also the preferred treatment for stepping down treatment of patients who are well controlled on a higher treatment step.

- **Alternative treatments at this step include (listed in alphabetical order) cromolyn, LTRA, nedocromil, and theophylline (Evidence B).** Three comparator studies in children 5–17 years of age demonstrated that montelukast is not as efficacious as ICS on a range of asthma outcomes (Garcia-Garcia et al. 2005; Ostrom et al. 2005; Sorkness et al. 2007) (See "Component 4: Medications" and Evidence Table 14, Leukotriene Receptor Antagonist: Monotherapy/Effectiveness Studies.). One study that examined factors that might predict response to therapy found that children who had lower lung function (impairment domain) and/or higher levels of markers of allergic airway inflammation were more likely to respond favorably to ICS and not respond to montelukast in the impairment domain of FEV_1.

Children who did not have these characteristics may respond equally well to both medications (Szefler et al. 2005). Montelukast, then, is an appropriate treatment option. Of the LTRAs, montelukast may be more desirable, as it requires only once daily dosing; furthermore, zafirlukast has several potential drug interactions and a small risk for hepatotoxicity. Cromolyn and nedocromil, although having excellent safety profiles, require administration four times per day and have shown benefit inconsistently. Theophylline is less desirable because of its safety profile and the need to adjust dose based on diet, drug interactions, and variable metabolism with age (See figure 4–4a.). Theophylline may be considered, however, when cost and adherence to inhaled medications are concerns.

If an alternative treatment is selected and well-controlled asthma is not achieved and maintained, then discontinue that treatment and use the preferred medication before stepping up treatment.

Step 3 Care, Children 5–11 Years of Age

- **Low-dose ICS plus the addition of some form of adjunctive therapy or medium-dose ICS are equivalent options in step 3 care, based on extrapolation from studies in adults (Evidence B—extrapolation). Because of the lack of comparative data in this age group, however, the adjunctive therapies are listed in alphabetical order: LABA, LTRA, or, with appropriate monitoring, theophylline.**

  In adult patients whose asthma is not well controlled on low-dose ICS, the clinician has several options: (1) increasing the ICS dose, (2) adding a LABA, (3) adding a leukotriene modifier, or (4) adding theophylline. Based on considerable available evidence, the first two are preferred. In children, none of these options has been studied adequately or compared in the age range of 5–11 years, and the options have not been studied at all in those <5 years of age.

  — **Low-dose ICS plus the addition of adjunctive therapy (listed alphabetically):**

    - **Adding LABA to ICS:** Two trials demonstrated that children 4–11 years of age who had asthma not completely controlled by ICS achieved improved lung function and symptom control with the addition of LABA compared to placebo (Russell et al. 1995; Zimmerman et al. 2004). FDA approval for the combination in 4- to 11-year-old children, however, is based primarily on safety and extrapolation of efficacy from adolescents and adults (Malone et al. 2005; Van den Berg et al. 2000). To date, studies have not shown a reduction in significant asthma exacerbations from the addition of LABA to ICS treatment in children (Bisgaard 2003). One negative study of LABA in combination with ICS in children who had mild or moderate persistent asthma failed to establish a need in the study participants, at baseline, for more therapy than low-dose ICS, and thus did not sufficiently address the question of combination therapy with LABA (Verberne et al. 1998).

    - **Adding LTRA to ICS:** One trial of medications for children compared the addition of montelukast to budesonide, 400 mcg/day, and reported a slight increase in lung function (PEF, although not FEV_1) and a reduction in as-needed SABA use (Simons et al. 2001).

- **Adding theophylline:** A small trial in 36 children, 6–18 years of age, reported a small improvement in PEF, but not FEV_1 or bronchial reactivity, from the addition of theophylline to ICS (Suessmuth et al. 2003). Because of the risk of toxicity, multiple drug interactions, and the need to monitor serum concentrations regularly, with no significant beneficial effect over other adjunctive treatments, theophylline would be considered the less desirable option for adjunctive therapy.

— **Increasing the dose of ICS to medium dose:** A recent systematic review in children 4–16 years of age (Masoli et al. 2004) reported that the dose-response to fluticasone propionate for improvement in lung function and symptom control (in the impairment domain) appears to plateau between 100–200 mcg/day (low dose), although patients who have severe asthma may achieve additional response at 400 mcg/day (medium dose). A large prospective trial of budesonide in children 4–8 years of age who had moderate to severe asthma showed similar improvements in symptom control with low and high doses, with small improvements in lung function upon increasing the daily dose fourfold from 200 mcg/day to 800 mcg/day (medium dose) (Shapiro et al. 1998). None of these studies, however, evaluated whether patients not initially controlled on low-dose ICS had an improved response after increasing the dose. In adult studies, increasing the dose from 200 mcg budesonide further reduced exacerbations (Pauwels et al. 1997). The Expert Panel concludes that, while the benefits from ICS in the impairment domain may begin to plateau at low doses, increasing the dose for children who have asthma not well controlled at low dose ICS may benefit children who have more severe impairment and may also reduce the risk of exacerbations. Increasing the dose of ICS may increase the risk of systemic activity, although the clinical significance of the potential systemic effects is unclear (See component 4—Medications.).

In summary, based on the small amount of data available concerning asthma in children 5–11 years of age, as well as the lack of comparison studies for various long-term control regimens, it is not possible to recommend firmly whether administering higher doses of ICS or maintaining the low dose of ICS and adding adjunctive therapy is the best treatment approach for step 3 care. Thus, the Expert Panel considers increasing the dose of ICS to the medium-dose range or using lower doses of ICS plus adjunctive therapy to be equivalent options. Decisions at this juncture should consider which component of control (impairment or risk) is more affected. For the impairment domain, based on studies in older children and adults, children who have low lung function and >2 days/week impairment may be better served by adding LABA to a low-dose of ICS. One study in children suggests some benefit in the impairment domain with adding LTRA. Studies in children show that increasing the dose of ICS to medium dose can improve symptoms and lung function in those children who have greater levels of impairment. For the risk domain, studies have not demonstrated that adding LABA or LTRA reduces exacerbations in children. Adding LABA has the potential risk of rare life-threatening or fatal exacerbations. Studies in older children and adults show that increasing the dose of ICS can reduce the risk of exacerbations, but this may require up to a fourfold increase in the dose. This may increase the potential risk of systemic effects, although within the medium-dose range the risk is small.

Step 4 Care, Children 5–11 Years of Age

- **Medium-dose ICS AND LABA is the preferred step 4 treatment (Evidence B—extrapolated from studies in youths ≥12 years and adults).**

  Many children who have asthma that is not well controlled on step 3 therapy have low lung function contributing to their impairment; thus, extrapolating from studies on LABA as adjunctive therapy for older children and adults is particularly relevant, because the data show that a key benefit of adding LABA is improvement in lung function.

- **Alternative, but not preferred, treatment is medium-dose ICS AND either LTRA or theophylline (Evidence B—extrapolated from studies in youths ≥12 years of age and adults).**

  No data specifically address the comparative effects of the various choices of treatments to add on to ICS in children <11 years of age. Based on comparative studies in older children and adults (Evidence A), the preferred add-on treatment is LABA. If the physician has concerns regarding use of LABA, an LTRA can be given a therapeutic trial first. If a trial of LTRA is deemed ineffective, then the LTRA should be discontinued, and theophylline could be added. Theophylline is a less desirable option because of its safety profile and the need to monitor serum concentration levels. Cromolyn has not been demonstrated to be effective as add-on therapy.

- In the opinion of the Expert Panel, if the add-on therapy initially administered does not lead to improvement in asthma control, discontinue it and use a trial of a different add-on therapy before stepping up.

Step 5 Care, Children 5–11 Years of Age

- **High-dose ICS AND LABA is the preferred step 5 treatment based on extrapolation from studies in older children and adults (Evidence B—extrapolated).**

- **Alternative, but not preferred, add-on treatments include LTRA or theophylline (Evidence B—extrapolated).**

Step 6 Care, Children 5–11 Years of Age

- **High-dose ICS AND LABA AND oral systemic corticosteroids long term is the preferred treatment (Evidence D).**

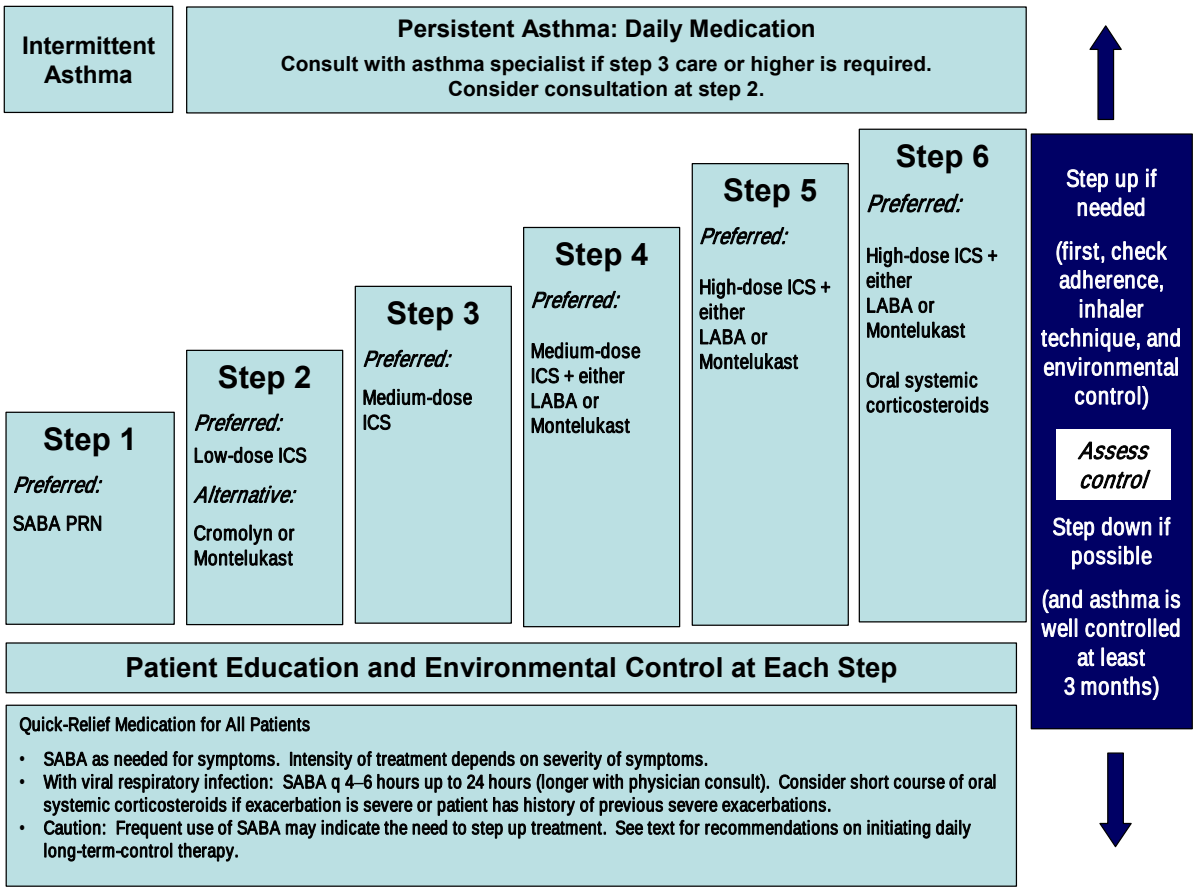
- **Alternative, but not preferred, add-on treatments are either an LTRA or theophylline AND oral systemic corticosteroids (Evidence D).**

Before maintenance prednisone therapy is initiated, consider a 2-week course of oral corticosteroids to confirm clinical reversibility and the possibility of effective response to therapy. At this level of treatment, it is strongly recommended to add measures of pulmonary function to assess response to oral corticosteroid therapy. If response is poor, a careful review for other pulmonary conditions or concomitant medical conditions should be conducted to ensure the primary diagnosis is indeed severe asthma.

For patients who require long-term oral systemic corticosteroids:

- Use the lowest possible dose (single dose daily or on alternate days).
- Monitor patients closely for corticosteroid adverse side effects (See box 4–1, “Patient Record: Monitoring Risk of Asthma Progression and Potential Adverse Effects of Corticosteroid Therapy.”).
- When well-controlled asthma is achieved, make persistent attempts to reduce oral systemic corticosteroids. High-dose ICS therapy is preferable to oral systemic corticosteroids.
- Recommend consultation with an asthma specialist.

FIGURE 4–1a. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE

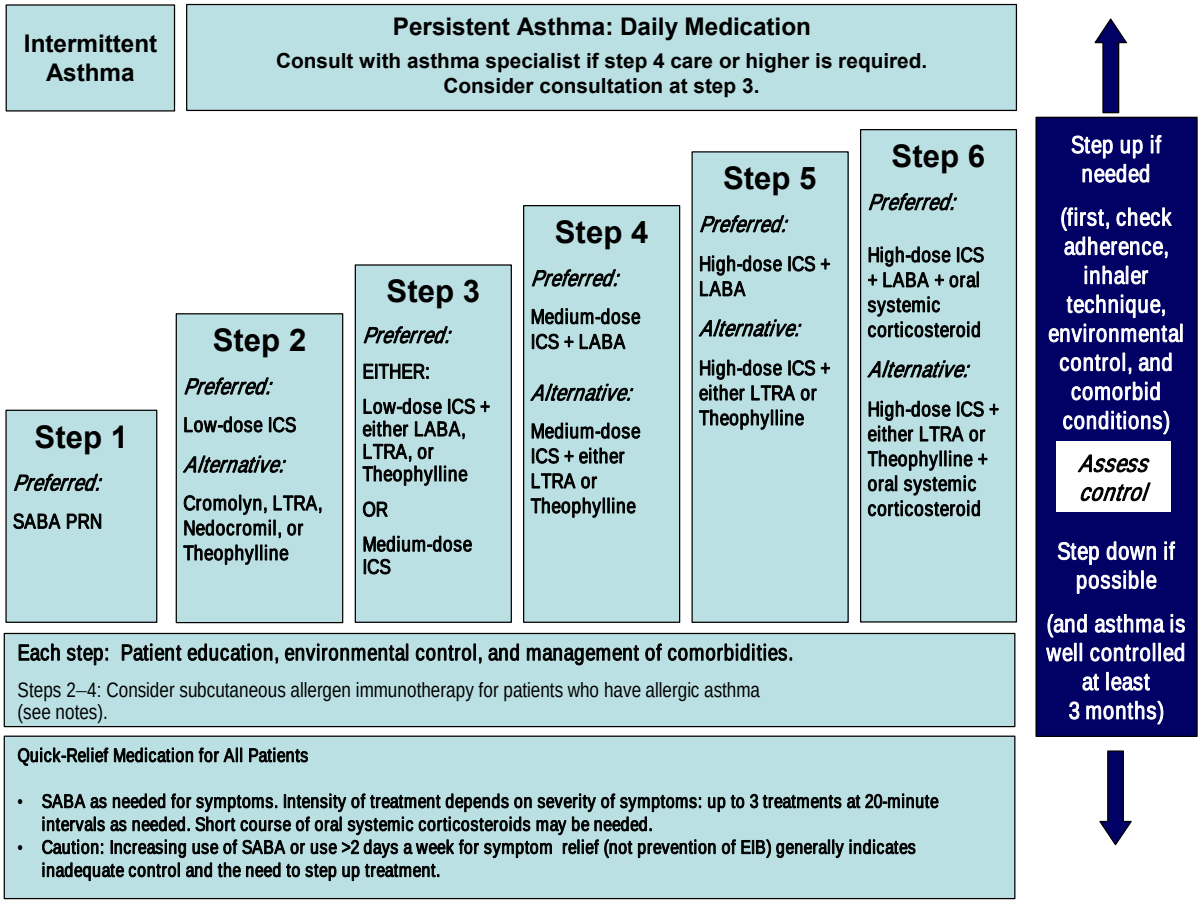


Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

FIGURE 4–1b. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta$_2$-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

FIGURE 4–2a. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 0–4 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (0–4 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. → Exacerbations of any severity may occur in patients in any severity category.			
Recommended Step for Initiating Therapy (See figure 4–1a for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			

Key: EIB, exercise-induced bronchospasm

Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 4–2b. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 5–11 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (5–11 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy (See figure 4–1b for treatment steps.)		Step 1	Step 2	Step 3, medium-dose ICS option and consider short course of oral systemic corticosteroids	Step 3, medium-dose ICS option, or step 4 and consider short course of oral systemic corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of the previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 4–3a. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 0–4 YEARS OF AGE

Components of Control		Classification of Asthma Control (0–4 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	>1x/month	>1x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	2–3/year	>3/year
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See figure 4–1a for treatment steps.)		• Maintain current treatment. • Regular followup every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up (1 step) and • Reevaluate in 2–6 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up (1–2 steps), and • Reevaluate in 2 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.

Key: EIB, exercise-induced bronchospasm

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Before step up in therapy:
  - — Review adherence to medications, inhaler technique, and environmental control.
  - — If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FIGURE 4–3b. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 5–11 YEARS OF AGE

Components of Control		Classification of Asthma Control (5–11 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function • FEV_1 or peak flow • FEV_1/FVC	 >80% predicted/ personal best >80%	 60–80% predicted/ personal best 75–80%	 <60% predicted/ personal best <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long-term followup.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment **(See figure 4–1b for treatment steps.)**		• Maintain current step. • Regular followup every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up at least 1 step and • Reevaluate in 2–6 weeks. • For side effects: consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
- Before step up in therapy:
  - — Review adherence to medications, inhaler technique, environmental control, and comorbid conditions.
  - — If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN*

Medication	Dosage Form	0–4 years	5–11 years	Comments
Inhaled Corticosteroids (ICSs) ***(See figure 4–4b, Estimated Comparative Daily Dosages for ICSs in Children.)***				
Systemic Corticosteroids				***(Applies to all three corticosteroids)***
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control	■ For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression).
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	Short-course "burst": 1–2 mg/kg/day, maximum 30 mg/day for 3–10 days	Short-course "burst": 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days	■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration.
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc			■ There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse.
				■ Patients receiving the lower dose (1 mg/kg/day) experience fewer behavioral side effects (Kayani and Shannon 2002), and it appears to be equally efficacious (Rachelefsky 2003).
				■ For patients unable to tolerate the liquid preparations, dexamethasone syrup at 0.4 mg/kg/day may be an alternative. Studies are limited, however, and the longer duration of activity increases the risk of adrenal suppression (Hendeles 2003).
Long-Acting Beta$_2$-Agonists (LABAs)				■ **Should not be used for symptom relief or exacerbations. Use only with ICSs.**
Salmeterol	DPI 50 mcg/ blister	Safety and efficacy not established in children <4 years	1 blister q 12 hours	■ Decreased duration of protection against EIB may occur with regular use.
				■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery.
				■ Do not blow into inhaler after dose is activated.
Formoterol	DPI 12 mcg/ single-use capsule	Safety and efficacy not established in children <5 years	1 capsule q 12 hours	■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery.
				■ Each capsule is for single use only; additional doses should not be administered for at least 12 hours.
				■ Capsules should be used only with the inhaler and should not be taken orally.

*Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN* (CONTINUED)

Medication	Dosage Form	0–4 years	5–11 years	Comments
Combined Medication				
Fluticasone/ Salmeterol	DPI 100 mcg/ 50 mcg	Safety and efficacy not established in children <4 years	1 inhalation bid	■ There have been no clinical trials in children <4 years of age. ■ Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery. ■ Do not blow into inhaler after dose is activated.
Budesonide/ Formoterol	HFA MDI 80 mcg/4.5 mcg	Safety and efficacy not established	2 puffs bid	■ There have been no clinical trials in children <4 years of age. ■ Currently approved for use in youths ≥12. Dose for children 5–12 years of age based on clinical trials using DPI with slightly different delivery characteristics (Pohunek et al. 2006; Tal et al. 2002; Zimmerman et al. 2004).
Cromolyn/Nedocromil				
Cromolyn	MDI 0.8 mg/puff	Safety and efficacy not established	2 puffs qid	■ 4–6 week trial may be needed to determine maximum benefit. ■ Dose by MDI may be inadequate to affect hyperresponsiveness. ■ One dose before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective as inhaled beta$_2$-agonists for EIB. ■ Once control is achieved, the frequency of dosing may be reduced.
	Nebulizer 20 mg/ampule	1 ampule qid Safety and efficacy not established <2 years	1 ampule qid	
Nedocromil	MDI 1.75 mg/puff	Safety and efficacy not established <6 years	2 puffs qid	
Leukotriene Receptor Antagonists (LTRAs)				
Montelukast	4 mg or 5 mg chewable tablet 4 mg granule packets	4 mg qhs (1–5 years of age)	5 mg qhs (6–14 years of age)	■ Montelukast exhibits a flat dose-response curve. ■ No more efficacious than placebo in infants 6–24 months (van Adelsberg et al. 2005).
Zafirlukast	10 mg tablet	Safety and efficacy not established	10 mg bid (7–11 years of age)	■ For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ Monitor for signs and symptoms of hepatic dysfunction.
Methylxanthines				
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual maximum: ■ <1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day ■ ≥1 year of age: 16 mg/kg/day	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	■ Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage). ■ Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential. ■ See next page for factors that can affect theophylline levels.

Key: DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane (inhaler propellant); MDI, metered dose inhaler

FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN* (CONTINUED)

Factors Affecting Serum Theophylline Concentrations†

Factor	Decreases Theophylline Concentrations	Increases Theophylline Concentrations	Recommended Action
Food	↓ or delays absorption of some sustained-release theophylline (SRT) products	↑ rate of absorption (fatty foods)	Select theophylline preparation that is not affected by food.
Diet	↑ metabolism (high protein)	↓ metabolism (high carbohydrate)	Inform patients that major changes in diet are not recommended while taking theophylline.
Systemic, febrile viral illness (e.g., influenza)		↓ metabolism	Decrease theophylline dose according to serum concentration. Decrease dose by 50 percent if serum concentration measurement is not available.
Hypoxia, cor pulmonale, and decompensated congestive heart failure, cirrhosis		↓ metabolism	Decrease dose according to serum concentration.
Age	↑ metabolism (1–9 years)	↓ metabolism (<6 months, elderly)	Adjust dose according to serum concentration.
Phenobarbital, phenytoin, carbamazepine	↑ metabolism		Increase dose according to serum concentration.
Cimetidine		↓ metabolism	Use alternative H_2 blocker (e.g., famotidine or ranitidine).
Macrolides: erythromycin, clarithromycin, troleandomycin		↓ metabolism	Use alternative macrolide antibiotic, azithromycin, or alternative antibiotic or adjust theophylline dose.
Quinolones: ciprofloxacin, enoxacin, perfloxacin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose. Circumvent with ofloxacin if quinolone therapy is required.
Rifampin	↑ metabolism		Increase dose according to serum concentration.
Ticlopidine		↓ metabolism	Decrease dose according to serum concentration.
Smoking	↑ metabolism		Advise patient to stop smoking; increase dose according to serum concentration.

†This list is not all inclusive; for discussion of other factors, see package inserts.

FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Child 0–4	Child 5–11	Child 0–4	Child 5–11	Child 0–4	Child 5–11
Beclomethasone HFA 40 or 80 mcg/puff	NA	80–160 mcg	NA	>160–320 mcg	NA	>320 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	NA	180–400 mcg	NA	>400–800 mcg	NA	>800 mcg
Budesonide inhaled Inhalation suspension for nebulization (child dose)	0.25–0.5 mg	0.5 mg	>0.5–1.0 mg	1.0 mg	>1.0 mg	2.0 mg
Flunisolide 250 mcg/puff	NA	500–750 mcg	NA	1,000–1,250 mcg	NA	>1,250 mcg
Flunisolide HFA 80 mcg/puff	NA	160 mcg	NA	320 mcg	NA	≥640 mcg
Fluticasone **HFA/MDI:** 44, 110, or 220 mcg/puff	176 mcg	88–176 mcg	>176–352 mcg	>176–352 mcg	>352 mcg	>352 mcg
DPI: 50, 100, or 250 mcg/inhalation	NA	100–200 mcg	NA	>200–400 mcg	NA	>400 mcg
Mometasone DPI 200 mcg/inhalation	NA	NA	NA	NA	NA	NA
Triamcinolone acetonide 75 mcg/puff	NA	300–600 mcg	NA	>600–900 mcg	NA	>900 mcg

Key: HFA, hydrofluoroalkane; NA, not approved and no data available for this age group

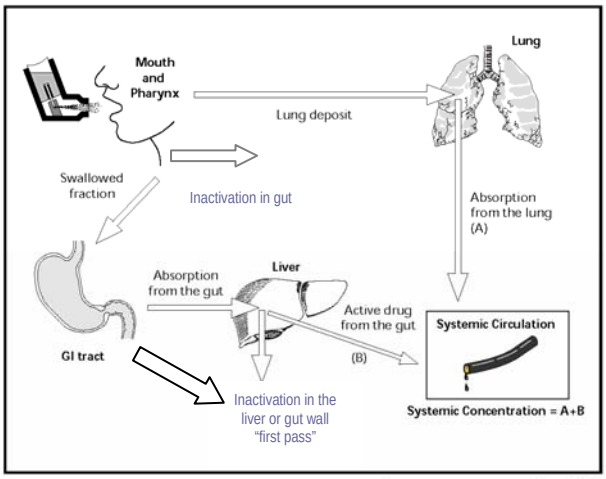
Notes:

- **The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy.** The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effect.
- Some doses may be outside package labeling, especially in the high-dose range. Budesonide nebulizer suspension is the only ICS with FDA approved labeling for children <4 years of age.
- Metered-dose inhaler (MDI) dosages are expressed as the actuator dose (the amount of the drug leaving the actuator and delivered to the patient), which is the labeling required in the United States. This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, not all of which is available to the patient), which is used in many European countries and in some scientific literature. Dry powder inhaler (DPI) doses are expressed as the amount of drug in the inhaler following activation.
- For children <4 years of age: The safety and efficacy of ICSs in children <1 year has not been established. Children <4 years of age generally require delivery of ICS (budesonide and fluticasone HFA) through a face mask that should fit snugly over nose and mouth and avoid nebulizing in the eyes. Wash face after each treatment to prevent local corticosteroid side effects. For budesonide, the dose may be administered 1–3 times daily. Budesonide suspension is compatible with albuterol, ipratropium, and levalbuterol nebulizer solutions in the same nebulizer. Use only jet nebulizers, as ultrasonic nebulizers are ineffective for suspensions.
- For fluticasone HFA, the dose should be divided 2 times daily; the low dose for children <4 years is higher than for children 5–11 years of age due to lower dosedelivered with face mask and data on efficacy in young children.

FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN (CONTINUED)

- Comparative dosages are based on published comparative clinical trials (Adams et al. 2005; Barnes et al. 1998; Kelly 1998; Lasserson et al. 2005; Pedersen and O'Byrne 1997). The rationale for some key comparisons is summarized as follows:
  - The high dose is the dose that appears likely to be the threshold beyond which significant hypothalamic-pituitary-adrenal (HPA) axis suppression is produced, and, by extrapolation, the risk is increased for other clinically significant systemic effects if used for prolonged periods of time (Martin et al. 2002; Szefler et al. 2002).
  - The low- to medium-doses reflect findings from dose-ranging studies in which incremental efficacy within the low- to medium dose ranges was established without increased systemic effect as measured by overnight cortisol excretion. The studies demonstrated a relatively flat dose-response curve for efficacy at the medium-dose range; that is, increasing the dose of high-dose range did not significantly increase efficacy but did increase systemic effect (Adams et al. 2001; Martin et al. 2002; Szefler et al. 2002).
  - The dose for budesonide DPI is based on recently available comparative data with other medications. These new data, including meta-analyses, show that budesonide DPI is comparable to approximately twice the microgram dose of fluticasone MDI or DPI (Adams et al. 2005; Barnes et al. 1998; Nielsen and Dahl 2000).
  - The dose for beclomethasone in HFA inhaler should be approximately one-half the dose for beclomethasone chlorofluorocarbon (CFC) inhaler for adults and children, based on studies demonstrating that the different pharmaceutical properties of the medications result in enhanced lung delivery for the HFA (a less forceful spray from the HFA propellant and a reengineered nozzle that allows a smaller particle size) and clinical trials demonstrating similar potency to fluticasone at 1:1 dose ratio (Boulet et al. 2004; Busse et al. 1999; Gross et al. 1999; Lasserson et al. 2005; Leach et al. 1998; Pedersen et al. 2002; Szefler et al. 2002; Thompson et al. 1998).
  - The dose for budesonide nebulizer suspension is based on efficacy and safety studies (Baker et al. 1999; Kemp et al. 1999; Shapiro et al. 1998). It is noted that the efficacy studies did not demonstrate a clear or consistent dose-response, although the high dose of 2.0 mg was effective in a placebo-controlled study in 40 infants who had severe asthma (de Blic et al. 1996). In a small, open-label, long-term safety study, the ACTH-stimulated cortisols appeared lower in the 13 infants receiving a high dose of 2.0 mg budesonide compared to infants receiving lower doses, but this result was not statistically significant, perhaps due to the small study size (Scott and Skoner 1999).
  - The dose for flunisolide HFA is based on product information and current literature (Corren et al. 2001; Gillman et al. 2002; Richards et al. 2001).
  - The dose of budesonide/formoterol in children is based on product information and current literature (Pohunek et al. 2006; Tal et al. 2002; Zimmerman et al. 2004).
  - The dose for fluticasone HFA in children <5 years of age is based on clinical studies demonstrating efficacy at this dose of 176 mcg/day (Bisgaard et al. 2004; Guilbert et al. 2006).
- **Bioavailability**

  Both the relative potency and the relative bioavailability (systemic availability) determine the potential for systemic activity of an ICS preparation. As illustrated here, the bioavailability of an ICS is dependent on the absorption of the dose delivered to the lungs and the oral bioavailability of the swallowed portion of the dose received.
  - Absorption of the dose delivered to the lungs:
    - Approximately 10–50 percent of the dose from the MDI is delivered to the lungs. This amount varies among preparations and delivery devices.
    - Nearly all of the amount delivered to the lungs is bioavailable.



Adapted with permission from Barnes 1995.

FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN (CONTINUED)

— Oral bioavailability of the swallowed portion of the dose received:

- Approximately 50–80 percent of the dose from the MDI without a spacer or valved holding chamber is swallowed.
- The oral bioavailability of this amount varies:

  Either a high first-pass metabolism or the use of a spacer/holding chamber with an MDI can decrease oral bioavailability, thus enhancing safety (Lipworth 1995).

  The approximate oral bioavailability of ICS has been reported as: beclomethasone dipropionate, 20 percent; flunisolide, 21 percent; triamcinolone acetonide, 10.6 percent; budesonide, 11 percent; fluticasone propionate, 1 percent; mometasone, <1 percent (Affrime et al. 2000; Chaplin et al. 1980; Check and Kaliner 1990; Clissold and Heel 1984; Davies 1993; Harding 1990; Heald et al. 1995; Martin et al. 1974; Mollmann et al. 1985; Szefler 1991; Wurthwein and Rohdewald 1990).

Potential drug interactions

- A number of the ICSs, including fluticasone, budesonide, and mometasone, are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as ritonavir and ketoconazole, have the potential for increasing systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported (Johnson et al. 2006; Samaras et al. 2005).

FIGURE 4–4c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS IN CHILDREN*

Medication	Dosage Form	0–4 Years	5–11 Years	Comments
Inhaled Short-Acting Beta$_2$-Agonists				
	MDI			
Albuterol CFC	90 mcg/puff, 200 puffs/canister	1–2 puffs 5 minutes before exercise	2 puffs 5 minutes before exercise	■ Differences in potencies exist, but all products are essentially comparable on a per puff basis. ■ An increasing use or lack of expected effect indicates diminished control of asthma. ■ Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need for additional long-term control therapy. ■ May double usual dose for mild exacerbations.
Albuterol HFA	90 mcg/puff, 200 puffs/canister	2 puffs every 4–6 hours as needed	2 puffs every 4–6 hours as needed	
Levalbuterol HFA	45 mcg/puff, 200 puffs/canister	Safety and efficacy not established in children <4 years	2 puffs every 4–6 hours as needed	■ Should prime the inhaler by releasing 4 actuations prior to use. ■ Periodically clean HFA actuator, as drug may plug orifice.
Pirbuterol CFC Autohaler	200 mcg/puff, 400 puffs/canister	Safety and efficacy not established	Safety and efficacy not established	■ Children <4 years may not generate sufficient inspiratory flow to activate an auto-inhaler. ■ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.
	Nebulizer solution			
Albuterol	0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5 mg/mL (0.5%)	0.63–2.5 mg in 3 cc of saline q 4–6 hours, as needed	1.25–5 mg in 3 cc of saline q 4–8 hours, as needed	■ May mix with cromolyn solution, budesonide inhalant suspension, or ipratropium solution for nebulization. May double dose for severe exacerbations.
Levalbuterol (R-albuterol)	0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/0.5 mL 1.25 mg/3 mL	0.31–1.25 mg in 3 cc q 4–6 hours, as needed	0.31–0.63 mg, q 8 hours, as needed	■ Does not have FDA-approved labeling for children <6 years of age. ■ The product is a sterile-filled preservative-free unit dose vial. ■ Compatible with budesonide inhalant suspension.

FIGURE 4–4c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS IN CHILDREN* (CONTINUED)

Medication	Dosage Form	0–4 Years	5–11 Years	Comments
Anticholinergics				
	MDI			
Ipratropium HFA	17 mcg/puff, 200 puffs/ canister	Safety and efficacy not established	Safety and efficacy not established	■ Evidence is lacking for anticholinergics producing added benefit to beta$_2$-agonists in long-term control asthma therapy. ■ See "Management of Acute Asthma" for dosing in ED.
	Nebulizer solution			
	0.25 mg/mL (0.025%)	Safety and efficacy not established	Safety and efficacy not established	
Systemic Corticosteroids				***Applies to the first three corticosteroids***
Methylprednisolone	2, 4, 6, 8, 16, 32 mg tablets	Short course "burst": 1–2 mg/kg/day, maximum 60 mg/day, for 3–10 days	Short course "burst": 40–60 mg/day as single or 2 divided doses for 3–10 days	■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ■ The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc			
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc			
	Repository injection			
(Methylprednisolone acetate)	40 mg/mL 80 mg/mL	7.5 mg/kg IM once	240 mg IM once	■ May be used in place of a short burst of oral steroids in patients who are vomiting or if adherence is a problem.

Key: CFC, chlorofluorocarbon; ED, emergency department; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow

*Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

References

Adams N, Bestall J, Jones P. Inhaled beclomethasone at different doses for long-term asthma. *Cochrane Database Syst Rev* 2001;(1):CD002879.

Adams NP, Bestall JC, Lasserson TJ, Jones PW, Cates C. Fluticasone versus placebo for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005;(4):CD003135.

Affrime MB, Cuss F, Padhi D, Wirth M, Pai S, Clement RP, Lim J, Kantesaria B, Alton K, Cayen MN. Bioavailability and metabolism of mometasone furoate following administration by metered-dose and dry-powder inhalers in healthy human volunteers. *J Clin Pharmacol* 2000;40(11):1227–36.

Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88(5):373–81.

Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000;343(15):1064–69.

Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999;103(2):414–21.

Barbot O, Platt R, Marchese C. Using preprinted rescue medication order forms and health information technology to monitor and improve the quality of care for students with asthma in New York City public schools. *J Sch Health* 2006;76(6):329–32.

Barnes NC, Hallett C, Harris TA. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. *Respir Med* 1998;92(1):95–104.

Bisgaard H. Future options for aerosol delivery to children. *Allergy* 1999;54 Suppl 49:97–103.

Bisgaard H. Effect of long-acting beta$_2$ agonists on exacerbation rates of asthma in children. *Pediatr Pulmonol* 2003;36(5):391–8.

Bisgaard H, Allen D, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. *Pediatrics* 2004;113(2):e87–94.

Bisgaard H, Szefler S. Long-acting beta$_2$ agonists and paediatric asthma. *Lancet* 2006;367(9507):286–8.

Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, Tozzi CA, Polos P. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;171(4):315–22. Epub November 2004.

Borgmeyer A, Jamerson P, Gyr P, Westhus N, Glynn E. The school nurse role in asthma management: can the action plan help? *J Sch Nurs* 2005;21(1):23–30.

Boulet LP, Cartier A, Ernst P, Larivee P, Laviolette M. Safety and efficacy of HFA-134a beclomethasone dipropionate extra-fine aerosol over six months. *Can Respir J* 2004;11(2):123–30.

Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, Donnell D, Hannon S, Colice GL. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999;104(6):1215–22.

Byrne J, Schreiber ME, Nguyen TQ. Community hospital-school partnership to treat asthma episodes at school and improve management. *J Sch Health* 2006;76(6):336–9.

Chaplin MD, Rooks W, Swenson EW, Cooper WC, Nerenberg C, Chu NI. Flunisolide metabolism and dynamics of a metabolite. *Clin Pharmacol Ther* 1980;27(3):402–13.

Check WA, Kaliner MA. Pharmacology and pharmacokinetics of topical corticosteroid derivatives used for asthma therapy. *Am Rev Respir Dis* 1990;141(2 Pt 2):S44–51.

Childhood Asthma Management Program Research Group (CAMP). Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343(15):1054–63.

Clissold SP, Heel RC. Budesonide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. *Drugs* 1984;28(6):485–518.

Corren J, Nelson H, Greos LS, Bensch G, Goldstein M, Wu J, Wang S, Newman K. Effective control of asthma with hydrofluoroalkane flunisolide delivered as an extrafine aerosol in asthma patients. *Ann Allergy Asthma Immunol* 2001;87(5):405–11.

Covar RA, Spahn JD, Murphy JR, Szefler SJ; Childhood Asthma Management Program Research Group. Progression of asthma measured by lung function in the childhood asthma management program. *Am J Respir Crit Care Med* 2004;170(3):234–41. Epub March 2004.

Davies B. A comparison of beclomethasone dipropionate and budesonide in the treatment of asthma. *Br J Clin Pract* 1993;47(2):87–93.

de Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C, Scheinmann P. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *J Allergy Clin Immunol* 1996;98(1):14–20.

EPR—2. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

Erickson CD, Splett PL, Mullett SS, Jensen C, Belseth SB. The Healthy Learner Model for Student Chronic Condition Management—Part II: The Asthma Initiative. *J Sch Nurs* 2006;22(6):319–29.

Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, Weiss ST. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 2001;107(1):61–7.

Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics* 2006;118(2):e347–55. Epub July 2006.

Garcia-Garcia ML, Wahn U, Gilles L, Swern A, Tozzi CA, Polos P. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatrics* 2005;116(2):360–9.

Gillman SA, Anolik R, Schenkel E, Newman K. One-year trial on safety and normal linear growth with flunisolide HFA in children with asthma. *Clin Pediatr (Phila)* 2002;41(5):333–40.

Gross G, Thompson PJ, Chervinsky P, Vanden Burgt J. Hydrofluoroalkane-134a beclomethasone dipropionate, 400 microg, is as effective as chlorofluorocarbon beclomethasone dipropionate, 800 microg, for the treatment of moderate asthma. *Chest* 1999;115(2):343–51.

Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, Bacharier LB, Lemanske RF Jr, Strunk RC, Allen DB, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354(19):1985–97.

Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990;84(Suppl A):25–9.

Heald D, Argenti D, Jensen B, Vaccaro S. The disposition of ^{14}C triamcinolone acetonide administrated as single oral dose of 100 microCi (800 mcg) to healthy volunteers. Presented at Asthma Theory to Treatment; 1995 July 15–17, Chicago, IL (data on file Rhône-Poulenc Rorer).

Hendeles L. Selecting a systemic corticosteroid for acute asthma in young children. *J Pediatr* 2003;142(2 Suppl):S40–4.

Johnson SR, Marion AA, Vrchoticky T, Emmanuel PJ, Lujan-Zilbermann J. Cushing syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. *J Pediatr* 2006;148(3):386–8.

Johnston NW, Johnston SL, Norman GR, Dai J, Sears MR. The September epidemic of asthma hospitalization: school children as disease vectors. *J Allergy Clin Immunol* 2006;117(3):557–62. Epub January 2006.

Kayani S, Shannon DC. Adverse behavioral effects of treatment for acute exacerbation of asthma in children: a comparison of two doses of oral steroids. *Chest* 2002;122(2):624–8.

Kelly HW. Comparison of inhaled corticosteroids. *Ann Pharmacother* 1998;32(2):220–32.

Kemp JP, Skoner DP, Szefler SJ, Walton-Bowen K, Cruz-Rivera M, Smith JA. Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children. *Ann Allergy Asthma Immunol* 1999;83(3):231–9.

Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, Michele TM, Reiss TF, Nguyen HH, Bratton DL. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;108(3):E48.

Krawiec ME, Westcott JY, Chu HW, Balzar S, Trudeau JB, Schwartz LB, Wenzel SE. Persistent wheezing in very young children is associated with lower respiratory inflammation. *Am J Respir Crit Care Med* 2001;163(6):1338–43.

Lasserson TJ, Cates CJ, Jones AB, Steele EH, White J. Fluticasone versus HFA-beclomethasone dipropionate for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005;(4):CD005309. Update in *Cochrane Database Syst Rev* 2006;(2):CD005309.

Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998;12(6):1346–53.

Lipworth BJ. New perspectives on inhaled drug delivery and systemic bioactivity. *Thorax* 1995;50(2):105–10.

Malone R, LaForce C, Nimmagadda S, Schoaf L, House K, Ellsworth A, Dorinsky P. The safety of twice-daily treatment with fluticasone propionate and salmeterol in pediatric patients with persistent asthma. *Ann Allergy Asthma Immunol* 2005;95(1):66–71.

Martin LE, Tanner RJ, Clark TJ, Cochrane GM. Absorption and metabolism of orally administered beclomethsone dipropionate. *Clin Pharmacol Ther* 1974;15(3):267–75.

Martin RJ, Szefler SJ, Chinchilli VM, Kraft M, Dolovich M, Boushey HA, Cherniack RM, Craig TJ, Drazen JM, Fagan JK, et al. Systemic effect comparisons of six inhaled corticosteroid preparations. *Am J Respir Crit Care Med* 2002;165(10):1377–83.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133–38.

Masoli M, Weatherall M, Holt S, Beasley R. Systematic review of the dose-response relation of inhaled fluticasone propionate. *Arch Dis Child* 2004;89(10):902–7.

Mollmann H, Rohdewald P, Schmidt EW, Salomon V, Derendorf H. Pharmacokinetics of triamcinolone acetonide and its phosphate ester. *Eur J Clin Pharmacol* 1985;29(1):85–9.

Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, Taussig LM, Wright AL, Martinez FD. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172(10):1253–8. Epub August 2005.

Nielsen LP, Dahl R. Therapeutic ratio of inhaled corticosteroids in adult asthma. A dose-range comparison between fluticasone propionate and budesonide, measuring their effect on bronchial hyperresponsiveness and adrenal cortex function. *Am J Respir Crit Care Med* 2000;162(6):2053–7.

Ostrom NK, Decotiis BA, Lincourt WR, Edwards LD, Hanson KM, Carranza Rosenzweig JR, Crim C. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. *J Pediatr* 2005;147(2):213–20.

Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;337(20):1405–11. Erratum in: *N Engl J Med* 1998;338(2):139.

Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy* 1997;52(39 Suppl):1–34.

Pedersen S, Warner J, Wahn U, Staab D, Le Bourgeois M, Essen-Zandvliet E, Arora S, Szefler SJ; Pediatric Study Group. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: an open-label, randomized comparison of extrafine and conventional aerosols in children. *Pediatrics* 2002;109(6):e92.

Pohunek P, Kuna P, Jorup C, De Boeck K. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. *Pediatr Allergy Immunol* 2006;17(6):458–65.

Rachelefsky G. Treating exacerbations of asthma in children: the role of systemic corticosteroids. *Pediatrics* 2003;112(2):382–97.

Richards J, Hirst P, Pitcairn G, Mahashabde S, Abramowitz W, Nolting A, Newman SP. Deposition and pharmacokinetics of flunisolide delivered from pressurized inhalers containing non-CFC and CFC propellants. *J Aerosol Med* 2001;14(2):197–208.

Roorda RJ, Mezei G, Bisgaard H, Maden C. Response of preschool children with asthma symptoms to fluticasone propionate. *J Allergy Clin Immunol* 2001;108(4):540–6.

Russell G, Williams DA, Weller P, Price JF. Salmeterol xinafoate in children on high dose inhaled steroids. *Ann Allergy Asthma Immunol* 1995;75(5):423–8.

Saglani S, Malmstrom K, Pelkonen AS, Malmberg LP, Lindahl H, Kajosaari M, Turpeinen M, Rogers AV, Payne DN, Bush A, et al. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005;171(7):722–7. Epub January 2005.

Samaras K, Pett S, Gowers A, McMurchie M, Cooper DA. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab* 2005;90(7):4394–8. Epub March 2005.

Scott MB, Skoner DP. Short-term and long-term safety of budesonide inhalation suspension in infants and young children with persistent asthma. *J Allergy Clin Immunol* 1999;104(4 Pt 2):200–9.

Shapiro G, Mendelson L, Kraemer MJ, Cruz-Rivera M, Walton-Bowen K, Smith JA. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol* 1998;102(5):789–96.

Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, Laessig W, Schuster A, Perez-Frias J, Sekerel BE, et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001;138(5):694–8.

Sorkness CA, Lemanske RF, Jr., Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, Strunk RC, Szefler SJ, Zeiger RS, Bacharier LB, et al.; for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: The Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007;119(1):64–72. Epub November 2006.

Strunk RC, Mrazek DA, Fuhrmann GS, LaBrecque JF. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. A case-controlled study. *JAMA* 1985;254(9):1193–8.

Suessmuth S, Freihorst J, Gappa M. Low-dose theophylline in childhood asthma: a placebo-controlled, double-blind study. *Pediatr Allergy Immunol* 2003;14(5):394–400.

Szefler SJ. Glucocorticoid therapy for asthma: clinical pharmacology. *J Allergy Clin Immunol* 1991;88(2):147–65.

Szefler SJ, Eigen H. Budesonide inhalation suspension: a nebulized corticosteroid for persistent asthma. *J Allergy Clin Immunol* 2002;109(4):730–42.

Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, Craig TJ, Dolovich M, Drazen JM, Fagan JK, et al.; Asthma Clinical Research Network of the National Heart Lung, and Blood Institute. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;109(3):410–418.

Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, Zeiger RS, Larsen G, Spahn JD, Bacharier LB, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115(2):233–42.

Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, De Boeck K. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. *Pediatr Pulmonol* 2002;34(5):342–50.

Tasche MJ, Uijen JH, Bernsen RM, de Jongste JC, van der Wouden JC. Inhaled disodium cromoglycate (DSCG) as maintenance therapy in children with asthma: a systematic review. *Thorax* 2000;55(11):913–20.

Thompson PJ, Davies RJ, Young WF, Grossman AB, Donnell D. Safety of hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol. *Respir Med* 1998;92 Suppl A:33–9.

van Adelsberg J, Moy J, Wei LX, Tozzi CA, Knorr B, Reiss TF. Safety, tolerability, and exploratory efficacy of montelukast in 6- to 24-month-old patients with asthma. *Curr Med Res Opin* 2005;21(6):971–9.

Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/fluticasone propionate (50/100 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in children with asthma. *Pediatr Pulmonol* 2000;30(2):97–105.

Verberne AA, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. The Dutch Asthma Study Group. *Am J Respir Crit Care Med* 1998;158(1):213–9.

Waalkens HJ, Van Essen-Zandvliet EE, Hughes MD, Gerritsen J, Duiverman EJ, Knol K, Kerrebijn KF. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. The Dutch CNSLD Study Group. *Am Rev Respir Dis* 1993;148(5):1252–7.

Wurthwein G, Rohdewald P. Activation of beclomethasone dipropionate by hydrolysis to beclomethasone-17-monopropionate. *Biopharm Drug Dispos* 1990;11(5):381–94.

Zimmerman B, D'Urzo A, Berube D. Efficacy and safety of formoterol Turbuhaler when added to inhaled corticosteroid treatment in children with asthma. *Pediatr Pulmonol* 2004;37(2):122–7.

SECTION 4, MANAGING ASTHMA LONG TERM IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

KEY POINTS: MANAGING ASTHMA LONG TERM IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

- The goal for therapy is to control asthma by (Evidence A):
  - Reducing impairment
    - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion)
    - Require infrequent use (≤2 days a week) of SABA for quick relief of symptoms
    - Maintain (near) normal pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients' and families' expectations of and satisfaction with asthma care
  - Reducing risk
    - Prevent recurrent exacerbations of asthma and minimize the need for ED visits or hospitalizations
    - Prevent progressive loss of lung function; for youths, prevent reduced lung growth
    - Provide optimal pharmacotherapy with minimal or no adverse effects
- A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma in both the impairment and risk domains (Evidence A):
  - The type, amount, and frequency of medication is determined by asthma severity for initiating therapy and by the level of asthma control for adjusting therapy (Evidence A).
  - Step-down therapy is essential to identify the minimum medication necessary to maintain control (Evidence D).
- Monitoring and followup is essential (Evidence B).
  - When initiating therapy, monitor at 2- to 6-week intervals to ensure that asthma control is achieved (Evidence D).
  - Regular followup contacts at 1- to 6-month intervals, depending on the level of control, are recommended to ensure that control is maintained and appropriate adjustments in therapy are made—step up if necessary and step down if possible. Consider 3-month intervals if a step down in therapy is anticipated (Evidence D).

- Because asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations, persistent asthma is most effectively controlled with daily long-term control medication, specifically, anti-inflammatory therapy (Evidence A).
  - ICSs are the preferred treatment option for initiating long-term control therapy (Evidence A).
  - Selection of an alternative treatment option includes consideration of treatment effectiveness, the domain of particular relevance to the patient (impairment, risk, or both), the individual patient's history of previous response to therapies, the ability of the patient and family to use the medication correctly, and anticipated patient's and family's adherence to the treatment regime (Evidence D).
- Therapeutic strategies should be considered in concert with clinician-patient partnership strategies; education of patients is essential for achieving optimal pharmacologic therapy (Evidence A).
- At each step, patients should be advised to avoid or control allergens (Evidence A), irritants, or comorbid conditions that make the patient's asthma worse (Evidence B).
- A written asthma action plan detailing for the individual patient daily management (medications and environmental control strategies) and how to recognize and handle worsening asthma is recommended for all patients; written asthma action plans are particularly recommended for patients who have moderate or severe persistent asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B). The written asthma action plan can be either symptom or peak-flow based; evidence shows similar benefits for each (Evidence B).
- Referral to an asthma specialist for consultation or comanagement is recommended if there are difficulties achieving or maintaining control of asthma; if the patient requires step 4 care or higher; if immunotherapy or omalizumab are considered; or if the patient has had an exacerbation requiring hospitalization. Consider referral if the patient requires step 3 care (Evidence D).
- Special considerations for youths (EPR—2 1997):
  - Pulmonary function testing should use appropriate reference populations. Adolescents compare better to childhood than to adult predicted norms.
  - Adolescents (and younger children as appropriate) should be directly involved in establishing goals for therapy and developing their asthma management plans.
  - Active participation in physical activities, exercise, and sports should be promoted.
  - A written asthma management plan should be prepared for the student's school, including plans to ensure reliable, prompt access to medications. Either encourage parents to take a copy to the child's school or obtain parental permission and send a copy to the school nurse or designee.

- Special considerations for older adults (EPR—2 1997):
  - Chronic bronchitis/emphysema may coexist with asthma. A trial of systemic corticosteroids will determine the presence of reversibility and the extent of therapeutic benefit.
  - Asthma medications may aggravate coexisting medical conditions (e.g., cardiac disease, osteoporosis); adjustments in the medication plan may be necessary.
  - Be aware of increased potential for adverse drug/disease interaction (e.g., aspirin, beta-blockers).
  - Review of patient technique in using medications and devices is essential; physical (e.g., arthritis or visual) or cognitive impairments may make proper technique difficult.

SECTION 4, STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Treatment: Principles of Stepwise Therapy in Youths ≥12 Years of Age and Adults

The Expert Panel recommends that the goal of asthma therapy is to maintain control of asthma with the least amount of medication and hence minimal risk for adverse effects (Evidence A). Control of asthma is viewed in the context of two domains, impairment and risk, and is defined as:

- Reducing impairment
  - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion)
  - Require infrequent use (≤2 days a week) of SABA for quick relief of symptoms
  - Maintain (near) normal pulmonary function
  - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
  - Meet patients' and families' expectations of and satisfaction with asthma care
- Reducing risk
  - Prevent recurrent exacerbations of asthma, and minimize the need for ED visits or hospitalizations
  - Prevent progressive loss of lung function; for youths, prevent reduced lung growth
  - Provide optimal pharmacotherapy with minimal or no adverse effects

The stepwise approach to therapy, in which the dose and number of medications and frequency of administration are increased as necessary and decreased when possible, is used to achieve and maintain this control. This approach is illustrated in figure 4–5. Because asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations, therapy for persistent asthma must emphasize efforts to suppress inflammation over the long term and to prevent exacerbations. Recommendations in the stepwise approach to therapy are based on the Expert Panel's review of the literature (See "Component 4: Medications.") and the Expert Panel's experience.

The steps of care for managing asthma are presented in figure 4–5. Deciding which step of care is appropriate for a patient depends on whether long-term control therapy is being initiated for the first time or whether therapy is being adjusted. Care is stepped up to regain control, and it is stepped down for patients who have maintained control for a sufficient length of time to determine the minimal amount of medication required to maintain control and/or reduce the risk of side effects. The classification of asthma severity (figure 4–6), which considers the severity of both impairment and risk domains, provides a guide for initiating therapy for patients who are not currently taking long-term control medications. Once therapy is selected, or if the patient is already taking long-term control medication, the patient's response to therapy will guide decisions about adjusting therapy based on the level of control achieved in both the impairment and risk domains (See figure 4–7.).

ACHIEVING CONTROL OF ASTHMA

Selecting Initial Therapy for Patients Not Currently Taking Long-Term Control Medications

The Expert Panel recommends the following actions to achieve asthma control in patients who are not currently taking long-term control medications.

- **Assess asthma severity (EPR—2 1997).** Asthma severity is based on measurements of impairment and risk; see figure 4–6 and the discussion in "Component 1: Measures of Asthma Assessment and Monitoring."

- **Select treatment that corresponds to the patient's level of asthma severity (EPR—2 1997).** See figure 4–6 for the recommended step of care at different levels of severity, and see figure 4–5 for treatment options at each step of care. See figures 4–8 a, b, and c for usual dosages of medications. However, the clinician must also judge the individual patient's needs and circumstances to determine at what step to initiate therapy. For example, patients who have moderate or severe asthma that frequently interferes with sleep or normal activity often benefit from a course of oral corticosteroids to gain control of asthma more rapidly. Each patient's response to treatment must also be assessed.

- **If at a followup visit in 2–6 weeks after starting treatment, depending on severity, asthma is not well controlled (see below), then treatment should be advanced to the next step. If uncontrolled asthma persists, then the diagnosis should be reevaluated, and, if confirmed, treatment should be advanced another step (Evidence D).**

Adjusting Therapy

The Expert Panel recommends that, once therapy is selected, or if the clinician sees a patient for the first time who is already taking a long-term control medication, treatment

decisions are based on the level of the patient's asthma control (See figure 4–7.) (Evidence A).

- **Assess asthma control.** As in assessment of asthma severity, asthma control can be considered in terms of impairment and risk domains (Evidence C). Both domains should be addressed to select appropriate therapy; the level of control is generally judged on the most severe indicator of impairment or risk (Evidence D).

Impairment Domain

This domain is multifactorial because the different manifestations of asthma do not necessarily correlate with each other, and each factor should be assessed if possible (Evidence C).

Symptoms. Three types of symptom assessments each appear to provide unique information regarding asthma control: symptom frequency, nighttime awakening, and activity limitation (Fuhlbrigge et al. 2002; Nathan et al. 2004; Vollmer et al. 1999). Frequency of shortness of breath appears to be particularly related to asthma control (Nathan et al. 2004) and quality of life (Moy et al. 2001).

SABA use. Frequency of SABA use is a good measure of short-term (past month) (Nathan et al. 2004; Vollmer et al. 1999) and long-term (past year) asthma control (Schatz et al. 2006). Frequent use of SABA before exercise may confound these measures unless quick relief and prophylactic use can be separated.

Pulmonary function. Office spirometry (prebronchodilator) or home peak flow measures reflect control in treated patients (Bateman et al. 2004; Juniper et al. 1999, 2001). Pulmonary function measures may be poorly correlated with asthma symptoms (Shingo et al. 2001; Stahl 2000).

Validated questionnaires. Several validated tools have been developed to measure asthma control (Juniper et al. 1999; Nathan et al. 2004; Vollmer et al. 1999) and can be used to classify asthma control. (See "Component 1: Measures of Asthma Assessment and Monitoring," figure 3–8.)

Risk Domain

The risk domain includes frequency and severity of exacerbations and the occurrence of treatment-related adverse effects. Patients at any level of control of impairment may experience severe exacerbations. A history of previous exacerbations, especially exacerbations leading to ED visits or hospitalizations in the previous year, significantly increases the risk of subsequent exacerbations (Adams et al. 2000; Cowie et al. 2001; Eisner et al. 2001; Lieu et al. 1998; Schatz et al. 2004; Yurk et al. 2004). This highlights the need to obtain a history of previous exacerbations requiring hospitalization (including need for intensive care unit (ICU) admission or intubation), ED visits, and other unscheduled physician visits. In addition, increasing exacerbation rates are noted with decreasing FEV_1 categories >80 percent, 60–79 percent, and <60 percent predicted (Fuhlbrigge et al. 2001, 2006; Kitch et al. 2004).

It is generally hoped that control of *impairment* will reduce the risk of exacerbations (Schatz et al. 2005; Vollmer et al. 1999), but there may be a disassociation between the two. It has been demonstrated that control based on bronchial hyperreactivity (Sont et al. 1999), sputum eosinophilia (Green et al. 2002), or possibly fractional exhaled nitric oxide (FeNO) (Smith et al.

2005) is more effective in reducing exacerbations than control based on clinical markers alone, but more studies are needed, and only FeNO monitoring may become practical enough to be used clinically for this purpose.

- **Adjust therapy based on level of asthma control (Evidence A).** The following considerations will guide selection of therapy based on level of asthma control. Classify current level of asthma control, generally, by the most severe indicator of impairment or risk (figure 4–7) (Evidence D).

  — If the patient's asthma is not well controlled:

    - Identify the patient's current treatment step (figure 4–5), based on what he or she is actually taking. In general, step up one step for patients whose asthma is not well controlled. For patients who have very poorly controlled asthma, consider increasing by two steps, a course of oral corticosteroids, or both. Before increasing pharmacologic therapy, consider poor inhaler technique, adverse environmental exposures, poor adherence, or comorbidities as targets for intervention.

    - If the office spirometry suggests worse control than does the assessment of impairment based on other measures, (1) consider fixed airway obstruction as the explanation (Aburuz et al. 2005) (See "Component 1: Measures of Asthma Assessment and Monitoring".), and use changes from percent personal best rather than percent predicted to guide therapy; (2) reassess the other measures of impairment; and (3) if fixed airway obstruction does not appear to be the explanation, consider a step up in therapy, especially if the patient has a history of frequent moderate or severe exacerbations.

    - If the history of exacerbations suggests poorer control than does the assessment of impairment, (1) reassess impairment; (2) review control of factors capable of making asthma worse (e.g., lack of adherence, adverse environmental exposure, or comorbidities); (3) review the written action plan, and be sure it includes oral prednisone for patients who have histories of severe exacerbations; and (4) consider a step up in therapy, especially if the patient has reduced FEV_1.

    - For troublesome or debilitating side effects, explore a change in therapy. In addition, confirm maximal efforts to control factors capable of making asthma worse (See "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma.").

    - After treatment is adjusted, reevaluate in 2–6 weeks, depending on the level of control.

  — If the patient's asthma is well controlled, see the following section on "Maintaining Control of Asthma."

MAINTAINING CONTROL OF ASTHMA

The Expert Panel recommends that regular followup contact is essential (Evidence B). Contact at 1- to 6-month intervals is recommended, depending on the level of control; consider 3-month intervals if a step down in therapy is anticipated (Evidence D). Clinicians need to assess whether control of asthma has been maintained and whether a step

up or down in therapy is appropriate. Clinicians also need to monitor and review the patient's written asthma action plan, the medications, and the patient's self-management behaviors (e.g., inhaler and peak flow monitoring techniques, actions to control factors that aggravate their asthma) (See "Component 2: Education for a Partnership in Asthma Care," figures 3–11 and 3–15.).

The Expert Panel recommends that, once asthma is well controlled and the control is achieved and maintained for at least 3 months, a reduction in pharmacologic therapy—a step down—can be considered. This will be helpful to identify the minimum therapy for maintaining good control of asthma (Evidence D). Reduction in therapy should be gradual and closely monitored, because asthma can deteriorate at a highly variable rate and intensity. The patient should be instructed to contact the clinician if and when asthma worsens. Guidelines for the rate of reduction and intervals for evaluation have not been validated, and clinical judgment of the individual patient's response to therapy is important. The opinion of the Expert Panel is that the dose of ICS may be reduced about 25–50 percent every 3 months to the lowest dose possible that is required to maintain control (Hawkins et al. 2003; Lemanske et al. 2001). Patients may relapse when the ICS is completely discontinued (Lemanske et al. 2001; Waalkens et al. 1993).

The Expert Panel recommends that, if asthma control is not achieved and maintained at any step of care (See figure 4–7.), several actions may be considered:

- **Patient adherence and technique in using medications correctly should be assessed (Evidence B).** See "Component 2: Education for a Partnership in Asthma Care" for discussion on assessing adherence. Key questions to consider asking patients include:

  — Which medicines are you currently taking? How often?
  — Please show me how you take the medicine.
  — How many times a week do you miss taking the medication?
  — What problems have you had taking the medicine (cost, time, lack of perceived need)?
  — What concerns do you have about your asthma medicines?

- **A temporary increase in anti-inflammatory therapy may be indicated to reestablish asthma control (Evidence D).** A deterioration of asthma may be characterized by gradual reduction in PEF (approximately 20 percent), by failure of SABA bronchodilators to produce a sustained response, by a reduced tolerance to activities or exercise, and by the development of increasing symptoms or nocturnal awakenings from asthma. To regain control of asthma, a short course of oral prednisone (See figure 4–8a.) is often effective. If asthma symptoms do not recur and pulmonary functions remain normal, no additional therapy is necessary. However, if the prednisone burst does not control symptoms, is effective only for a short period of time (e.g., less than 1–2 weeks), or is repeated frequently, the patient should be managed according to the next higher step of care.

- **Other factors that diminish control may have to be identified and addressed (Evidence C).** These factors include the presence of a coexisting condition (e.g., rhinitis/sinusitis, gastroesophageal reflux, obesity), a new or increased exposure to allergens or irritants, patient or family barriers to adequate self-management behaviors, or psychosocial problems. In some cases, alternative diagnoses, such as VCD, should be considered.

- **A step up to the next higher step of care may be necessary (Evidence A).**

- **Consultation with an asthma specialist may be indicated (See "Component 1: Measures of Asthma Assessment and Monitoring.") (Evidence D). The Expert Panel recommends referral to an asthma specialist for consultation or comanagement if: there are difficulties achieving or maintaining control of asthma; immunotherapy or omalizumab is being considered; the patient requires step 4 care or higher; or the patient has had an exacerbation requiring a hospitalization.** (See "Component 1: Measures of Asthma Assessment and Monitoring."). Referral may be *considered* if a patient requires step 3 care (Evidence D).

Treatment: Pharmacologic Steps

The Expert Panel recommends that specific therapy should be tailored to the needs and circumstances of individual patients. Pharmacologic therapy must be accompanied at every step by patient education and measures to control those environmental factors or comorbid conditions that can make asthma worse (EPR—2 1997). See "Component 3: Control of Environmental Factors and Comorbid Conditions That Affect Asthma" which includes discussion of the role of allergen immunotherapy, and "Component 2: Education for a Partnership in Asthma Care." Figure 4–5 presents treatment options for the stepwise approach for managing asthma youths ≥12 years of age and adults. The recommendations for steps of pharmacologic therapy are intended to be general guidelines for assisting, not replacing, clinical decisionmaking. The recommendations are not intended to be prescriptions for individual treatment.

INTERMITTENT ASTHMA

The Expert Panel recommends the following therapy for intermittent asthma:

Step 1 Care

- **SABA taken as needed to treat symptoms is usually sufficient therapy for intermittent asthma (EPR—2 1997).** If effective in relieving infrequent symptoms and normalizing pulmonary function, intermittent use of SABA can continue on an as-needed basis. If significant symptoms recur or SABA is required for quick-relief treatment more than 2 days a week (with the exception of using SABA for exacerbations caused by viral infections and for EIB), the patient should be treated for persistent asthma (See below.).

- **Patients who have intermittent asthma and experience EIB benefit from taking SABA, cromolyn, or nedocromil shortly before exercise (EPR—2 1997) (See in "Exercise-Induced Bronchospasm" in "Managing Special Situations in Asthma.").** Cromolyn or nedocromil may be beneficial if taken before unavoidable exposure to an aeroallergen known to exacerbate the patient's asthma (Cockcroft and Murdock 1987).

- **The following actions for managing exacerbations due to viral respiratory infections are recommended (EPR—2 1997).** If the symptoms are mild, SABA (every 4–6 hours for 24 hours, longer with a physician consult) may be sufficient to control symptoms and improve lung function. If this therapy must be repeated more frequently than every 6 weeks, a step up in long-term care is recommended. If the viral respiratory infection provokes a moderate-to-severe exacerbation, a short course of systemic corticosteroids should be considered. For those patients who have a history of severe exacerbations with viral

respiratory infections, systemic corticosteroids should be considered at the first sign of the infection.

- **A detailed written asthma action plan is recommended for those patients who have intermittent asthma and particularly those who have a history of severe exacerbations (Evidence B)** (See "Component 2: Education for a Partnership in Asthma Care."). Intermittent asthma—infrequent exacerbations separated by periods of no symptoms and normal pulmonary function—is often mild. Some patients who have intermittent asthma experience sudden, severe, and life-threatening exacerbations. It is essential to treat these exacerbations accordingly. The patient's written asthma action plan should include indicators of worsening asthma (specific symptoms and PEF measurements), as well as specific recommendations for using SABA, early administering a course of oral systemic corticosteroids, and seeking medical care. Furthermore, periodic monitoring (See "Component 1: Measures of Asthma Assessment and Monitoring.") of the patient is appropriate to evaluate whether the patient's asthma is indeed intermittent or whether a stepup in long-term therapy is warranted.

PERSISTENT ASTHMA

The Expert Panel recommends the following therapy for persistent asthma:

- **Daily long-term control medication is recommended for patients who have persistent asthma. The long-term control medication should be one with anti-inflammatory effects. Of the available medications, ICSs are the most effective single agents (Evidence A)** (see component 4—Medications).

- **Quick-relief medication must be available to all patients who have persistent asthma. SABA should be taken as needed to relieve symptoms (EPR—2 1997).** The intensity of treatment will depend on the severity of the exacerbation (See section 5, "Managing Exacerbations of Asthma."). Increasing use of SABA or use more than 2 days a week for symptom control (not for preventing EIB) indicates the need to step up therapy.

- **Consider treating patients who may have seasonal asthma (asthma symptoms only in relation to certain seasonal molds or pollens with few symptoms the rest of the year) as having persistent asthma during the season and as having intermittent asthma the rest of the year. Confirm characteristics of intermittent asthma out of season (Evidence D).** Some patients experience asthma symptoms only in relationship to certain pollens and molds. Asthma exacerbations in children are common in the fall and seem to correlate with increased exposure to viral respiratory infections in the school environment (Hammerman et al. 2002; Johnston et al. 2005).

- **Consider treating patients who had two or more exacerbations requiring oral corticosteroids in the past year the same as patients who have persistent asthma, even in the absence of an impairment level consistent with persistent asthma (Evidence D).**

Step 2 Care, Long-Term Control Medication

- **Preferred treatment for step 2 care is daily ICS at a low dose (Evidence A).**

- **Alternative, but not preferred, treatments include (listed alphabetically) cromolyn, LTRA, nedocromil (Evidence A), and sustained release theophylline (Evidence B). There is insufficient evidence to recommend LABA in combination with ICS for step 2 therapy.**

  — Cromolyn and nedocromil have some, but limited, effectiveness and a strong safety profile.

  — LTRAs (montelukast and zafirlukast) provide long-term control, prevent symptoms, and are alternative, but not preferred, therapies for patients who have mild persistent asthma, because studies comparing overall efficacy of ICS and LTRA favor ICS on most asthma outcome measures (Evidence A). (See section 3, "Component 4: Medications.") Zileuton, a leukotriene inhibitor, is not recommended in step 2 care, because no studies of zileuton specifically in patients who have mild persistent asthma have been reported, and zileuton requires liver function test monitoring (Evidence D).

  — Sustained-release theophylline is an alternative, but not preferred, long-term control medication. It is not preferred because the modest clinical effectiveness (theophylline is primarily a bronchodilator and its anti-inflammatory activity demonstrated thus far is modest) must be balanced against concerns about potential toxicity (See "Component 4: Medications."). Theophylline remains a therapeutic option for certain patients due to expense or need for tablet-form medication. Sustained-release theophylline is given to achieve a serum concentration of between 5 and 15 mcg/mL. Periodic theophylline monitoring is necessary to maintain a therapeutic—but not toxic—level.

  — Insufficient evidence is available to recommend LABA in combination with ICS in step 2 care (O'Byrne et al. 2001). In steroid naïve patients who have mild persistent asthma, the initiation of an ICS in combination with a LABA does not significantly reduce the rate of exacerbations or the use of SABA for quick relief over that achieved with ICS alone, although the combination therapy can improve lung function and symptom days compared to ICS alone (Ni et al. 2005). Thus, there is insufficient efficacy evidence to recommend this combination therapy in step 2 care. In addition, the possibility of rare but potentially life-threatening outcomes with LABAs (See "Component 4: Medications.") supports this recommendation.

  — A recent study has suggested that some patients who have mild persistent asthma may be successfully managed with intermittent use of low-dose ICS, because study participants taking daily budesonide, daily zafirlukast, or intermittent treatment with ICS and SABA (according to a symptom-based action plan) had similar improvement in morning PEF and a similarly low number of exacerbations (Boushey et al. 2005). However, other outcomes in this study were significantly better in patients taking regular versus intermittent ICS therapy (symptom-free days, prebronchodilator FEV_1, airway hyperresponsiveness, and inflammatory markers). Currently, data are insufficient to recommend intermittent use of ICS for most patients who have mild persistent asthma, although it may be considered as a step-down therapy strategy for patients who are well controlled on step 2 therapy. Further studies are needed to evaluate the use of intermittent therapy with either ICSs or leukotriene modifiers.

Step 3 Care, Long-Term Control Medications

- **Consultation with an asthma specialist may be considered because the therapeutic options at this juncture pose a number of challenging risk/benefit considerations (Evidence D). Before increasing therapy, however, the clinician should review the patient's inhaler technique and adherence to therapy (Evidence B), as well as determine whether environmental factors, particularly allergens (Evidence A), or comorbid conditions are contributing to the patient's worsening asthma (Evidence C).**

- **Preferred step 3 care options: Two equally acceptable options are available, given the consideration of both benefits and risks for each.**

  — **Add a LABA to a low dose of ICS (Evidence A).** Studies on LABAs as adjunctive therapy have revealed both benefit and some risk. See "Component 4: Medications," section on "Safety of Long-Acting Beta$_2$-Agonists," for a complete discussion. In summary:

    - Studies demonstrate the addition of a LABA (salmeterol or formoterol) to medications for patients whose asthma is not well controlled on a low to medium dose of ICSs improves lung function, decreases symptoms, and reduces exacerbations and use of quick-relief medication in most patients who have asthma (Bateman et al. 2004; EPR—2 1997; Greenstone et al. 2005; Masoli et al. 2005). See also Evidence Table 11: Inhaled Corticosteroids—Combination Therapy.

    - A large clinical trial comparing daily treatment with salmeterol or placebo added to usual asthma therapy (Nelson et al. 2006) demonstrated an increased risk of asthma-related deaths in patients treated with salmeterol (13 deaths out of 13,176 patients treated for 28 weeks with salmeterol versus 3 deaths out of 13,179 patients treated with placebo). In addition, an increased number of severe asthma exacerbations were noted in the pivotal trials submitted to the FDA for formoterol approval, particularly in the higher dose formoterol arms of the trials (Mann et al. 2003). Thus the FDA determined that a Black Box warning was warranted on all preparations containing a LABA.

    - The Expert Panel recommends that the established, beneficial effects of LABAs for the great majority of patients who have asthma not sufficiently controlled with ICS therapy alone be weighed carefully against the increased risk for potentially deleterious, although uncommon, side effects associated with the daily use of LABAs.

    - Therefore, the Expert Panel has modified its previous recommendation (EPR—Update 2002) and has now concluded that, for patients who have asthma not sufficiently controlled with a low-dose ICS alone, the step-up option to increase the ICS dose should be given equal weight to that of the addition of a LABA to ICS.

OR

  — **Continue the ICS as monotherapy by increasing the dose to the medium-dose range (Evidence A).** Studies of adults in whom the dose of ICS was at least doubled demonstrate some improvements in lung function and other outcomes in those patients who have asthma not completely controlled on a low-to-medium dose of ICS, although

these results are generally less effective than adding a LABA (Ind et al. 2003). In the GOAL study of 3,421 patients who had uncontrolled asthma, a substantial proportion of the patients who received a dose escalation of ICS achieved well-controlled (59 percent) or totally controlled (28 percent) asthma (Bateman et al. 2004). Furthermore, a study of 2,670 patients showed similar rates of exacerbations and nighttime awakenings among the daily medium-dose ICS and daily combination low-dose (ICS/formoterol) study treatment groups (O'Byrne et al. 2005). Both studies confirm the benefits of increasing the dose of ICS (see below for further discussion on weighing the benefits and risks of different step 3 care options).

Based on review of the evidence and in consideration of the potential benefits for improvements in the asthma control domains of impairment and risk, as well as consideration of the potential for adverse effects that exist for each therapeutic option, the Expert Panel recommends that either increasing the dose of the ICS to medium dose or adding LABA to low-dose ICS is an equally acceptable step-up option for patients whose asthma is not adequately controlled on a low dose of ICS.

Overall, the results of the Expert Panel's review of the evidence indicate that the choice one makes at this juncture of stepping up therapy should be based on which therapeutic outcome should be the focus for each individual patient: that is, the desired degree of asthma control in the domains of either *impairment* or *risk,* or both, weighed against the relative risks of side effects for the therapeutic options.

- For the impairment domain, adding LABA, rather than increasing the dose of ICS, more consistently results in improvements in the impairment domain (EPR—Update 2002).

- If the risk domain is of particular concern, then a balance of potential risks needs to be considered (See also "Component 4: Medications.").

  — Adding LABA to low-dose ICS reduces the frequency of exacerbations to a greater extent than doubling the dose of ICS (Masoli et al. 2005), but adding LABA has the potential risk of rare life-threatening or fatal exacerbations.

  — Increasing the dose of ICS can significantly reduce the risk of exacerbations, but this benefit may require up to a fourfold increase in the ICS dose (Pauwels et al. 1997). This may increase the potential risk of systemic effects, although within the medium-dose range the risk is small.

- **Alternative, but not preferred, step 3 therapy is to add (listed alphabetically) an LTRA (Evidence A), theophylline (Evidence B), or zileuton (Evidence D) to low-dose ICS.**

  Considerations favoring one of these alternative combinations would be the patient's lack of response to or intolerance of the side effects of the LABA if that option was tried; marked preference for oral therapy; previous demonstration of superior responsiveness to the alternative class of drug; and/or financial considerations (theophylline is the least expensive).

  The addition of either LTRA, theophylline, or zileuton has produced modest improvement in lung function and some other outcomes in patients who have asthma that is not completely controlled by an ICS. The addition of theophylline, however, has not been shown to be more effective than doubling the dose of the ICS (Evans et al. 1997; Ukena et al. 1997).

LTRAs have produced improvements in lung function and in some but not all measures of asthma control in both adults (Laviolette et al. 1999) and children (Simons et al. 2001) whose asthma is not well controlled by ICSs. When the addition of the LTRA to an ICS has been compared with doubling the dose of the ICS, similar results were observed for a number of outcome measures (Price et al. 2003). Direct comparisons of the addition of an LTRA or a LABA to therapy for patients whose asthma is not well controlled by ICS show significantly greater improvement in lung function and other measures of asthma control for patients receiving the LABA and ICS combination (Ram et al. 2005). Because efficacy data are limited for zileuton as add-on therapy (Dahlen et al. 1998; Lazarus et al. 1998), and zileuton requires monitoring of liver function tests, the Expert Panel considers zileuton a less desirable alternative than LTRA or theophylline for step 3 add-on therapy.

- **If an alternative, but not preferred, treatment is initially administered and does not lead to improvement in asthma control, discontinue it and use a preferred step 3 option before stepping up to step 4 (Evidence D).**

Step 4 Care, Long-Term Control Medications

- **The preferred option is to increase the dose of ICS to the medium-dose range AND add a LABA (Evidence B).** This step is recommended for patients who have asthma not controlled by step 3 therapy. This approach is also recommended for those patients who experience recurring severe exacerbations requiring oral prednisone, ED visits, or hospitalizations. In a 1-year trial of combination therapy, the addition of a LABA to either low-dose or high-dose ICS significantly reduced both mild and severe exacerbation (Pauwels et al. 1997). In addition, fewer exacerbations occurred in the group receiving high-dose ICS compared with the group receiving the lower dose, although statistical analysis was not done. See also the discussion on LABA and combination therapy in "Component 4: Medications."

- **Alternative, but not preferred, step 4 therapy includes medium-dose ICS AND either LTRA or theophylline (Evidence B), or zileuton (Evidence D).**

- If the add-on therapy initially administered does not lead to improvement in asthma control, discontinue it and consider a trial of a different add-on therapy before stepping up (Evidence D).

Step 5 Care, Long-Term Control Medications

- **High-dose ICS and LABA is the preferred treatment (Evidence B).**

- **Omalizumab may be considered at this step for patients who have sensitivity to relevant perennial allergens (e.g., dust mites, cockroach, cat, or dog) (Evidence B) (Bousquet et al. 2004; Humbert et al. 2005).**

- **Clinicians who administer omalizumab are advised to be prepared and equipped for the identification and treatment of anaphylaxis that may occur, to observe patients for an appropriate period of time following each omalizumab injection (the optimal length of the observation is not established), and to educate patients about the risks of anaphylaxis and how to recognize and treat it if it occurs (e.g., using prescription auto injectors for emergency self-treatment, and seeking immediate medical care) (FDA 2007).**

- **Consultation with an asthma specialist is recommended for patients who require this step of therapy (Evidence D).**

Step 6 Care, Long-Term Control Medications

- **Add oral corticosteroids to step 5 therapy. Patients who are not controlled on step 5 therapy may require regular oral corticosteroids to achieve well-controlled asthma (EPR—2 1997).**

  — Two studies have examined the benefit of LTRA as adjunctive therapy in patients who have asthma that is not controlled by ICS and LABA. One 2-week study found no benefit for the addition of an LTRA to high-dose ICS and, for most patients in the study, another medication (either theophylline, a LABA, oral corticosteroid, or a combination) (Robinson et al. 2001). Nathan et al. (2005) reported that adding montelukast for patients who had mild or moderate persistent asthma treated with combined fluticasone (100 mcg)–salmeterol did not improve asthma outcome compared to adding placebo. Studies are not available of other long-term control medications added to the combination of medium- to high-dose ICS and LABA in severe persistent asthma. These data are not definitive; therefore, due to the side effects associated with chronic oral corticosteroid therapy, before maintenance prednisone therapy is initiated, the following may be considered: a 2-week course of oral corticosteroids to confirm reversibility; or a combination of high-dose ICS + LABA + trial of either LTRA, low-dose theophylline, or zileuton (Evidence D).

  — For patients who require long-term systemic corticosteroids:

    - Use the lowest possible dose (single dose daily or on alternate days).
    - Monitor patients closely for corticosteroid adverse side effects (See “Component 4: Medications.”).
    - When well-controlled asthma is achieved, make persistent attempts to reduce systemic corticosteroids. High-dose ICS therapy is preferable to oral systemic corticosteroids because ICSs have fewer systemic effects.
    - Consultation with an asthma specialist is recommended.

SPECIAL ISSUES FOR ADOLESCENTS

The Expert Panel recommends that the pharmacologic management of asthma in school-age children and adolescents follows the same basic principles as those for adults, but the special circumstances of school and social development require special consideration (EPR—2 1997).

Assessment Issues

The Expert Panel recommends that pulmonary function testing should be performed by using comparison data from an appropriate reference population (ATS 1995; EPR—2 1997). Adolescents generally compare better to childhood norms than to adult predicted norms. Testing in a laboratory or clinic that specializes in children can result in higher pulmonary function values and more consistent data. Technicians who conduct pulmonary function testing

for children should have special training in achieving the best possible effort from young patients.

Treatment Issues

The Expert Panel recommends that adolescents (and younger children as appropriate) be directly involved in developing their written asthma action plans (See "Component 2: Education for a Partnership in Asthma Care."). Adolescents may experience more difficulties than younger children in adhering to a medication plan because they may fail to recognize the danger of poorly controlled asthma (Strunk et al. 1985), they may not accept having a chronic illness, or they may view the plan as infringing on their emerging independence and adulthood. In teaching adolescents the same asthma self-management techniques expected of adults, the clinician should address adolescent developmental issues, such as building a positive self-image and confidence, increasing personal responsibility, and gaining problem-solving skills. To accomplish this approach, it is often helpful to see the adolescent initially without parents present and to involve the adolescent directly in setting goals for therapy, developing an appropriate asthma action plan, and reviewing the effectiveness of the plan at repeated visits. The parents can be brought in at the end of the visit to review the plan together and to emphasize the parents' important role in supporting the adolescent's efforts.

School Issues

The Expert Panel recommends that the clinician prepare a written asthma action plan for the student's school. Either encourage the youth or the parents to take a copy of the plan to the youth's school or obtain parental permission and send a copy to the school nurse or designee (Evidence C). The written asthma action plan should include the following information: instructions for handling exacerbations (including the clinician's recommendation regarding self-administration of medication); recommendations for long-term control medications and prevention of EIB, if appropriate; and identification of those factors that make the student's asthma worse, so the school may help the student avoid exposure. For a sample plan, See "Asthma Care," figure 3–21.

It is preferable to schedule daily, long-term medications so that they are not taken at school, even if this results in unequal dosing intervals throughout the day. In school districts that have more comprehensive school nurse coverage, however, youths who would benefit from close supervision to promote adherence may be given medications at school. In this way, daily medication can be administered, and patient education can be supplemented most days of the week.

Students who have asthma often require medication during school to treat acute symptoms or to prevent EIB that may develop during physical education class, school recess, or organized sports. Reliable, prompt access to medication is essential, but it may be difficult because of school rules that preclude the student from carrying medications. The NAEPP and several member organizations have adopted resolutions that endorse allowing students to carry and self-administer medications when the physician and parent consider this appropriate. It may be helpful for some children to have a compressor-driven nebulizer available at the school.

Sports Issues

The Expert Panel recommends that clinicians encourage full participation in physical activities; physical activity at play or in organized sports is an essential part of a child's

life (EPR—2 1997). Many children who have asthma experience cough, wheeze, or excessive fatigue when they exercise. Treatment immediately before vigorous activity or exercise usually prevents EIB. If symptoms occur during usual play activities, a step up in long-term therapy is warranted. Poor endurance or EIB can be an indication of poorly controlled persistent asthma; appropriate use of long-term control medication can reduce EIB (See "Exercise-Induced Bronchospasm."). Activity should be limited or curtailed only as a last resort.

SPECIAL ISSUES FOR OLDER ADULTS

Assessment Issues

The Expert Panel recommends that the extent of reversible airflow obstruction be determined because of the high prevalence of other obstructive lung disease (e.g., chronic bronchitis, emphysema) among the elderly (EPR—2 1997). Careful evaluation is required, because the precise cause of severe airflow obstruction can be difficult to identify in older patients who have asthma. A 2- to 3-week trial of therapy with systemic corticosteroids can help detect the presence of significant reversibility of the airway disease. Long-term control asthma medication can then be offered.

Treatment Issues

The Expert Panel recommends that adjustments in therapy may be necessary because asthma medications may have increased adverse effects in the elderly patient (EPR—2 1997).

- Airway response to *bronchodilators* may change with age, although this is not clearly established. Older patients, especially those with preexisting ischemic heart disease, may also be more sensitive to beta$_2$-agonist side effects, including tremor and tachycardia. Concomitant use of an anticholinergic and a SABA may be beneficial to the older patient (Barros and Rees 1990; Gross et al. 1989; Ullah et al. 1981).

- *Theophylline* clearance is reduced in elderly patients (Nielsen-Kudsk et al. 1988), causing increased blood levels of theophylline. In addition, age is an independent risk factor for developing life-threatening events from iatrogenic chronic theophylline overdose (patients 75 years of age or older have a 16-fold greater risk of death from theophylline overdose than do 25-year-old patients) (Shannon and Lovejoy 1990). The potential for drug interaction—especially with antibiotics and H_2-histamine antagonists such as cimetidine—is greater because of the increased use of medications in this age group. Theophylline and epinephrine may exacerbate underlying heart conditions.

- *Systemic corticosteroids* can provoke confusion, agitation, and changes in glucose metabolism.

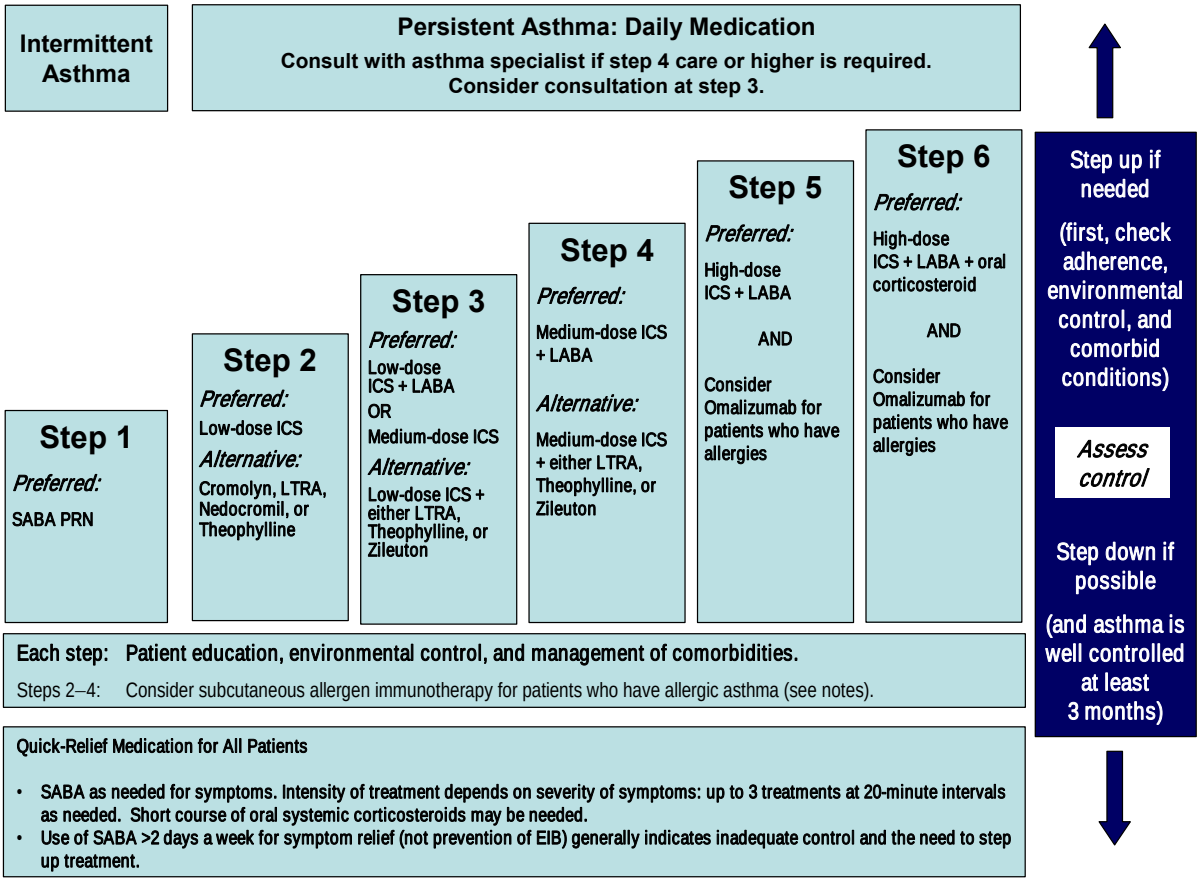
- *Inhaled corticosteroid.* **Consider concurrent treatments with calcium supplements and vitamin D, and bone-sparing medications (e.g., bisphosphonates) in patients who have risk factors for osteoporosis or low bone mineral density (Evidence D).** ICS use may be associated with a dose-dependent reduction in bone mineral content, although low or medium doses appear to have no major adverse effect. Elderly patients may be more at risk due to preexisting osteoporosis, changes in estrogen levels that affect calcium utilization, and a sedentary lifestyle. The risk of not adequately controlling asthma may limit unnecessarily the patient's mobility and activities (See "Component 4: Medications."). An

approach for identifying patients at risk for accelerated bone loss from high-dose ICS therapy is to conduct bone densitometry when treatment begins and again 6 months later (NHLBI 1996), although the benefits of this approach have not yet been evaluated in clinical trials.

The Expert Panel recommends that medications taken for other diseases and conditions be adjusted as necessary, because some medications may exacerbate asthma (EPR—2 1997). Nonsteroidal anti-inflammatory agents for treating arthritis, beta-blockers for treating hypertension (particularly nonselective beta-blockers), or beta-blockers found in some eye drops used to treat glaucoma may exacerbate asthma. See "Component 4: Medications" for more details on drugs that can complicate asthma management.

The Expert Panel recommends that review of the patient's technique in using medications and devices is essential (Evidence B). Observation of technique for use of inhaler devices, peak flow meters, and spirometry is especially important in the elderly because physical (e.g., arthritis, visual) and cognitive impairments (recognized or unrecognized) can make acquisition and retention of proper technique difficult (Allen et al. 2003; Barr et al. 2002; Pezzoli et al. 2003; Wolfenden et al. 2002).

FIGURE 4–5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS



— Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR—2 1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

FIGURE 4–6. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

— **Assessing severity and initiating treatment for patients who are not currently taking long-term control medications**

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1. →			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3	Step 4 or 5
				and consider short course of oral systemic corticosteroids	
(See figure 4–5 for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

—

Key: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 4–7. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Components of Control		Classification of Asthma Control (≥12 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ ACQ ACT	 0 ≤0.75* ≥20	 1–2 ≥1.5 16–19	 3–4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (see figure 4–5 for treatment steps)		• Maintain current step. • Regular followups every 1–6 months to maintain control. • Consider step down if well controlled for at least 3 months.	• Step up 1 step and • Reevaluate in 2–6 weeks. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids, • Step up 1–2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

■
— *ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.
— Key: EIB, exercise-induced bronchospasm; ICU, intensive care unit

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Validated Questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain)
  - ATAQ = Asthma Therapy Assessment Questionnaire© (See sample in "Component 1: Measures of Asthma Assessment and Monitoring.")
  - ACQ = Asthma Control Questionnaire© (user package may be obtained at www.qoltech.co.uk or juniper@qoltech.co.uk)
  - ACT = Asthma Control Test™ (See sample in "Component 1: Measures of Asthma Assessment and Monitoring.")
  - Minimal Important Difference: 1.0 for the ATAQ; 0.5 for the ACQ; not determined for the ACT.
- Before step up in therapy:
  - Review adherence to medication, inhaler technique, environmental control, and comorbid conditions.
  - If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step.

FIGURE 4–8a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS

Medication	Dosage Form	Adult Dose	Comments
Inhaled Corticosteroids (ICS) ***(See figure 4–8b, "Estimated Comparative Daily Dosages for Inhaled Corticosteroids.")***			
Systemic Corticosteroids			***(Applies to all three corticosteroids)***
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	7.5–60 mg daily in a single dose in a.m. or qod as needed for control	■ For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression). Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. ■ There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	Short-course "burst": to achieve control, 40–60 mg per day as single or 2 divided doses for 3–10 days	
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc		
Inhaled Long-Acting Beta$_2$-Agonists (LABA)			■ **Should not be used for symptom relief or exacerbations. Use with ICS.**
Salmeterol	DPI 50 mcg/ blister	1 blister q 12 hours	■ Decreased duration of protection against EIB may occur with regular use.
Formoterol	DPI 12 mcg/ single-use capsule	1 capsule q 12 hours	■ Each capsule is for single use only; additional doses should not be administered for at least 12 hours. ■ Capsules should be used only with the Aerolizor™ inhaler and should not be taken orally.
Combined Medication			
Fluticasone/Salmeterol	DPI 100 mcg/50 mcg, 250 mcg/50 mcg, or 500 mcg/50 mcg HFA 45 mcg/21 mcg 115 mcg/21 mcg 230 mcg/21 mcg	1 inhalation bid; dose depends on severity of asthma	■ 100/50 DPI or 45/21 HFA for patient not controlled on low- to medium-dose ICS 250/50 DPI or 115/21 HFA for patients not controlled on medium- to high-dose ICS
Budesonide/ Formoterol	HFA MDI 80 mcg/4.5 mcg 160mcg/4.5 mcg	2 inhalations bid; dose depends on severity of asthma	■ 80/4.5 for patients who have asthma not controlled on low- to medium-dose ICS ■ 160/4.5 for patients who have asthma not controlled on medium- to high-dose ICS

■

FIGURE 4–8a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS (CONTINUED)

Medication	Dosage Form	Adult Dose	Comments
Cromolyn and Nedocromil			
Cromolyn	MDI 0.8 mg/puff	2 puffs qid	■ 4–6 week trial may be needed to determine maximum benefit. ■ Dose by MDI may be inadequate to affect hyperresponsiveness. ■ One dose before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective for EIB as SABA. ■ Once control is achieved, the frequency of dosing may be reduced.
	Nebulizer 20 mg/ampule	1 ampule qid	
Nedocromil	MDI 1.75 mg/puff	2 puffs qid	
Leukotriene Modifiers			
Leukotriene Receptor Antagonists			
Montelukast	4 mg or 5 mg chewable tablet 10 mg tablet	10 mg qhs	■ Montelukast exhibits a flat dose-response curve. Doses >10 mg will not produce a greater response in adults.
Zafirlukast	10 or 20 mg tablet	40 mg daily (20 mg tablet bid)	■ For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ Monitor for signs and symptoms of hepatic dysfunction.
5-Lipoxygenase Inhibitor			
Zileuton	600 mg tablet	2,400 mg daily (give tablets qid)	■ For zileuton, monitor hepatic enzymes (ALT).
Methylxanthines			
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/day	Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage). ■ Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is important. ■ See next page for factors that can affect theophylline levels.
Immunomodulators			
Omalizumab	Subcutaneous injection, 150 mg/1.2 mL following reconstitution with 1.4 mL sterile water for injection	150–375 mg SC q 2–4 weeks, depending on body weight and pretreatment serum IgE level	■ Do not administer more than 150 mg per injection site. ■ Monitor for anaphylaxis for 2 hours following at least the first 3 injections.

Key: DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; IgE, immunoglobulin E; MDI, metered-dose inhaler; SABA, short-acting beta$_2$-agonist

FIGURE 4–8a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS (CONTINUED)

Factors Affecting Serum Theophylline Concentrations*

Factor	Decreases Theophylline Concentrations	Increases Theophylline Concentrations	Recommended Action
Food	↓ or delays absorption of some sustained-release theophylline (SRT) products	↑ rate of absorption (fatty foods)	Select theophylline preparation that is not affected by food.
Diet	↑ metabolism (high protein)	↓ metabolism (high carbohydrate)	Inform patients that major changes in diet are not recommended while taking theophylline.
Systemic, febrile viral illness (e.g., influenza)		↓ metabolism	Decrease theophylline dose according to serum concentration. Decrease dose by 50 percent if serum concentration measurement is not available.
Hypoxia, cor pulmonale, and decompensated congestive heart failure, cirrhosis		↓ metabolism	Decrease dose according to serum concentration.
Age	↑ metabolism (1–9 years)	↓ metabolism (<6 months, elderly)	Adjust dose according to serum concentration.
Phenobarbital, phenytoin, carbamazepine	↑ metabolism		Increase dose according to serum concentration.
Cimetidine		↓ metabolism	Use alternative H_2 blocker (e.g., famotidine or ranitidine).
Macrolides: erythromycin, clarithromycin, troleandomycin		↓ metabolism	Use alternative macrolide antibiotic, azithromycin, or alternative antibiotic or adjust theophylline dose.
Quinolones: ciprofloxacin, enoxacin, perfloxacin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose. Circumvent with ofloxacin if quinolone therapy is required.
Rifampin	↑ metabolism		Increase dose according to serum concentration.
Ticlopidine		↓ metabolism	Decrease dose according to serum concentration.
Smoking	↑ metabolism		Advise patient to stop smoking; increase dose according to serum concentration.

*This list is not all inclusive; for discussion of other factors, see package inserts.

■

FIGURE 4–8b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS

Drug	Low Daily Dose Adult	Medium Daily Dose Adult	High Daily Dose Adult
Beclomethasone HFA 40 or 80 mcg/puff	80–240 mcg	>240–480 mcg	>480 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	180–600 mcg	>600–1,200 mcg	>1,200 mcg
Flunisolide 250 mcg/puff	500–1,000 mcg	>1,000–2,000 mcg	>2,000 mcg
Flunisolide HFA 80 mcg/puff	320 mcg	>320–640 mcg	>640 mcg
Fluticasone			
HFA/MDI: 44, 110, or 220 mcg/puff	88–264 mcg	>264–440 mcg	>440 mcg
DPI: 50, 100, or 250 mcg/inhalation	100–300 mcg	>300–500 mcg	>500 mcg
Mometasone DPI 200 mcg/inhalation	200 mcg	400 mcg	>400 mcg
Triamcinolone acetonide 75 mcg/puff	300–750 mcg	>750–1,500 mcg	>1,500 mcg

Key: DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler

Notes:

- **The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy.** The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effect.
- Some doses may be outside package labeling, especially in the high-dose range.
- MDI dosages are expressed as the actuator dose (the amount of the drug leaving the actuator and delivered to the patient), which is the labeling required in the United States. This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, not all of which is available to the patient), which is used in many European countries and in some scientific literature. DPI doses are expressed as the amount of drug in the inhaler following activation.
- Comparative dosages are based on published comparative clinical trials (Adams et al. 2005; Barnes et al. 1998; Kelly 1998; Lasserson et al. 2005; Pedersen and O'Byrne 1997). The rationale for some key comparisons is summarized as follows:
  - The high dose is the dose that appears likely to be the threshold beyond which significant hypothalamic-pituitary-adrenal (HPA) axis suppression is produced, and, by extrapolation, the risk is increased for other clinically significant systemic effects if used for prolonged periods of time (Martin et al. 2002; Szefler et al. 2002).
  - The low- and medium-doses reflect findings from dose-ranging studies in which incremental efficacy within the low- to medium-dose ranges was established without increased systemic effect as measured by overnight cortisol excretion. The studies demonstrated a relatively flat dose-response curve for efficacy at the medium-dose range; that is, increasing the dose of high-dose range did not significantly increase efficacy but did increase systemic effect (Adams et al. 2001; Martin et al. 2002; Szefler et al. 2002).
  - The dose for budesonide DPI is based on recently available comparative data with other medications. These new data, including meta-analyses, show that budesonide DPI is comparable to approximately twice the microgram dose of fluticasone MDI or DPI (Adams et al. 2005; Barnes et al. 1998; Nielsen and Dahl 2000).

FIGURE 4–8b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS (CONTINUED)

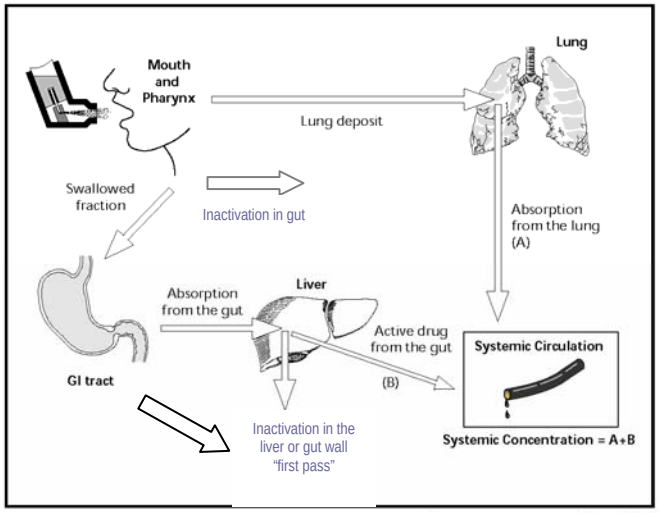
— The dose for beclomethasone in HFA inhaler should be approximately one-half the dose for beclomethasone in chlorofluorocarbon (CFC) inhaler for adults and children, based on studies demonstrating that the different pharmaceutical properties of the medications result in enhanced lung delivery for the HFA (a less forceful spray from the HFA propellant and a reengineered nozzle that allows a smaller particle size) and clinical trials demonstrating similar potency to fluticasone at 1:1 dose ratio (Boulet et al. 2004; Busse et al. 1999; Gross et al. 1999; Lasserson et al. 2005; Leach et al. 1998; Pedersen et al. 2002; Szefler et al. 2002; Thompson et al. 1998).

— The dose for mometasone DPI is based on product information and current literature (Bousquet et al. 2000; Fardon et al. 2004; Kemp et al. 2000; O'Connor et al. 2001). Mometasone is approved for once daily administration. Mometasone furoate by dry powder achieved effects similar to twice the dose of budesonide by dry powder (Bousquet et al. 2000) and comparable to a slightly higher dose of fluticasone propionate by dry powder (O'Connor et al. 2001).

— The dose for flunisolide HFA is based on product information and current literature (Corren et al. 2001; Gillman et al. 2002; Richards et al. 2001).

■ **Bioavailability**

Both the relative potency and the relative bioavailability (systemic availability) determine the potential for systemic activity of an ICS preparation. As illustrated here, the bioavailability of an ICS is dependent on the absorption of the dose delivered to the lungs and the oral bioavailability of the swallowed portion of the dose received.



Adapted with permission from Barnes 1995.

— Absorption of the dose delivered to the lungs:

- ♦ Approximately 10–50 percent of the dose from the MDI is delivered to the lungs. This amount varies among preparations and delivery devices.
- ♦ Nearly all of the amount delivered to the lungs is bioavailable.

— Oral bioavailability of the swallowed portion of the dose received:

- ♦ Approximately 50–80 percent of the dose from the MDI without a spacer/holding chamber is swallowed.
- ♦ The oral bioavailability of this amount varies:

  Either a high first-pass metabolism or the use of a spacer/holding chamber with an MDI can decrease oral bioavailability, thus enhancing safety (Lipworth 1995).

  The approximate oral bioavailability of ICSs has been reported as: beclomethasone dipropionate 20 percent; flunisolide, 21 percent; triamcinolone acetonide, 10.6 percent; budesonide, 11 percent; fluticasone propionate, 1 percent; mometasone, <1 percent (Affrime et al. 2000; Chaplin et al. 1980; Check and Kaliner 1990; Clissold and Heel 1984; Davies 1993; Harding 1990; Heald et al. 1995; Martin et al. 1974; Mollmann et al. 1985; Szefler 1991; Wurthwein and Rohdewald 1990).

■ **Potential drug interactions**

A number of the ICSs, including fluticasone, budesonide, and mometasone, are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as ritonavir and ketoconazole, have the potential for increasing systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported (Johnson et al. 2006; Samaras et al. 2005).

FIGURE 4–8c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS

Medication	Dosage Form	Adult Dose	Comments
Inhaled Short-Acting Beta$_2$-Agonists (SABA)			
	MDI		***Applies to all four SABAs***
Albuterol CFC	90 mcg/puff, 200 puffs/canister	■ 2 puffs 5 minutes before exercise	■ An increasing use or lack of expected effect indicates diminished control of asthma.
Albuterol HFA	90 mcg/puff, 200 puffs/canister	■ 2 puffs every 4–6 hours as needed	■ Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need to step up therapy.
Pirbuterol CFC	200 mcg/puff, 400 puffs/canister		■ Differences in potency exist, but all products are essentially comparable on a per puff basis.
Levalbuterol HFA	45 mcg/puff, 200 puffs/canister		■ May double usual dose for mild exacerbations.
			■ Should prime the inhaler by releasing 4 actuations prior to use.
			■ Periodically clean HFA activator, as drug may block/plug orifice.
			■ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.
	Nebulizer solution		
Albuterol	0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5 mg/mL (0.5%)	1.25–5 mg in 3 cc of saline q 4–8 hours as needed	■ May mix with budesonide inhalant suspension, cromolyn or ipratropium nebulizer solutions. May double dose for severe exacerbations.
Levalbuterol (R-albuterol)	0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/0.5 mL 1.25 mg/3 mL	0.63 mg–1.25 mg q 8 hours as needed	■ Compatible with budesonide inhalant suspension. The product is a sterile-filled, preservative-free, unit dose vial.

■

FIGURE 4–8c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS FOR YOUTHS ≥12 YEARS OF AGE AND ADULTS (CONTINUED)

Medication	Dosage Form	Adult Dose	Comments
Anticholinergics			
	MDI		
Ipratropium HFA	17 mcg/puff, 200 puffs/canister	2–3 puffs q 6 hours	■ Evidence is lacking for anticholinergics producing added benefit to beta$_2$-agonists in long-term control asthma therapy.
	Nebulizer solution		
	0.25 mg/mL (0.025%)	0.25 mg q 6 hours	
	MDI		
Ipratropium with albuterol	18 mcg/puff of ipratropium bromide and 90 mcg/puff of albuterol	2–3 puffs q 6 hours	
	200 puffs/canister		
	Nebulizer solution		
	0.5 mg/3 mL ipratropium bromide and 2.5 mg/3 mL albuterol	3 mL q 4–6 hours	■ Contains EDTA to prevent discoloration of the solution. This additive does not induce bronchospasm.
Systemic Corticosteroids			***Applies to the first three corticosteroids***
Methylprednisolone	2, 4, 6, 8, 16, 32 mg tablets	■ Short course "burst": 40–60 mg/day as single or 2 divided doses for 3–10 days	■ Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration.
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc		■ The burst should be continued until symptoms resolve and the PEF is at least 80 percent of personal best. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc		
	Repository injection		
(Methylprednisolone acetate)	40 mg/mL 80 mg/mL	240 mg IM once	■ May be used in place of a short burst of oral steroids in patients who are vomiting or if adherence is a problem.

Key: CFC, chlorofluorocarbon; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow

■

References

Aburuz S, McElnay J, Gamble J, Millership J, Heaney L. Relationship between lung function and asthma symptoms in patients with difficult to control asthma. *J Asthma* 2005;42(10):859–64.

Adams N, Bestall J, Jones P. Inhaled beclomethasone at different doses for long-term asthma. *Cochrane Database Syst Rev* 2001;(1):CD002879.

Adams N, Bestall JM, Lasserson TJ, Jones PW. Inhaled fluticasone versus inhaled beclomethasone or inhaled budesonide for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005;(2):CD002310.

Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax* 2000;55(7):566–73.

Affrime MB, Cuss F, Padhi D, Wirth M, Pai S, Clement RP, Lim J, Kantesaria B, Alton K, Cayen MN. Bioavailability and metabolism of mometasone furoate following administration by metered-dose and dry-powder inhalers in healthy human volunteers. *J Clin Pharmacol* 2000;40(11):1227–36.

Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. *Age Ageing* 2003;32(3):299–302.

American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152(3):1107–36.

Barnes NC, Hallett C, Harris TA. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. *Respir Med* 1998;92(1):95–104.

Barr RG, Somers SC, Speizer FE, Camargo CA Jr; National Asthma Education and Prevention Program (NAEPP). Patient factors and medication guideline adherence among older women with asthma. *Arch Intern Med* 2002;162(15):1761–8.

Barros MJ, Rees PJ. Bronchodilator responses to salbutamol followed by ipratropium bromide in partially reversible airflow obstruction. *Respir Med* 1990;84(5):371–5.

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004;170(8):836–44.

Boulet LP, Cartier A, Ernst P, Larivee P, Laviolette M. Safety and efficacy of HFA-134a beclomethasone dipropionate extra-fine aerosol over six months. *Can Respir J* 2004;11(2):123–30.

Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, Chinchilli VM, Craig TJ, DiMango EA, Deykin A, et al.; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352(15):1519–28.

Bousquet J, D'Urzo A, Hebert J, Barraza CH, Boulet LP, Suarez-Chacon R, Harnest U, Lundback B, Martinez Morales G, Nieminen MM, et al. Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler. *Eur Respir J* 2000;16(5):808–16.

Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 2004;125(4):1378–86.

Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, Donnell D, Hannon S, Colice GL. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999;104(6):1215–22.

Chaplin MD, Rooks W, Swenson EW, Cooper WC, Nerenberg C, Chu NI. Flunisolide metabolism and dynamics of a metabolite. *Clin Pharmacol Ther* 1980;27(3):402–13.

Check WA, Kaliner MA. Pharmacology and pharmacokinetics of topical corticosteroid derivatives used for asthma therapy. *Am Rev Respir Dis* 1990;141(2 Pt 2):S44–51.

Clissold SP, Heel RC. Budesonide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. *Drugs* 1984;28(6):485–518.

Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses, and increased bronchial responsiveness to histamine. *J Allergy Clin Immunol* 1987;79(5):734–40.

Corren J, Nelson H, Greos LS, Bensch G, Goldstein M, Wu J, Wang S, Newman K. Effective control of asthma with hydrofluoroalkane flunisolide delivered as an extrafine aerosol in asthma patients. *Ann Allergy Asthma Immunol* 2001;87(5):405–11.

Cowie RL, Underwood MF, Revitt SG, Field SK. Predicting emergency department utilization in adults with asthma: a cohort study. *J Asthma* 2001;38(2):179–184.

Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, Mastalerz L, Pinis G, Swanson LJ, Boodhoo TI, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1187–94.

Davies B. A comparison of beclomethasone dipropionate and budesonide in the treatment of asthma. *Br J Clin Pract* 1993;47(2):87–93.

Eisner MD, Katz PP, Yelin EH, Shiboski SC, Blanc PD. Risk factors for hospitalization among adults with asthma: the influence of sociodemographic factors and asthma severity. *Respir Res* 2001;2(1):53–60. Epub December 2000.

EPR—2. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

EPR—Update 2002. Expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics 2002 (EPR—Update 2002). NIH Publication No. 02-5074. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf.

Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997;337(20):1412–8.

Fardon TC, Lee DK, Haggart K, McFarlane LC, Lipworth BJ. Adrenal suppression with dry powder formulations of fluticasone propionate and mometasone furoate. *Am J Respir Crit Care Med* 2004;170(9):960–6. Epub June 2004.

Food and Drug Administration (FDA). 2007. FDA alert: Omalizumab (marketed as Xolair) information 2/2007. Available at: http://www.fda.gov/cder/drug/infopage/omalizumab/default.htm.

Fuhlbrigge AL, Adams RJ, Guilbert TW, Grant E, Lozano P, Janson SL, Martinez F, Weiss KB, Weiss ST. The burden of asthma in the United States: level and distribution are dependent on interpretation of the National Asthma Education and Prevention Program guidelines. *Am J Respir Crit Care Med* 2002;166(8):1044–9.

Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, Weiss ST. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 2001;107(1):61–7.

Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics* 2006;118(2):e347–55. Epub July 2006.

Gillman SA, Anolik R, Schenkel E, Newman K. One-year trial on safety and normal linear growth with flunisolide HFA in children with asthma. *Clin Pediatr (Phila)* 2002;41(5):333–40.

Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, Wardlaw AJ, Pavord ID. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360(9347):1715–21.

Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X, Ducharme FM. Combination of inhaled long-acting beta$_2$-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane Database Syst Rev* 2005;(4):CD005533.

Gross G, Thompson PJ, Chervinsky P, Vanden Burgt J. Hydrofluoroalkane-134a beclomethasone dipropionate, 400 microg, is as effective as chlorofluorocarbon beclomethasone dipropionate, 800 microg, for the treatment of moderate asthma. *Chest* 1999;115(2):343–51.

Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study. *Am Rev Respir Dis* 1989;139(5):1188–91.

Hammerman SI, Becker JM, Rogers J, Quedenfeld TC, D'Alonzo GE Jr. Asthma screening of high school athletes: identifying the undiagnosed and poorly controlled. *Ann Allergy Asthma Immunol* 2002;88(4):380–4.

Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990;84(Suppl A):25–9.

Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *BMJ* 2003;326(7399):1115.

Heald D, Argenti D, Jensen B, Vaccaro S. The disposition of ^{14}C triamcinolone acetonide administrated as single oral dose of 100 microCi (800 mcg) to healthy volunteers. Presented at Asthma Theory to Treatment; 1995 July 15–17, Chicago, IL (data on file Rhône-Poulenc Rorer).

Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, Beeh KM, Ramos S, Canonica GW, Hedgecock S, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60(3):309–16.

Ind PW, Dal Negro R, Colman NC, Fletcher CP, Browning D, James MH. Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma. *Respir Med* 2003;97(5):555–62.

Johnson SR, Marion AA, Vrchoticky T, Emmanuel PJ, Lujan-Zilbermann J. Cushing syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. *J Pediatr* 2006;148(3):386–8.

Johnston NW, Johnston SL, Duncan JM, Greene JM, Kebadze T, Keith PK, Roy M, Waserman S, Sears MR. The September epidemic of asthma exacerbations in children: a search for etiology. *J Allergy Clin Immunol* 2005;115(1):132–8.

Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14(1):32–38.

Juniper EF, O'Byrne PM, Roberts JN. Measuring asthma control in group studies: do we need airway calibre and rescue beta$_2$-agonist use? *Respir Med* 2001;95(5):319–23.

Kelly HW. Comparison of inhaled corticosteroids. *Ann Pharmacother* 1998;32(2):220–32.

Kemp JP, Berkowitz RB, Miller SD, Murray JJ, Nolop K, Harrison JE. Mometasone furoate administered once daily is as effective as twice-daily administration for treatment of mild-to-moderate persistent asthma. *J Allergy Clin Immunol* 2000;106(3):485–92.

Kitch BT, Paltiel AD, Kuntz KM, Dockery DW, Schouten JP, Weiss ST, Fuhlbrigge AL. A single measure of FEV_1 is associated with risk of asthma attacks in long-term follow-up. *Chest* 2004;126(6):1875–82.

Lasserson TJ, Cates CJ, Jones AB, Steele EH, White J. Fluticasone versus HFA-beclomethasone dipropionate for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2005;(4):CD005309. Update in *Cochrane Database Syst Rev* 2006;(2):CD005309.

Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I, Zhang J, Reiss TF. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. *Am J Respir Crit Care Med* 1999;160(6):1862–8.

Lazarus SC, Lee T, Kemp JP, Wenzel S, Dube LM, Ochs RF, Carpentier PJ, Lancaster JF. Safety and clinical efficacy of zileuton in patients with chronic asthma. *Am J Manag Care* 1998;4(6):841–8.

Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998;12(6):1346–53.

Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, Drazen JM, Chinchilli VM, Craig T, Fish JE, et al.; Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *JAMA* 2001;285(20):2594–603.

Lieu TA, Quesenberry CP, Sorel ME, Mendoza GR, Leong AB. Computer-based models to identify high-risk children with asthma. *Am J Respir Crit Care Med* 1998;157(4 Pt 1):1173–80.

Lipworth BJ. New perspectives on inhaled drug delivery and systemic bioactivity. *Thorax* 1995;50(2):105–10.

Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest* 2003;124(1):70–4.

Martin LE, Tanner RJ, Clark TJ, Cochrane GM. Absorption and metabolism of orally administered beclomethsone dipropionate. *Clin Pharmacol Ther* 1974;15(3):267–75.

Martin RJ, Szefler SJ, Chinchilli VM, Kraft M, Dolovich M, Boushey HA, Cherniack RM, Craig TJ, Drazen JM, Fagan JK, et al. Systemic effect comparisons of six inhaled corticosteroid preparations. *Am J Respir Crit Care Med* 2002;165(10):1377–83.

Masoli M, Weatherall M, Holt S, Beasley R. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroids in symptomatic asthma. *Thorax* 2005;60(9):730–4.

Mollmann H, Rohdewald P, Schmidt EW, Salomon V, Derendorf H. Pharmacokinetics of triamcinolone acetonide and its phosphate ester. *Eur J Clin Pharmacol* 1985;29(1):85–9.

Moy ML, Israel E, Weiss ST, Juniper EF, Dube L, Drazen JM; NHBLI Asthma Clinical Research Network. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med* 2001;163(4):924–9.

Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113(1):59–65.

Nathan RA, Yancey SW, Waitkus-Edwards K, Prillaman BA, Stauffer JL, Philpot E, Dorinsky PM, Nelson HS. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest* 2005;128(4):1910–20.

National Heart, Lung, and Blood Institute (NHLBI). *NAEPP Working Group Report*: *Considerations for Diagnosing and Managing Asthma in the Elderly* (NHLBI 1996). NIH Publication No. 96-3662. U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute, 1996.

Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129(1):15–26. Erratum in: *Chest* 2006;129(5):1393.

Ni CM, Greenstone IR, Ducharme FM. Addition of inhaled long-acting beta$_2$-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults. *Cochrane Database Syst Rev* 2005;(2):CD005307.

Nielsen LP, Dahl R. Therapeutic ratio of inhaled corticosteroids in adult asthma. A dose-range comparison between fluticasone propionate and budesonide, measuring their effect on bronchial hyperresponsiveness and adrenal cortex function. *Am J Respir Crit Care Med* 2000;162(6):2053–7.

Nielsen-Kudsk JE, Mellemkjaer S, Siggaard C, Nielsen CB. Effects of pinacidil on guinea-pig airway smooth muscle contracted by asthma mediators. *Eur J Pharmacol* 1988;157(2–3):221–6.

O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, Tattersfield A. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164(8 Pt 1):1392–7.

O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekstrom T, Bateman ED. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171(2):129–36. Epub October 2004.

O'Connor B, Bonnaud G, Haahtela T, Luna JM, Querfurt H, Wegener T, Lutsky BN. Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator. *Ann Allergy Asthma Immunol* 2001;86(4):397–404.

Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;337(20):1405–11. Erratum in: *N Engl J Med* 1998;338(2):139.

Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy* 1997;52(39 Suppl):1–34.

Pedersen S, Warner J, Wahn U, Staab D, Le Bourgeois M, Essen-Zandvliet E, Arora S, Szefler SJ; Pediatric Study Group. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: an open-label, randomized comparison of extrafine and conventional aerosols in children. *Pediatrics* 2002;109(6):e92.

Pezzoli L, Giardini G, Consonni S, Dallera I, Bilotta C, Ferrario G, Cristina SM, Annoni G, Vergani C. Quality of spirometric performance in older people. *Age Ageing* 2003;32(1):43–6.

Price DB, Hernandez D, Magyar P, Fiterman J, Beeh KM, James IG, Konstantopoulos S, Rojas R, van Noord JA, Pons M, et al.; Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) International Study Group. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;58(3):211–6.

Ram FS, Cates CJ, Ducharme FM. Long-acting beta$_2$-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev* 2005;(1):CD003137.

Richards J, Hirst P, Pitcairn G, Mahashabde S, Abramowitz W, Nolting A, Newman SP. Deposition and pharmacokinetics of flunisolide delivered from pressurized inhalers containing non-CFC and CFC propellants. *J Aerosol Med* 2001;14(2):197–208.

Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet* 2001;357(9273):2007–11.

Samaras K, Pett S, Gowers A, McMurchie M, Cooper DA. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab* 2005;90(7):4394–8. Epub March 2005.

Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB, Leong A, Johnson MS, Mendoza G, Cook EF. Relationship of validated psychometric tools to subsequent medical utilization for asthma. *J Allergy Clin Immunol* 2005;115(3):564–570.

Schatz M, Nakahiro R, Jones CH, Roth RM, Joshua A, Petitti D. Asthma population management: development and validation of a practical 3-level risk stratification scheme. *Am J Manag Care* 2004;10(1):25–32.

Schatz M, Zeiger RS, Vollmer WM, Mosen D, Cook EF. Determinants of future long-term asthma control. *J Allergy Clin Immunol* 2006;118(5):1048–53. Epub October 2006.

Shannon M, Lovejoy FH Jr. The influence of age vs peak serum concentration on life-threatening events after chronic theophylline intoxication. *Arch Intern Med* 1990;150(10):2045–8.

Shingo S, Zhang J, Reiss TF. Correlation of airway obstruction and patient-reported endpoints in clinical studies. *Eur Respir J* 2001;17(2):220–4.

Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, Laessig W, Schuster A, Perez-Frias J, Sekerel BE, et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001;138(5):694–8.

Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352(21):2163–73. Epub May 2005.

Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1043–51.

Stahl E. Correlation between objective measures of airway calibre and clinical symptoms in asthma: a systematic review of clinical studies. *Respir Med* 2000;94(8):735–41.

Strunk RC, Mrazek DA, Fuhrmann GS, LaBrecque JF. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. A case-controlled study. *JAMA* 1985;254(9):1193–8.

Szefler SJ. Glucocorticoid therapy for asthma: clinical pharmacology. *J Allergy Clin Immunol* 1991;88(2):147–65.

Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, Craig TJ, Dolovich M, Drazen JM, Fagan JK, et al.; Asthma Clinical Research Network of the National Heart Lung, and Blood Institute. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;109(3):410–8.

Thompson PJ, Davies RJ, Young WF, Grossman AB, Donnell D. Safety of hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol. *Respir Med* 1998;92 Suppl A:33–9.

Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H, Leichtl S, Rathgeb F, Keller A, Steinijans VW. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. *Eur Respir J* 1997;10(12):2754–60.

Ullah MI, Newman GB, Saunders KB. Influence of age on response to ipratropium and salbutamol in asthma. *Thorax* 1981;36(7):523–9.

Vollmer WM, Markson LE, O'Connor E, Sanocki LL, Fitterman L, Berger M, Buist AS. Association of asthma control with health care utilization and quality of life. *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1647–52.

Waalkens HJ, Van Essen-Zandvliet EE, Hughes MD, Gerritsen J, Duiverman EJ, Knol K, Kerrebijn KF. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. The Dutch CNSLD Study Group. *Am Rev Respir Dis* 1993;148(5):1252–7.

Wolfenden LL, Diette GB, Skinner EA, Steinwachs DM, Wu AW. Gaps in asthma care of the oldest adults. *J Am Geriatr Soc* 2002;50(5):877–83.

Wurthwein G, Rohdewald P. Activation of beclomethasone dipropionate by hydrolysis to beclomethasone-17-monopropionate. *Biopharm Drug Dispos* 1990;11(5):381–94.

Yurk RA, Diette GB, Skinner EA, Dominici F, Clark RD, Steinwachs DM, Wu AW. Predicting patient-reported asthma outcomes for adults in managed care. *Am J Manag Care* 2004;10(5):321–8.

SECTION 4, MANAGING ASTHMA LONG TERM—SPECIAL SITUATIONS

Introduction

Patients who have asthma may encounter situations that will require adjustments to their asthma management to keep their asthma under control. Special situations described in this section include: EIB, pregnancy, and surgery.

Exercise-Induced Bronchospasm

The Expert Panel concludes that exercise may be the only precipitant of asthma symptoms for some patients. These patients should be monitored regularly to ensure that they have no symptoms of asthma or reductions in PEF in the absence of exercise, because EIB is often a marker of inadequate asthma management and responds well to regular anti-inflammatory therapy (EPR—2 1997).

EIB—which can limit and disrupt otherwise normal lives if not treated—should be anticipated in all asthma patients. EIB is a bronchospastic event that is caused by a loss of heat, water, or both from the lung during exercise because of hyperventilation of air that is cooler and dryer than that of the respiratory tree. Some, but not all, studies suggest that release of inflammatory mediators is involved in the etiology of EIB (Anderson 2004; Anderson and Brannan 2004; Carlsen and Carlsen 2002; Jarjour and Calhoun 1992; McFadden and Gilbert 1994; Tan and Spector 2002). EIB usually occurs during or minutes after vigorous activity, reaches its peak 5–10 minutes after stopping the activity, and resolves in another 20–30 minutes. Some reports indicate that there is a refractory period of less than 1 hour after EIB that allows for an asthma-symptom-free interval after warmup exercises (Edmunds et al. 1978). There is uncertainty, however, concerning the existence of a late-phase reaction hours after exercise (Chhabra and Ojha 1998).

DIAGNOSIS

The Expert Panel recommends that a history of cough, shortness of breath, chest pain or tightness, wheezing, or endurance problems during exercise suggests EIB. An exercise challenge can be used to establish the diagnosis (EPR—2 1997). Use of history alone has been shown both to underdiagnose and overdiagnose the problem (McKenzie et al. 2002; Tan and Spector 2002). VCD, in particular, can be confused with EIB (Huggins et al. 2004; Sullivan et al. 2001). An exercise challenge, useful for establishing the diagnosis, can be performed in a formal laboratory setting or as a free-run challenge sufficiently strenuous to increase the baseline heart rate to 80 percent of maximum for 4–6 minutes. Alternatively, the patient may simply undertake the task that previously caused the symptoms. A 15-percent decrease in PEF or FEV_1 (with measurements taken before and after exercise at 5-minute intervals for 20–30 minutes) is compatible with EIB.

MANAGEMENT STRATEGIES

The Expert Panel recommends that an important dimension of adequate asthma control is a patient's ability to participate in any activity he or she chooses without experiencing asthma symptoms. EIB should not limit either participation or success in vigorous activities. Recommended treatments include:

- **Long-term control therapy, if appropriate (Evidence A).** There is evidence that appropriate long-term control of asthma with anti-inflammatory medication will reduce airway responsiveness, and this is associated with a reduction in the frequency and severity of EIB (Vathenen et al. 1991; Vidal et al. 2001). Frequent, severe EIB may indicate poorly controlled asthma and thus a need to initiate or increase daily long-term control therapy.

- **Pretreatment before exercise:**

  — **Inhaled beta$_2$-agonists** will prevent EIB in more than 80 percent of patients (Evidence A).

    - **SABA** used shortly before exercise (or as close to exercise as possible) may be helpful for 2–3 hours.

    - **LABAs** can be protective up to 12 hours (Ferrari et al. 2002; Newnham et al. 1993; Richter et al. 2002; Shapiro et al. 2002). When LABAs are administered on a daily basis, however, there is some shortening of the duration of protection, even in patients using ICSs (Simons et al. 1997). Frequent and chronic use of LABAs for EIB should be discouraged. Such use may disguise poorly controlled persistent asthma, which should be managed with daily anti-inflammatory therapy.

  — **LTRAs** can attenuate EIB in up to 50 percent of patients (Evidence B). The onset of action is generally hours after administration. Few comparisons with other protective agents are currently available (Mastalerz et al. 2002; Moraes and Selvadurai 2004; Steinshamn et al. 2002).

  — **Cromolyn or nedocromil** taken shortly before exercise is an alternative treatment to prevent EIB, but it is not as effective as SABAs (Spooner et al. 2003) (Evidence B). The addition of cromolyn to a SABA is helpful in some individuals who have EIB (Spooner et al. 2003). These studies (Spooner et al. 2003) indicate that anticholinergics may also attenuate EIB, but they are less likely to be protective than either mast cell stabilizers or SABAs.

  — **A warmup period before exercise** may reduce the degree of EIB (de Bisschop et al. 1999) (Evidence C).

  — **A mask or scarf over the mouth may attenuate cold-induced EIB (Beuther and Martin 2006) (Evidence C).**

The Expert Panel recommends that teachers and coaches be notified that a child has EIB, that the child should be able to participate in activities, and that the child may need inhaled medication before activity (Evidence D). Individuals involved in

competitive athletics need to be aware that their medication use should be disclosed, and they should adhere to standards set by the sports-governing bodies (Anderson et al. 2003). The U.S. Anti-Doping Agency Drug Reference Line is 1–800–233–0393.

Surgery and Asthma

The Expert Panel recommends consideration that patients who have asthma are at risk for specific complications during and after surgery (EPR—2 1997). These complications include acute bronchoconstriction triggered by intubation, hypoxemia and possible hypercapnia, impaired effectiveness of cough, atelectasis, and respiratory infection (Kingston and Hirshman 1984); latex exposure (Slater 1994; Sussman and Beezhold 1995); and even some anesthetic agents (Nishiyama and Hanaoka 2001). The likelihood of these complications depends on the severity of the patient's airway hyperresponsiveness, airflow obstruction, mucus hypersecretions, latex sensitivity, and history of prior surgeries, because the latter is a risk factor for both latex and anesthetic agent sensitivities.

The Expert Panel recommends the following actions to reduce risk of complications during surgery (EPR—2 1997):

- **Patients who have asthma should have an evaluation before surgery that includes a review of symptoms, medication use (particularly the use of oral systemic corticosteroids for longer than 2 weeks in the past 6 months), and measurement of pulmonary function.**

- **If possible, attempts should be made to improve lung function preoperatively (FEV_1 or peak expiratory flow rate [PEFR]) to either their predicted values or their personal best level. A short course of oral systemic corticosteroids may be necessary to optimize lung function.**

- **For patients who have received oral systemic corticosteroids during the past 6 months and for selected patients on a long-term high dose of an ICS, give 100 mg hydrocortisone every 8 hours intravenously during the surgical period and reduce the dose rapidly within 24 hours after surgery. Stress doses of corticosteroids may be considered for select patients treated with prior high-dose ICS therapy as well, because clinically important adrenal suppression has been reported in such patients, particularly children (Todd et al. 2002a, b).**

Pregnancy and Asthma

The NAEPP "Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004" (NAEPP 2005) emphasizes that maintaining adequate control of asthma during pregnancy is important for the health and well-being of both the mother and her baby. Maternal asthma increases the risk of perinatal mortality, preeclampsia, preterm birth, and low-birth-weight infants. More severe asthma is associated with increased risks, while better-controlled asthma is associated with decreased risks. It is safer for pregnant women who have asthma to be treated with asthma medications than to have asthma symptoms and exacerbations. Monitoring and making appropriate adjustments in

therapy may be required to maintain lung function and, hence, blood oxygenation that ensures oxygen supply to the fetus.

The following is a summary of the recommendations made in the 2004 update. See that report for evidence reviews.

- **Monitoring of asthma status during prenatal visits is encouraged.** Because the course of asthma improves for about one-third of women and worsens for about one-third of women during pregnancy, monthly evaluations of asthma history and pulmonary function (spirometry is preferred, but measurement with a peak flow meter is generally sufficient) are recommended. This evaluation will allow the opportunity to step down treatment, if possible, or to increase treatment if necessary.

- **Albuterol is the preferred SABA** because it has an excellent safety profile and the most data related to safety during human pregnancy are available for this medication.

- **ICSs are the preferred treatment for long-term control medication. Budesonide is the preferred ICS because more data are available on using budesonide in pregnant women than are available on other ICSs, and the data are reassuring.** Preference for ICSs is based on strong data on effectiveness in nonpregnant women as well as effectiveness and safety data in pregnant women; the data show no increased risk of adverse perinatal outcomes. Although budesonide is the preferred ICS, it is important to note that no data indicate that the other ICS preparations are unsafe during pregnancy. Cromolyn has an excellent safety profile but has limited effectiveness compared with ICSs. Minimal published data are available on the use of LTRAs during pregnancy; however, animal safety data submitted to the FDA are reassuring. Data are limited describing the effectiveness and/or safety of LABAs during pregnancy, although there is justification for expecting LABAs to have a safety profile similar to that of albuterol, for which there are data related to safety during pregnancy.

- **For the treatment of comorbid conditions, intranasal corticosteroids are recommended for treatment of allergic rhinitis because they have a low risk of systemic effect. LTRAs can also be used, but minimal data are available on their use during pregnancy. The current second-generation antihistamines of choice are loratadine or cetirizine.**

For more information, see the NAEPP "Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004" (NAEPP 2005).

Racial and Ethnic Disparity in Asthma

The Expert Panel recommends heightened awareness of cultural barriers between the clinician and patient that may influence asthma management as well as modification of educational/communication strategies to address these barriers (Evidence D) (See "Component 3: Education for a Partnership in Asthma Care.").

Aggressive efforts have been made to understand better the growing problem of racial and ethnic disparity in asthma. It has been documented that racial and ethnic minorities

tend to receive lower quality health care than whites even when insurance status, age, income, and severity of conditions are comparable (Institute of Medicine 2002). The paradox is that, despite our increased understanding of asthma and the availability of highly effective drugs for controlling asthma, no substantial improvement in asthma morbidity and mortality has occurred among certain racial and ethnic minority populations. Multiple initiatives have been launched recently to develop strategies to eliminate disparities in asthma care that are based on race and culture (AHRQ 2003; NIH 2004). Assessment of asthma status, health care use, and processes of asthma care among children in managed Medicaid programs demonstrated that Black and Hispanic children had worse asthma than white children, but the minorities used less anti-inflammatory medication (Lieu et al. 2002). This study and other studies suggest that underutilization of preventive therapy, especially ICSs, contributes to disparities in asthma and care for asthma (Halterman et al. 2000, 2002; Ortega et al. 2002; Warman et al. 2001). These studies suggest that lack of adherence—due to cost, inadequate literacy, or multiple competing priorities for the patient—may contribute to underuse of medication, but other factors are equally important.

Less than optimal use of preventive asthma medications may be due to nonfinancial barriers to optimal asthma care. A study of Medicaid pediatric patients who have asthma showed that black and hispanic children were much less likely than whites to receive followup care in a timely fashion after being seen in the ED for asthma (Shields et al. 2004), demonstrating important differences in the process of care. A prospective cohort study of Medicaid-insured children who had asthma found that practice-site policies predicted higher quality care for these children; policies included presence of ethnically diverse or bilingual clinicians, cross-cultural or diversity training, continuity in care, and use of feedback to clinicians about prescribing of medication (Lieu et al. 2004). Such observations have stimulated great interest in the study of culturally influenced health beliefs and attitudes, demonstrated the importance of cultural competency for health care providers, and shown the need for improved communication between provider and patient or family regarding use of asthma medication.

A large proportion of ethnic and racial minorities live in urban areas where exposure to indoor allergens (e.g., cockroach and mold) can be high; efforts to mitigate these allergens can reduce symptoms successfully and significantly for urban children who have asthma (Morgan et al. 2004).

Multivariate analysis models have been used in an attempt to disentangle the effects of race, ethnicity, income, and other individual-level risk factors that influence the expression of asthma in various populations. The influence of race versus socioeconomic status on asthma morbidity and mortality remains controversial. Some studies suggest that differences in patterns of asthma-related health care are driven largely by ethnicity and only partially by financial barriers (Boudreaux et al. 2003; Grant et al. 2000; Higgins et al. 2005; Miller 2000; Zoratti et al. 1998). On the other hand, some studies suggest that low socioeconomic status, not race, is largely responsible for poor asthma health outcomes and health care-seeking behavior (Apter et al. 1997; Haas et al. 1994).

Accumulating evidence suggests that biological and pathophysiological differences between ethnic groups may contribute to racial and ethnic disparities in the expression of asthma, and these differences may be independent of socioeconomic and educational influences. For example, there appears to be a significant racial difference between total

serum IgE and airway hyperresponsiveness, and a significant positive relationship between total serum IgE and reactivity to methacholine has been demonstrated in White children but not in Black children (Joseph et al. 2000). This difference supports the hypothesis that Black children may be predisposed to more severe asthma or that racial differences may predispose to more severe asthma.

While biological and pathophysiological differences between population groups may contribute to the heterogeneity of asthma and its variable expression, gene by environmental influences are not exclusive variables that affect the expression of this disease. The significance of social and geographical environmental differences and the significance of ethnocultural influences on the expression of asthma warrant additional investigations, especially with regard to their effect on asthma outcomes and asthma disparities.

Hispanic populations are characterized by diverse racial, ethnic, national, and cultural expressions. Among Hispanics, the highest mortality rates from asthma occur among Puerto Ricans, followed by Cuban Americans and Mexican Americans (Homa et al. 2000; Sly 2006). These differences cannot be explained by geographic location; neither can they be explained by other demographic variables (Ledogar et al. 2000). Our evolving understanding of the natural history of asthma may eventually confirm or challenge some current notions about how asthma is expressed in various populations.

References

Agency for Healthcare Research and Quality (AHRQ). *National Healthcare Disparities Report* (AHRQ 2003). Rockville, MD, Agency for Healthcare Research and Quality (AHRQ), July 2003.

Anderson SD. Single-dose agents in the prevention of exercise-induced asthma: a descriptive review. *Treat Respir Med* 2004;3(6):365–79.

Anderson SD, Brannan JD. Long-acting beta$_2$-adrenoceptor agonists and exercise-induced asthma: lessons to guide us in the future. *Paediatr Drugs* 2004;6(3):161–75.

Anderson SD, Fitch K, Perry CP, Sue-Chu M, Crapo R, McKenzie D, Magnussen H. Responses to bronchial challenge submitted for approval to use inhaled beta$_2$-agonists before an event at the 2002 Winter Olympics. *J Allergy Clin Immunol* 2003;111(1):45–50.

Apter AJ, Reisine ST, Kennedy DG, Cromley EK, Keener J, ZuWallack RL. Demographic predictors of asthma treatment site: outpatient, inpatient, or emergency department. *Ann Allergy Asthma Immunol* 1997;79(4):353–61.

Beuther DA, Martin RJ. Efficacy of a heat exchanger mask in cold exercise-induced asthma. *Chest* 2006;129(5):1188–93.

Boudreaux ED, Emond SD, Clark S, Camargo CA Jr. Acute asthma among adults presenting to the emergency department: the role of race/ethnicity and socioeconomic status. *Chest* 2003;124(3):803–12.

Carlsen KH, Carlsen KC. Exercise-induced asthma. *Paediatr Respir Rev* 2002;3(2):154–60.

Chhabra SK, Ojha UC. Late asthmatic response in exercise-induced asthma. *Ann Allergy Asthma Immunol* 1998;80(4):323–7.

de Bisschop C, Guenard H, Desnot P, Vergeret J. Reduction of exercise-induced asthma in children by short, repeated warm ups. *Br J Sports Med* 1999;33(2):100–4.

Edmunds AT, Tooley M, Godfrey S. The refractory period after exercise-induced asthma: its duration and relation to the severity of exercise. *Am Rev Respir Dis* 1978;117(2):247–54.

EPR—2. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

Ferrari M, Segattini C, Zanon R, Bertaiola M, Balestreri F, Brotto E, Lo Cascio V. Comparison of the protective effect of formoterol and of salmeterol against exercise-induced bronchospasm when given immediately before a cycloergometric test. *Respiration* 2002;69(6):509–12.

Grant EN, Lyttle CS, Weiss KB. The relation of socioeconomic factors and racial/ethnic differences in US asthma mortality. *Am J Public Health* 2000;90(12):1923–5.

Haas JS, Cleary PD, Guadagnoli E, Fanta C, Epstein AM. The impact of socioeconomic status on the intensity of ambulatory treatment and health outcomes after hospital discharge for adults with asthma. *J Gen Intern Med* 1994;9(3):121–126.

Halterman JS, Aligne CA, Auinger P, McBride JT, Szilagyi PG. Inadequate therapy for asthma among children in the United States. *Pediatrics* 2000;105(1 Pt 3):272–6.

Halterman JS, Yoos HL, Kaczorowski JM, McConnochie K, Holzhauer RJ, Conn KM, Lauver S, Szilagyi PG. Providers underestimate symptom severity among urban children with asthma. *Arch Pediatr Adolesc Med* 2002;156(2):141–6.

Higgins PS, Wakefield D, Cloutier MM. Risk factors for asthma and asthma severity in nonurban children in Connecticut. *Chest* 2005;128(6):3846–53.

Homa DM, Mannino DM, Lara M. Asthma mortality in U.S. Hispanics of Mexican, Puerto Rican, and Cuban heritage, 1990–1995. *Am J Respir Crit Care Med* 2000;161(2 Pt 1):504–9.

Huggins JT, Kaplan A, Martin-Harris B, Sahn SA. Eucalyptus as a specific irritant causing vocal cord dysfunction. *Ann Allergy Asthma Immunol* 2004;93(3):299–303.

Institute of Medicine. *Unequal Tretment: Confronting Racial and Ethnic Disparities in Health Care.* Smedley BD, Stith AY, Nelson AR (eds.). Washington, DC: National Academies Press, 2002.

Jarjour NN, Calhoun WJ. Exercise-induced asthma is not associated with mast cell activation or airway inflammation. *J Allergy Clin Immunol* 1992;89(1 Pt 1):60–8.

Joseph CL, Ownby DR, Peterson EL, Johnson CC. Racial differences in physiologic parameters related to asthma among middle-class children. *Chest* 2000;117(5):1336–44.

Kingston HG, Hirshman CA. Perioperative management of the patient with asthma. *Anesth Analg* 1984;63(9):844–55. Review.

Ledogar RJ, Penchaszadeh A, Garden CC, Iglesias G. Asthma and Latino cultures: different prevalence reported among groups sharing the same environment. *Am J Public Health* 2000;90(6):929–35.

Lieu TA, Finkelstein JA, Lozano P, Capra AM, Chi FW, Jensvold N, Quesenberry CP, Farber HJ. Cultural competence policies and other predictors of asthma care quality for Medicaid-insured children. *Pediatrics* 2004;114(1):e102–10.

Lieu TA, Lozano P, Finkelstein JA, Chi FW, Jensvold NG, Capra AM, Quesenberry CP, Selby JV, Farber HJ. Racial/ethnic variation in asthma status and management practices among children in managed Medicaid. *Pediatrics* 2002;109(5):857–65.

Mastalerz L, Gawlewicz-Mroczka A, Nizankowska E, Cmiel A, Szczeklik A. Protection against exercise-induced bronchoconstriction by montelukast in aspirin-sensitive and aspirin-tolerant patients with asthma. *Clin Exp Allergy* 2002;32(9):1360–5.

McFadden ER Jr, Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994;330(19):1362–7.

McKenzie DC, Stewart IB, Fitch KD. The asthmatic athlete, inhaled beta agonists, and performance. *Clin J Sport Med* 2002;12(4):225–8.

Miller JE. The effects of race/ethnicity and income on early childhood asthma prevalence and health care use. *Am J Public Health* 2000;90(3):428–30.

Moraes TJ, Selvadurai H. Management of exercise-induced bronchospasm in children: the role of leukotriene antagonists. *Treat Respir Med* 2004;3(1):9–15. Review.

Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R III, Stout J, Malindzak G, Smartt E, Plaut M, et al.; Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351(11):1068–80.

National Asthma Education Prevention Program (NAEPP). *Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004 (*NAEPP 2005). NIH Publication No. 05-5236. Rockville, MD, U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, March 2005. Available at http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm.

National Institutes of Health (NIH). *Strategic Plan and Budget To Reduce and Ultimately Eliminate Health Disparities, Vol. I: Fiscal Years 2002–2006* (NIH 2004). Bethesda, MD, National Institutes of Health, 2004. Available at http://ncmhd.nih.gov/our_programs/strategic/pubs/VolumeI_031003EDrev.pdf.

Newnham DM, Ingram CG, Earnshaw J, Palmer JB, Dhillon DP. Salmeterol provides prolonged protection against exercise-induced bronchoconstriction in a majority of subjects with mild, stable asthma. *Respir Med* 1993;87(6):439–44.

Nishiyama T, Hanaoka K. Propofol-induced bronchoconstriction: two case reports. *Anesth Analg* 2001;93(3):645–6.

Ortega AN, Gergen PJ, Paltiel AD, Bauchner H, Belanger KD, Leaderer BP. Impact of site of care, race, and Hispanic ethnicity on medication use for childhood asthma. *Pediatrics* 2002;109(1):E1.

Richter K, Janicki S, Jorres RA, Magnussen H. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. *Eur Respir J* 2002;19(5):865–71.

Shapiro GS, Yegen U, Xiang J, Kottakis J, Della Cioppa G. A randomized, double-blind, single-dose, crossover clinical trial of the onset and duration of protection from exercise-induced bronchoconstriction by formoterol and albuterol. *Clin Ther* 2002;24(12):2077–87.

Shields AE, Comstock C, Weiss KB. Variations in asthma care by race/ethnicity among children enrolled in a state Medicaid program. *Pediatrics* 2004;113(3 Pt 1):496–504.

Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997;99(5):655–9.

Slater JE. Latex allergy. *J Allergy Clin Immunol* 1994;94(2 Pt 1):139–49; quiz 150.

Sly RM. Decreases in Hispanic and non-Hispanic asthma mortality. *Ann Allergy Asthma Immunol* 2006;96(1):76–9.

Spooner CH, Spooner GR, Rowe BH. Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction. *Cochrane Database Syst Rev* 2003;(4):CD002307.

Steinshamn S, Sandsund M, Sue-Chu M, Bjermer L. Effects of montelukast on physical performance and exercise economy in adult asthmatics with exercise-induced bronchoconstriction. *Scand J Med Sci Sports* 2002;12(4):211–7.

Sullivan MD, Heywood BM, Beukelman DR. A treatment for vocal cord dysfunction in female athletes: an outcome study. *Laryngoscope* 2001;111(10):1751–5.

Sussman GL, Beezhold DH. Allergy to latex rubber. *Ann Intern Med* 1995;122(1):43–6. Review.

Tan RA, Spector SL. Exercise-induced asthma: diagnosis and management. *Ann Allergy Asthma Immunol* 2002;89(3):226–35; quiz 235–7, 297.

Todd GR, Acerini CL, Buck JJ, Murphy NP, Ross-Russell R, Warner JT, McCance DR. Acute adrenal crisis in asthmatics treated with high-dose fluticasone propionate. *Eur Respir J* 2002a;19(6):1207–9.

Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002b;87(6):457–61.

Vathenen AS, Knox AJ, Wisniewski A, Tattersfield AE. Effect of inhaled budesonide on bronchial reactivity to histamine, exercise, and eucapnic dry air hyperventilation in patients with asthma. *Thorax* 1991;46(11):811–6.

Vidal C, Fernandez-Ovide E, Pineiro J, Nunez R, Gonzalez-Quintela A. Comparison of montelukast versus budesonide in the treatment of exercise-induced bronchoconstriction. *Ann Allergy Asthma Immunol* 2001;86(6):655–8.

Warman KL, Silver EJ, Stein RE. Asthma symptoms, morbidity, and antiinflammatory use in inner-city children. *Pediatrics* 2001;108(2):277–82.

Zoratti EM, Havstad S, Rodriguez J, Robens-Paradise Y, Lafata JE, McCarthy B. Health service use by African Americans and Caucasians with asthma in a managed care setting. *Am J Respir Crit Care Med* 1998;158(2):371–7.

SECTION 5, MANAGING EXACERBATIONS OF ASTHMA

KEY POINTS: MANAGING EXACERBATIONS OF ASTHMA

- Early treatment of asthma exacerbations is the best strategy for management. Important elements of early treatment at the patient's home include (EPR—2 1997):

  — Patient education, including a written asthma action plan to guide patient self-management of exacerbations at home, especially for patients who have moderate or severe persistent asthma and any patient who has a history of severe exacerbations (Evidence B). A peak-flow-based plan may be particularly useful for patients who have difficulty perceiving airflow obstruction and worsening asthma (Evidence D).

  — Recognition of early signs of worsening asthma and taking prompt action (Evidence A).

  — Appropriate intensification of therapy by increasing inhaled short-acting beta$_2$-agonist (SABA) and, in some cases, adding a short course of oral systemic corticosteroids (Evidence A).

  — Removal or withdrawal of the environmental factor contributing to the exacerbation.

  — Prompt communication between patient and clinician about any serious deterioration in symptoms or peak flow, decreased responsiveness to SABAs, or decreased duration of effect.

- Management of asthma exacerbations requiring urgent medical care (e.g., in the urgent care setting or emergency department (ED)) includes:

  — Oxygen to relieve hypoxemia in moderate or severe exacerbations (EPR—2 1997).

  — SABA to relieve airflow obstruction, with addition of inhaled ipratropium bromide in severe exacerbations (Evidence A).

  — Systemic corticosteroids to decrease airway inflammation in moderate or severe exacerbations or for patients who fail to respond promptly and completely to a SABA (Evidence A).

  — Consideration of adjunct treatments, such as intravenous magnesium sulfate or heliox, in severe exacerbations unresponsive to the initial treatments listed above (Evidence B).

  — Monitoring response to therapy with serial measurements of lung function (Evidence B).

  — Preventing relapse of the exacerbation or recurrence of another exacerbation by providing: referral to followup asthma care within 1–4 weeks; an ED asthma discharge plan with instructions for medications prescribed at discharge and for increasing medications or seeking medical care if asthma worsens; review of inhaler techniques whenever possible; and consideration of initiating inhaled corticosteroids (ICSs) (Evidence B).

KEY DIFFERENCES FROM 1997 AND 2002 EXPERT PANEL REPORTS

- For the assessment of exacerbations, the current update (EPR—3: Full Report 2007):
  - Simplifies classification of severity of asthma exacerbations.
  - Reinstates, for use in the urgent or emergency care setting, the 1991 cut points of forced expiratory volume in 1 second (FEV_1) or peak expiratory flow (PEF) to indicate the goal for discharge from the urgent care or emergency care setting (≥70 percent predicted FEV_1 or PEF); patients for whom response to therapy is incomplete and who usually require continued treatment in the ED (40–69 percent predicted); and the exacerbation severity level where adjunct therapies may be considered (<40 percent predicted). These cut points differ from those used to determine long-term asthma control and treatments, thus underscoring the distinction between acute and chronic asthma management.
  - Acknowledges the limited value of pulmonary function measures in very severe exacerbations.
- For the treatment of exacerbations, the current update:
  - Adds levalbuterol as a SABA treatment for asthma exacerbations.
  - For home management of exacerbations, no longer recommends doubling the dose of ICSs.
  - For prehospital management (e.g., emergency transport), encourages standing orders for albuterol and—for prolonged transport—repeated treatments and protocols to allow consideration of ipratropium and oral corticosteroids.
  - For ED management, reduces dose and frequency of administration of oral corticosteroids in severe exacerbations, adds consideration of magnesium sulfate or heliox for severe exacerbations, and adds consideration of initiating an ICS upon discharge.
  - For hospital management, no longer recommends ipratropium bromide.

—

Introduction

In this section, recommendations are presented for the assessment and treatment of exacerbations in the home, ED, and hospital. See section 1, “Overall Methods Used To Develop This Report,” for literature search strategy and tally of results for this EPR—3: Full Report 2007 section on “Managing Exacerbations of Asthma.” Four Evidence Tables were prepared: 17, Increasing the Dose of Inhaled Corticosteroids; 18, IV Aminophylline; 19, Magnesium Sulfate; and 20, Heliox.

Asthma exacerbations are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness—or some combination of these symptoms.

Exacerbations are characterized by decreases in expiratory airflow that can be documented and quantified by simple measurement of lung function (spirometry or PEF). These objective measures more reliably indicate the severity of an exacerbation than does the severity of symptoms. In general, milder exacerbations may be managed "at home" (i.e., outside the health care system), whereas more serious exacerbations may require an unscheduled ("urgent") office visit, an ED visit, or a hospital admission (see figure 5–1). The most severe exacerbations require admission to the intensive care unit (ICU) for optimal monitoring and treatment. Although assessment and treatment of young children pose unique challenges, the management of asthma exacerbations in older children and adults is fairly similar.

Individuals who have their asthma under control with ICSs will decrease the risk of exacerbations. Nonetheless, patients in good control can still be vulnerable to exacerbations, for example, when they have clinical respiratory infections (Reddel et al. 1999). Diurnal variability, a marker of poor control, may not change during an exacerbation; thus, clinicians may fail to detect important changes in lung function. The striking difference between PEF

FIGURE 5–1. CLASSIFYING SEVERITY OF ASTHMA EXACERBATIONS IN THE URGENT OR EMERGENCY CARE SETTING

Note: Patients are instructed to use quick-relief medications if symptoms occur or if PEF drops below 80 percent predicted or personal best. If PEF is 50–79 percent, the patient should monitor response to quick-relief medication carefully and consider contacting a clinician. If PEF is below 50 percent, immediate medical care is usually required. In the urgent or emergency care setting, the following parameters describe the severity and likely clinical course of an exacerbation.

	Symptoms and Signs	Initial PEF (or FEV_1)	Clinical Course
Mild	Dyspnea only with activity (assess tachypnea in young children)	PEF ≥70 percent predicted or personal best	■ Usually cared for at home ■ Prompt relief with inhaled SABA ■ Possible short course of oral systemic corticosteroids
Moderate	Dyspnea interferes with or limits usual activity	PEF 40–69 percent predicted or personal best	■ Usually requires office or ED visit ■ Relief from frequent inhaled SABA ■ Oral systemic corticosteroids; some symptoms last for 1–2 days after treatment is begun
Severe	Dyspnea at rest; interferes with conversation	PEF <40 percent predicted or personal best	■ Usually requires ED visit and likely hospitalization ■ Partial relief from frequent inhaled SABA ■ Oral systemic corticosteroids; some symptoms last for >3 days after treatment is begun ■ Adjunctive therapies are helpful
***Subset:* Life threatening**	Too dyspneic to speak; perspiring	PEF <25 percent predicted or personal best	■ Requires ED/hospitalization; possible ICU ■ Minimal or no relief from frequent inhaled SABA ■ Intravenous corticosteroids ■ Adjunctive therapies are helpful

Key: ED, emergency department; FEV_1, forced expiratory volume in 1 second; ICU, intensive care unit; PEF, peak expiratory flow; SABA, short-acting $beta_2$-agonist

variations during exacerbations, as compared with during poor asthma control, suggests differences in $beta_2$-adrenoceptor function between these conditions. The decrease in responsiveness to SABA during some severe exacerbations may help to explain the benefit of ipratropium bromide and other "alternative" approaches to bronchodilation.

General Considerations

Based on the scientific literature and the opinion of the Expert Panel, the Panel recommends that clinicians consider the following general principles and goals for managing asthma exacerbations: early treatment, special attention to patients who are at high risk of asthma-related death, and special attention to infants (EPR—2 1997).

- **Early treatment is the best strategy for management of asthma exacerbations. Important elements of early treatment include:**
  - **A written asthma action plan** (See "Component 2: Education for a Partnership in Asthma Care," figure 3–10) to guide patient self-management, especially for patients who have moderate or severe persistent asthma and any patient who has a history of severe exacerbations.
  - **Recognition of early indicators of an exacerbation, including worsening PEF.** Patients are instructed to recognize early signs and symptoms of worsening asthma and to use quick-relief medications if symptoms occur or if PEF drops below 80 percent predicted or personal best. If PEF is 50–79 percent, the patient should carefully monitor the response to quick-relief medication and, based on the response, consider contacting a clinician. If PEF is below 50 percent, immediate medical care is usually required (See sample written asthma action plans, figures 3–10a, b, and c.). In the urgent or emergency care setting, different parameters are used to classify the severity of the exacerbation and determine the clinical course; see figure 5–1. The Panel chose cut points of 40 percent and 70 percent of predicted (or personal best) because 40 percent denotes an exacerbation severity below which several adjunct therapies are effective, and 70 percent is a posttreatment goal for discharge from the ED or hospital.
  - **Appropriate intensification of therapy, often including a short course of systemic corticosteroids.**
  - **Removal of or withdrawal from allergens or precipitating irritants in the environment that may be contributing to the exacerbation.**
  - **Prompt communication between patient and clinician about any serious deterioration in symptoms or peak flow, decreased responsiveness to SABA treatment, or decreased duration of effect.**
- **Patients who are at high risk for asthma-related death require special attention—** particularly intensive education, monitoring, and care. Such patients should be counseled to seek medical care early during an exacerbation and instructed about the availability of ambulance services. Such patients include those who have identifiable risk factors (See figure 5–2a.).
- **Infants require special attention,** especially due to their greater risk for respiratory failure (See figure 5–2b.).

FIGURE 5–2a. RISK FACTORS FOR DEATH FROM ASTHMA

Asthma history

Previous severe exacerbation (e.g., intubation or ICU admission for asthma)
Two or more hospitalizations for asthma in the past year
Three or more ED visits for asthma in the past year
Hospitalization or ED visit for asthma in the past month
Using >2 canisters of SABA per month
Difficulty perceiving asthma symptoms or severity of exacerbations
Other risk factors: lack of a written asthma action plan, sensitivity to *Alternaria*

Social history

Low socioeconomic status or inner-city residence
Illicit drug use
Major psychosocial problems

Comorbidities

Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease

Key: ED, emergency department; ICU, intensive care unit; SABA, short-acting beta$_2$-agonist

Sources: Abramson et al. 2001; Greenberger et al. 1993; Hardie et al. 2002; Kallenbach et al. 1993; Kikuchi et al. 1994; O'Hollaren et al. 1991; Rodrigo and Rodrigo 1993; Strunk and Mrazek 1986; Suissa et al. 1994

FIGURE 5–2b. SPECIAL CONSIDERATIONS FOR INFANTS

- Assessment depends on physical examination rather than objective measurements. Use of accessory muscles, inspiratory and expiratory wheezing, paradoxical breathing, cyanosis, and a respiratory rate >60 are key signs of serious distress.
- Objective measurements, such as oxygen saturation (SaO_2) of <90 percent, also indicate serious distress.
- Response to SABA therapy can be variable and may not be a reliable predictor of satisfactory outcome. However, because infants are at greater risk for respiratory failure, a lack of response noted by either physical examination or objective measurements should be an indication for hospitalization.
- Use of oral systemic corticosteroids early in the episode is essential but should not substitute for careful assessment by a physician.
- Most acute wheezing episodes result from viral infections and may be accompanied by fever. Antibiotics generally are not required.

Key: SABA, short-acting $beta_2$-agonist

Source: EPR—2 1997.

—

Treatment Goals

The principal goals and Expert Panel recommendations for treating asthma exacerbations are:

- **Correction of significant hypoxemia,** in moderate or severe exacerbations, by administering supplemental oxygen. In rare instances, alveolar hypoventilation requires mechanically assisted ventilation (EPR—2 1997).
- **Rapid reversal of airflow obstruction (Evidence A).** This is best achieved by:

  — Repetitive or continuous administration of a SABA (Camargo et al. 2003b; Karpel et al. 1997; McFadden 2003; Travers et al. 2001)

  AND

  — Early in the course of treatment, administration of systemic corticosteroids to patients who have moderate or severe exacerbations or to patients who fail to respond promptly and completely to SABA treatment (McFadden 2003; Rachelefsky 2003; Rowe et al. 2004).
- **Reduction of the likelihood of relapse of the exacerbation or future recurrence of severe airflow obstruction by intensifying therapy (Evidence A)**. Often, a short course of systemic corticosteroids is useful (Rachelefsky 2003; Rowe et al. 2004).

- **Achieving these goals requires careful assessment and monitoring (Evidence B).** The ability to predict care requirements, including the need for hospitalization, is based on repeated clinical assessments. In adults, repeated measurements of lung function are often helpful. The specific measurements chosen for monitoring will depend on the age of the patient and the available resources.

  — **Children.** In children, no single assessment tool appears to be the best for assessing the severity of the exacerbation or for monitoring response to treatment and predicting hospital admission (Chey et al. 1999; Gorelick et al. 2004a,b; Keahey et al. 2002; Keogh et al. 2001; Smith et al. 2002; Sole et al. 1999; Wright et al. 1997).

    - **Serial measurements of lung function.** Lung function measures using either FEV_1 or PEF may be useful for many children 5 years of age or older. However, neither maneuver may be obtainable during an exacerbation. Gorelick and colleagues (2004a) found that only 65 percent of children 5–18 years of age could complete either measurement during an acute exacerbation, and for children less than 5 years old, the maneuvers were almost impossible.

    - **Pulse oximetry.** An initial pulse oximetry in infants and young children might be useful for assessing exacerbation severity but not for predicting the need for hospital admission (Keahey et al. 2002; Kelly et al. 2004; Keogh et al. 2001; Sole et al. 1999; Wright et al. 1997). However, a repeat pulse oximetry of <92–94 percent (sea level) at 1 hour was a better predictor of need for hospitalization, and it may be useful to move those infants and children into the hospital and out of the ED at that time (Kelly et al. 2004; Sole et al. 1999; Wright et al. 1997).

    - **Signs and symptoms scores.** Several severity assessment scores have been developed and tested in children to help predict the need for hospitalization early in the course of ED treatment (Gorelick et al. 2004b; Keogh et al. 2001; Rodrigo and Rodrigo 1998b; Smith et al. 2002). None is 100 percent predictive, but the assessments may help to determine who should be transferred from the ED to the hospital after an initial 1- to 2-hour period of treatment, leaving the ED resources for those who are more likely to be able to go home after extended ED treatment and observation. These assessment scores combine physician- or nurse-observed signs and symptoms—such as shortness of breath, chest tightness, ability to speak in sentences or phrases, emotional impact, and alertness—plus respiratory rate, use of intercostals muscles, timing and volume of wheezes as well as pulse oximetry and, if available and feasible, FEV_1 or PEF. One score (Gorelick et al. 2004b) has added a parental assessment of asthma control over the past several months and history of previous exacerbations requiring ED or hospital management. Others add the continuing need for hourly SABA 4 or more hours after the administration of oral systemic corticosteroids.

      A recent study suggests that most children who require hospitalization can be identified by a repeat assessment 1 hour after initial treatment (Kelly et al. 2004). After 1 hour, those children who continue to meet the criteria for a severe exacerbation have >86 percent chance of requiring hospitalization; those who meet the criteria for moderate exacerbation at 1 hour have an 84 percent chance of requiring hospitalization; and those whose assessment has remained the same or dropped to the mild level have only an 18 percent chance of requiring hospitalization. These severity assessment studies highlight the importance of regular, multifaceted assessments and close observation of children and adolescents who present to the office or ED with acute asthma exacerbations (See figures 5–1 and 5–3.).

FIGURE 5–3. FORMAL EVALUATION OF ASTHMA EXACERBATION SEVERITY IN THE URGENT OR EMERGENCY CARE SETTING

	Mild	Moderate	Severe	Subset: Respiratory Arrest Imminent
Symptoms				
Breathlessness	While walking Can lie down	While at rest (infant—softer, shorter cry, difficulty feeding) Prefers sitting	While at rest (infant—stops feeding) Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Increased	Increased Guide to rates of breathing in awake children: *Age* <2 months 2–12 months 1–5 years 6–8 years	Often >30/minute *Normal rate* <60/minute <50/minute <40/minute <30/minute	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate, often only end expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse/minute	<100	100–120 Guide to normal pulse rates in children:: *Age* 2–12 months 1–2 years 2–8 years	>120 *Normal rate* <160/minute <120/minute <110/minute	Bradycardia
Pulsus paradoxus	Absent <10 mmHg	May be present 10–25 mmHg	Often present >25 mmHg (adult) 20–40 mmHg (child)	Absence suggests respiratory muscle fatigue
Functional Assessment				
PEF percent predicted or percent personal best	≥70 percent	Approx. 40–69 percent or response lasts <2 hours	<40 percent	<25 percent Note: PEF testing may not be needed in very severe attacks
PaO_2 (on air)	Normal (test not usually necessary)	≥60 mmHg (test not usually necessary)	<60 mmHg: possible cyanosis	
and/or PCO_2	<42 mmHg (test not usually necessary)	<42 mmHg (test not usually necessary)	≥42 mmHg: possible respiratory failure (See pages 393–394, 399.)	
SaO_2 percent (on air) at sea level	>95 percent (test not usually necessary)	90–95 percent (test not usually necessary)	<90 percent	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

Key: PaO_2, arterial oxygen pressure; PCO_2, partial pressure of carbon dioxide; PEF, peak expiratory flow; SaO_2, oxygen saturation

Notes:

- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides (Cham et al. 2002; Chey et al. 1999; Gorelick et al. 2004b; Karras et al. 2000; Kelly et al. 2002b and 2004; Keogh et al. 2001; McCarren et al. 2000; Rodrigo and Rodrigo 1998b; Rodrigo et al. 2004; Smith et al. 2002).
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and followup (Ritz et al. 2000; Strunk and Mrazek 1986; von Leupoldt and Dahme 2005).

— **Adults**

- **Serial measurements of lung function.** FEV_1 or PEF appear to be more useful in adults for categorizing the severity of the exacerbation and the response to treatment and in predicting the need for hospitalization. Repeated measurements of PEF or FEV_1 in adults at 1 hour and beyond are useful as isolated assessments in determining who will require hospitalization and who is likely to have sufficient response to treatment to allow continued ED care. Indeed, repeated FEV_1 or PEF measures at presentation to the ED and 1 hour after treatment were the strongest single predictor of hospitalization among adults who present to the ED with an asthma exacerbation (Karras et al. 2000; Kelly et al. 2004; McCarren et al. 2000; Rodrigo et al. 2004; Weber et al. 2002).

  When FEV_1 is unavailable, PEF may be substituted. Although percentage of personal best PEF or FEV_1 would be ideal for patient management, individuals may report erroneous values (Diner et al. 2001). Interpretation of percentage of predicted values is complicated by differences between formulas in the literature (Radeos and Camargo 2004). Regardless of the calculation chosen, for severe exacerbations with obvious airway compromise and even cyanosis, the immediate testing of FEV_1 or PEF provides little additional information, and the maneuver can be very uncomfortable for acutely ill patients (Kelly et al. 2004).

- **Pulse oximetry** is indicated for patients who are in severe distress, have FEV_1 or PEF <40 percent of predicted, or are unable to perform lung function measures.

- **Signs and symptoms scores.** As in children, some multifaceted prediction models have been tested and shown to improve slightly on the accuracy of the FEV_1 or PEF alone (Chey et al. 1999; Kelly et al. 2002b and 2004; McFadden 2003; Weber et al. 2002). Kelly and colleagues (2004) used multiple signs and symptoms to determine the level of the severity of the exacerbation at 1 hour after the first ED treatment as well as the duration of symptoms (either <6 hours or ≥6 hours) before the patient's arrival at the ED (Kelly et al. 2002b) and found the additional measures improved the prediction rate by 5–10 percent. (See paragraph above related to the same model used in children.) For EDs that have limited resources, the presence of drowsiness in a patient is a useful predictor of impending respiratory failure and reason to consider immediate transfer of the patient to a facility equipped to deal with ventilatory support (Cham et al. 2002). As in the case with children, the ability to predict future care requirements is based on repeated clinical assessments, and, in adults, repeated measures of FEV_1 or PEF (See figure 5–3.).

Home Management of Asthma Exacerbations

Beginning treatment at home avoids treatment delays, prevents exacerbations from becoming severe, and also adds to patients' sense of control over their asthma. The degree of care provided in the home depends on the patients' (or parents') abilities and experience and on the availability of emergency care. General guidelines for managing exacerbations at home are presented in figure 5–4.

The Expert Panel recommends preparing patients for home management of asthma exacerbations by taking the following actions (Also see "Component 1: Measures of Asthma Assessment and Monitoring," and "Component 2: Education for a Partnership in Asthma Care.").

FIGURE 5–4. MANAGEMENT OF ASTHMA EXACERBATIONS: HOME TREATMENT

Assess Severity

- **Patients at high risk for a fatal attack (see figure 5–2a) require immediate medical attention after initial treatment.**
- Symptoms and signs suggestive of a more serious exacerbation such as marked breathlessness, inability to speak more than short phrases, use of accessory muscles, or drowsiness (see figure 5–3) should result in initial treatment while immediately consulting with a clinician.
- Less severe signs and symptoms can be treated initially with assessment of response to therapy and further steps as listed below.
- If available, measure PEF—values of 50–79% predicted or personal best indicate the need for quick-relief mediation. Depending on the response to treatment, contact with a clinician may also be indicated. Values below 50% indicate the need for immediate medical care.

Initial Treatment

- Inhaled SABA: up to two treatments 20 minutes apart of 2–6 puffs by metered-dose inhaler (MDI) or nebulizer treatments.
- Note: Medication delivery is highly variable. Children and individuals who have exacerbations of lesser severity may need fewer puffs than suggested above.

Good Response

No wheezing or dyspnea (assess tachypnea in young children).

PEF ≥80% predicted or personal best.

- Contact clinician for followup instructions and further management.
- May continue inhaled SABA every 3–4 hours for 24–48 hours.
- Consider short course of oral systemic corticosteroids.

Incomplete Response

Persistent wheezing and dyspnea (tachypnea).

PEF 50–79% predicted or personal best.

- Add oral systemic corticosteroid.
- Continue inhaled SABA.
- Contact clinician urgently (this day) for further instruction.

Poor Response

Marked wheezing and dyspnea.

PEF <50% predicted or personal best.

- Add oral systemic corticosteroid.
- Repeat inhaled SABA immediately.
- If distress is severe and nonresponsive to initial treatment:
  - —Call your doctor AND
  - —**PROCEED TO ED;**
  - —Consider calling 9–1–1 (ambulance transport).

- To ED.

Key: ED, emergency department; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting beta$_2$-agonist (quick-relief inhaler)

- **Teach all patients how to monitor signs and symptoms so they can recognize early signs of deterioration and take appropriate action (Evidence A)** (See "Component 2: Education for a Partnership in Asthma Care."), particularly since many fatal asthma exacerbations occur out of hospital (Krishnan et al. 2006). Patients should be taught how to adjust their medications early in an exacerbation (Kelly et al. 2002b) and when to call for further help or seek medical care. Patients should seek medical help earlier if the exacerbation is severe; treatment does not give rapid, sustained improvement; or there is further deterioration.

- **Consider teaching how to monitor lung function, by using PEF to facilitate early and accurate assessment of exacerbations and response to treatment, to patients and parents of children who have moderate or severe persistent asthma or a history of severe exacerbations (Evidence B) and patients who are poor perceivers of airflow obstruction (Evidence D).** Signs and symptoms imperfectly mirror airflow obstruction; therefore, other tools may be required, especially in the group of people who are "poor perceivers" and have failed to recognize previous exacerbations or symptom deteriorations early (Hardie et al. 2002; Kikuchi et al. 1994). Exacerbations recognized and treated within 6 hours of onset may be less likely to result in hospitalizations (Kelly et al. 2002b). When using PEF expressed only as a percent of personal best, the impact of any irreversible airflow obstruction must be considered. For example, in a person whose personal best is only 160 L/min, a drop to 60 percent of personal best represents life-threatening airflow obstruction.

- **Provide to all patients a written asthma action plan that includes daily management and recognizing and handling worsening asthma, including self-adjustment of medications in response to acute symptoms or changes in PEF measures in the event of an exacerbation. A written asthma action plan is particularly recommended for patients who have moderate or severe persistent asthma and any patient who has a history of severe exacerbations or poorly controlled asthma (Evidence B). A peak-flow-based plan may be particularly useful for patients who have difficulty perceiving airflow obstruction and worsening asthma (Evidence D). See component 2—Education for a Partnership in Asthma Care, figure 3–10 for a sample plan.** Children should also receive a plan appropriate to the school setting (See "Component 2: Education for a Partnership in Asthma Care," figure 3–16.). The plan should direct the patient to adjust medications in response to particular signs, symptoms, and peak flow measurements and should state when to seek medical help. Review the plan with the patient and family. The clinician should tailor the plan to the needs of individual patients. Patients who are at risk for asthma death (See figure 5–2a.) require especially close monitoring.

- **Advise patients who have moderate or severe persistent asthma or a history of severe exacerbations to have the medication (e.g., corticosteroid tablets or liquid) and equipment (e.g., peak flow meter, compressor-driven nebulizer for young children) for treating exacerbations at home (Evidence A).**

The Expert Panel recommends the following pharmacologic therapy for home management of exacerbations:

- **Increase the frequency of SABA treatment (Evidence A).**

- **Initiate oral systemic corticosteroid treatment under certain circumstances (Evidence A).** Short courses or "bursts" of oral corticosteroids reduce the duration and may

prevent hospitalizations and relapse following an acute exacerbation (McFadden 2003; Rachelefsky 2003; Rowe et al. 2004). **The Expert Panel recommends that, unless working from a defined action plan, individuals contact their health care provider before instituting a course of oral systemic corticosteroids (Evidence D).**

- **Doubling the ICS dose is not sufficient (Evidence B)** (See Evidence Table 17, Increasing the Dose of Inhaled Corticosteroids.). Doubling the dose of an ICS in those patients already receiving ICS therapy has not been effective at reducing the severity or preventing progression of exacerbations (FitzGerald et al. 2004; Garrett et al. 1998; Harrison et al. 2004; Rice-McDonald et al. 2005). However, higher doses of an ICS may be effective in the ED management of acute asthma exacerbations. For example, preliminary evidence indicates that quadrupling the dose of an ICS for 7 days, starting at the first appearance of worsening symptoms, may prevent exacerbations requiring oral systemic corticosteroids (Foresi et al. 2000). For patients who experience substantial adverse effects with oral systemic corticosteroids (e.g., mood changes, worsening diabetes), high-dose ICS may be an effective alternative for mild to moderate exacerbations.

- **Continue more intensive treatment for several days (EPR—2 1997).** Recovery from an exacerbation varies, with symptom relief in 1–2 days for moderate exacerbations but in 3 or more days for severe exacerbations (See figure 5–1.). For many persons, the improvement is quite gradual. Even when symptoms have resolved, evidence of inflammation in the airways may continue for up to 2–3 weeks (McFadden 1975). In managing an exacerbation at home, patients' greater use of SABA should be continued until symptoms and PEF are stable. That said, patients should seek medical care rather than rely on bronchodilator therapy in excessive doses or for prolonged periods (e.g., >12 puffs/day for more than 24 hours).

The Expert Panel does *not* recommend the following home management techniques, because no studies have demonstrated effectiveness, and it is the opinion of the Panel that these techniques may delay patients from obtaining necessary care (EPR—2 1997).

- Drinking large volumes of liquids or breathing warm, moist air (e.g., the mist from a hot shower).

- Using over-the-counter products such as antihistamines or cold remedies. Over-the-counter bronchodilators may provide transient bronchodilation, but their use should not delay seeking medical care.

The Expert Panel also notes that although pursed-lip and other forms of controlled breathing may help to maintain calm during respiratory distress, these methods do *not* bring about improvement in lung function.

Prehospital Management of Asthma Exacerbations

The Expert Panel recommends that emergency medical services (EMS) providers administer supplemental oxygen and SABA to patients who have signs or symptoms of an asthma exacerbation (Evidence A).

Prehospital administration of SABA reduces airflow obstruction and relieves symptoms (Fergusson et al. 1995; Markenson et al. 2004; Richmond et al. 2005). Ideally, all EMS providers would receive a standing order to allow them to provide albuterol to their patients who

have asthma exacerbations. Such an order would be consistent with their legally authorized scope of practice and local medical direction (Camargo 2006). In such settings, EMS providers should have available a nebulizer and/or an inhaler plus spacer/holding chamber for SABA administration (see figure 5–5 for dosages). If these are not available, subcutaneous epinephrine or terbutaline should be given for severe exacerbations (See figure 5–5.) (Sly et al. 1977; Smith et al. 1977).

When initiating bronchodilatory use, EMS personnel should not delay transport of the patient to the appropriate medical facility. The treatment, however, may be repeated *while* transporting the patient. Prolonged transport times (e.g., in a rural setting or during transport on congested urban streets) may necessitate multiple inhaled SABA treatments before arrival at the medical facility (Crago et al. 1998). Patients should receive a maximum of three inhaled SABA treatments in the first hour, and then one per hour thereafter (consistent with practice in the ED setting; see figures 5–5 and 5–6). After each treatment, EMS personnel should reassess and record the patient's vital signs and lung sounds.

Ambulance services should develop prehospital protocols for the treatment of acute asthma in children and adults (Markenson et al. 2004; Stead and Whiteside 1999). With medical oversight, these protocols can allow for more frequent administration of several established acute asthma treatments, such as ipratropium bromide and oral systemic corticosteroids (Knapp and Wood 2003). The latter medication is particularly important during prolonged transport times. All prehospital providers should receive training in how to respond to the clinical signs and symptoms of severe airway obstruction and imminent respiratory failure (Camargo 2006).

Emergency Department and Hospital Management of Asthma Exacerbations

Severe exacerbations of asthma are potentially life threatening. Care must be prompt. Effective initial therapies (i.e., SABA and the means of giving it by aerosol and a source of supplemental oxygen) should be available in a physician's office. Serious exacerbations, however, require close observation for deterioration, frequent treatment, and repetitive measurement of lung function. Therefore, most severe exacerbations of asthma require prompt transfer to an ED for more complete therapy (McFadden 2003; Rowe et al. 2001). Despite appropriate therapy, approximately 10–25 percent of ED patients who have acute asthma will require hospitalization (Pollack et al. 2002; Weber et al. 2002). In the hospital, multidisciplinary (e.g., nursing and respiratory care) clinical pathways for asthma appear to be effective in reducing hospital length-of-stay and inpatient costs, but they have less clear impact on clinical outcomes (Banasiak and Meadows-Oliver 2004). An overview of the treatment strategies in EDs and hospitals is presented in figure 5–6 and detailed below.

ASSESSMENT

The Expert Panel recommends the following activities to assess exacerbations:

- **All clinicians treating patients who have asthma should be prepared to treat an asthma exacerbation, be familiar with the symptoms and signs of severe and life-threatening exacerbations (figures 5–1, 5–2a, and 5–3), and have procedures for facilitating immediate patient transfer to an emergency care facility (EPR—2 1997)**.

FIGURE 5–5. DOSAGES OF DRUGS FOR ASTHMA EXACERBATIONS

	Dosages		
Medication	**Child Dose**	**Adult Dose***	**Comments**
Inhaled Short-Acting Beta$_2$-Agonists (SABA)			
Albuterol			
Nebulizer solution A. (0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL, 5.0 mg/mL)	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization.	2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hour continuously.	Only selective beta$_2$-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min. Use large volume nebulizers for continuous administration. May mix with ipratropium nebulizer solution.
MDI B. (90 mcg/puff)	4–8 puffs every 20 minutes for 3 doses, then every 1–4 hours inhalation maneuver as needed. Use VHC; add mask in children <4 years.	4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed.	In mild-to-moderate exacerbations, MDI plus VHC is as effective as nebulized therapy with appropriate administration technique and coaching by trained personnel.
Bitolterol			
Nebulizer solution C. (2 mg/mL)	See albuterol dose; thought to be half as potent as albuterol on mg basis.	See albuterol dose.	Has not been studied in severe asthma exacerbations. Do not mix with other drugs.
MDI D. (370 mcg/puff)	See albuterol MDI dose.	See albuterol MDI dose.	Has not been studied in severe asthma exacerbations.
Levalbuterol			
(R-albuterol)			
Nebulizer solution E. (0.63 mg/3 mL, 1.25 mg/0.5 mL 1.25 mg/3 mL)	0.075 mg/kg (minimum dose 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed.	1.25–2.5 mg every 20 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed.	Levalbuterol administered in one-half the mg dose of albuterol provides comparable efficacy and safety. Has not been evaluated by continuous nebulization.
MDI F. (45 mcg/puff)	See albuterol MDI dose.	See albuterol MDI dose.	
Pirbuterol			
MDI G. (200 mcg/puff)	See albuterol MDI dose; thought to be half as potent as albuterol on a mg basis.	See albuterol MDI dose.	Has not been studied in severe asthma exacerbations.
Systemic (Injected) Beta$_2$-Agonists			
Epinephrine H. 1:1,000 (1 mg/mL)	0.01 mg/kg up to 0.3–0.5 mg every 20 minutes for 3 doses sq.	0.3–0.5 mg every 20 minutes for 3 doses sq.	No proven advantage of systemic therapy over aerosol.
Terbutaline I. (1 mg/mL)	0.01 mg/kg every 20 minutes for 3 doses then every 2–6 hours as needed sq.	0.25 mg every 20 minutes for 3 doses sq.	No proven advantage of systemic therapy over aerosol.

FIGURE 5–5. DOSAGES OF DRUGS FOR ASTHMA EXACERBATIONS (CONTINUED)

Medication	Dosages		
	Child Dose*	Adult Dose	Comments
Anticholinergics			
Ipratropium bromide			
Nebulizer solution J. (0.25 mg/mL)	0.25–5 mg every 20 minutes for 3 doses, then as needed	0.5 mg every 20 minutes for 3 doses then as needed	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to SABA therapy for severe exacerbations. The addition of ipratropium has not been shown to provide further benefit once the patient is hospitalized.
MDI K. (18 mcg/puff)	4–8 puffs every 20 minutes as needed up to 3 hours	8 puffs every 20 minutes as needed up to 3 hours	Should use with VHC and face mask for children <4 years. Studies have examined ipratropium bromide MDI for up to 3 hours.
Ipratropium with albuterol			
Nebulizer solution (Each 3 mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol.)	1.5 mL every 20 minutes for 3 doses, then as needed	3 mL every 20 minutes for 3 doses, then as needed	May be used for up to 3 hours in the initial management of severe exacerbations. The addition of ipratropium to albuterol has not been shown to provide further benefit once the patient is hospitalized.
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg of albuterol.)	4–8 puffs every 20 minutes as needed up to 3 hours	8 puffs every 20 minutes as needed up to 3 hours	Should use with VHC and face mask for children <4 years.
Systemic Corticosteroids			
	(Applies to all three corticosteroids)		
Prednisone Methylprednisolone Prednisolone	1 mg/kg in 2 divided doses (maximum = 60 mg/day) until PEF is 70% of predicted or personal best	40–80 mg/day in 1 or 2 divided doses until PEF reaches 70% of predicted or personal best	For outpatient "burst," use 40–60 mg in single or 2 divided doses for total of 5–10 days in adults (children: 1–2 mg/kg/day maximum 60 mg/day for 3–10 days).

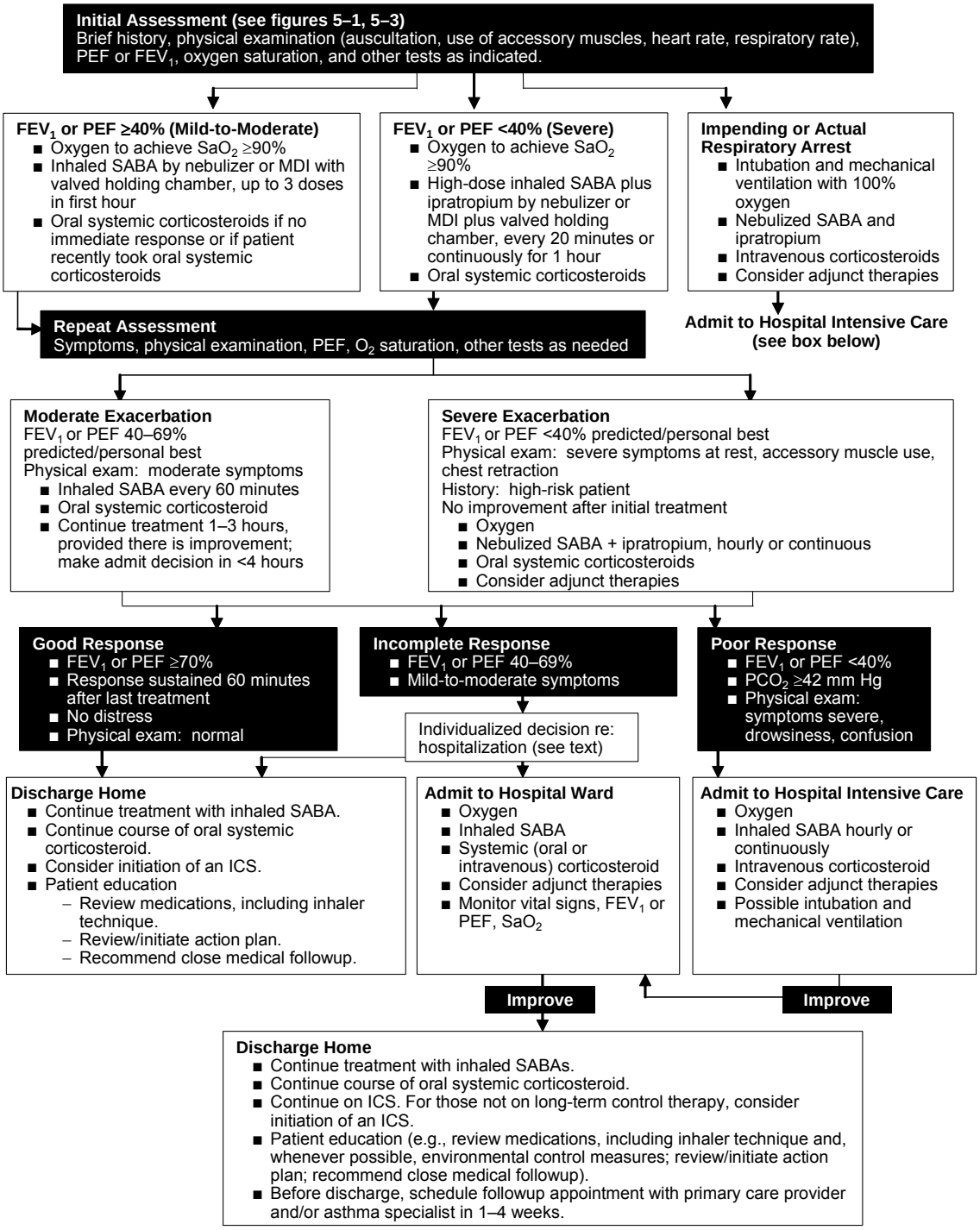
*Children ≤ 12 years of age

Key: ED, emergency department; MDI, metered-dose inhaler; PEF, peak expiratory flow; VHC, valved holding chamber

Notes:

- There is no known advantage for higher doses of corticosteroids in severe asthma exacerbations, nor is there any advantage for intravenous administration over oral therapy provided gastrointestinal transit time or absorption is not impaired.
- The total course of systemic corticosteroids for an asthma exacerbation requiring an ED visit of hospitalization may last from 3 to 10 days. For corticosteroid courses of less than 1 week, there is no need to taper the dose. For slightly longer courses (e.g., up to 10 days), there probably is no need to taper, especially if patients are concurrently taking ICSs.
- ICSs can be started at any point in the treatment of an asthma exacerbation.

FIGURE 5–6. MANAGEMENT OF ASTHMA EXACERBATIONS: EMERGENCY DEPARTMENT AND HOSPITAL-BASED CARE



Key: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered dose inhaler; PCO_2, partial pressure carbon dioxide; PEF, peak expiratory flow; SABA, short-acting beta$_2$-agonist; SaO_2, oxygen saturation

- **Initial assessment should include a brief history, brief physical examination, and, for most patients, objective measures of lung function. Initial laboratory studies may be helpful, but they are not required for most patients, and they should not delay initiation of asthma treatment (EPR—2 1997).**

- **In the ED, all patients presenting with a reported asthma exacerbation must be evaluated and triaged immediately, based on at least vital signs and an overall physical assessment (e.g., ability to breathe well enough to talk). Treatment should begin immediately following recognition of a moderate, severe, or life-threatening exacerbation by assessment of symptoms, signs, or, when possible, lung function (EPR—2 1997).**

- **While treatment is given, obtain a brief, focused history and physical examination pertinent to the exacerbation (See figure 5–3.). Take a more detailed history and complete physical examination and perform laboratory studies only after initial therapy has been completed (Evidence D).**

- **The objectives of *functional assessment* (the frequency and number of measurements) will depend on the severity of the exacerbation and the response to treatment (See figure 5–6.) are to:**

  — **Obtain objective lung function measurements.**

    - FEV_1 or PEF values provide important information about the level of airflow obstruction both initially and in response to treatment. Because low PEF values cannot distinguish between poor effort, restrictive ventilatory disorders (e.g., neuromuscular weakness, pneumonia), and obstructive ventilatory disorders (e.g., asthma), FEV_1 measurements are preferable if they are readily available (Evidence D).

    - In the initial assessment of a life-threatening asthma exacerbation, FEV_1 or PEF are not indicated (Evidence D).

    - Very severe exacerbations may preclude performance of a maximal expiratory maneuver and, in such cases, the clinical presentation should suffice for clinical assessment and prompt initiation of therapy (Evidence D).

    - In less severe exacerbations, in the office or ED, FEV_1 or PEF should be obtained on arrival and 30–60 minutes after initial treatment (Evidence B).

    - In the hospital, FEV_1 or PEF should be measured on admission and 15–20 minutes after bronchodilator therapy during the acute phase and at least daily thereafter until discharge (Evidence C).

    - Any FEV_1 or PEF value <25 percent of predicted that improves by <10 percent after treatment or values that fluctuate widely are potential indications for ICU admission and close monitoring for respiratory failure (Evidence C).

    - Flow-volume loops should be obtained to distinguish between upper and lower airway obstruction in patients who have atypical asthma symptoms (e.g., dysphonia)

or findings on exam (e.g., stridor) or if response to therapy is inadequate (Evidence D).

— **Monitor oxygen saturation.**

- ♦ Pulse oximetry is indicated for children unable to perform FEV_1 or PEF or for any patient who is in severe distress or has an FEV_1 or PEF <40 percent of predicted to assess the adequacy of arterial oxygen saturation (SaO_2) (Connett and Lenney 1993; Geelhoed et al. 1994; Sole et al. 1999; Wright et al. 1997) (Evidence C).

- ♦ Serial pulse oximetry measurements can be useful to assess both the severity of the exacerbation and improvement with treatment (Evidence B). By contrast, a single pulse oximetry value on admission is of relatively little value for predicting hospital admission (Boychuk et al. 2006; Keahey et al. 2002; Wright et al. 1997).

■ **Objectives of the *brief history* are to determine (EPR—2 1997):**

— Time of onset and any potential causes of current exacerbation.

— Severity of symptoms, especially compared with previous exacerbations, and response to any treatment given before admission to ED.

— All current medications and time of last dose, especially of asthma medications.

— Estimate of number of previous unscheduled office visits, ED visits, and hospitalizations for asthma, particularly within the past year.

— Any prior episodes of respiratory insufficiency due to asthma (loss of consciousness or intubation and mechanical ventilation).

— Other potentially complicating illness, especially other pulmonary or cardiac disease or diseases that may be aggravated by systemic corticosteroid therapy (such as diabetes, peptic ulcer, hypertension, and psychosis).

■ **Objectives of the initial brief *physical examination* are to (EPR—2 1997):**

— Assess the severity of the exacerbation, as indicated by the findings listed in figure 5–3.

— Assess overall patient status, including level of alertness, fluid status, and presence of cyanosis, respiratory distress, and wheezing. Wheezing can be an unreliable indicator of obstruction; in rare cases, extremely severe obstruction may be accompanied by a “silent chest” (Shim and Williams 1980).

— Identify possible complications (e.g., pneumonia, pneumothorax, or pneumomediastinum); although rare, these will influence management of the asthma exacerbation.

— Rule out upper airway obstruction. Both intrathoracic and extrathoracic central airway obstruction can cause severe dyspnea and may be diagnosed as asthma.

- Causes include upper airway foreign bodies, epiglottitis, organic diseases of the larynx, vocal cord dysfunction, and extrinsic and intrinsic tracheal narrowing (See "Component 1: Measures of Asthma Assessment and Monitoring.").

- Clues to the presence of alternative reasons for dyspnea include dysphonia, inspiratory stridor, monophonic wheezing loudest over the central airway, normal values for PO_2, and unexpectedly complete resolution of airflow obstruction with intubation.

- When upper airway obstruction is suspected, further evaluation is indicated by flow-volume curves and by referral for laryngoscopy (See "Component 1: Measures of Asthma Assessment and Monitoring.").

■ ***Laboratory studies.*** *Most patients who have an asthma exacerbation do not require any initial laboratory studies. If laboratory studies are ordered, they must not delay initiation of asthma treatment* (EPR—2 1997). The most important objective of laboratory studies is detection of actual or impending respiratory failure. Other objectives include detection of theophylline toxicity or conditions that complicate the treatment of asthma exacerbations (such as cardiovascular disease, pneumonia, or diabetes). For example:

— Consider *arterial blood gas* (ABG) measurement for evaluating arterial carbon dioxide tension (PCO_2) in patients who have suspected hypoventilation, severe distress, or FEV_1 or PEF $\leq$25 percent of predicted after initial treatment. (Note: Respiratory drive is typically increased in asthma exacerbations, so a "normal" PCO_2 of 40 mmHg indicates severe airflow obstruction and a heightened risk of respiratory failure.)

— *Venous levels of PCO_2* have been tested as a substitute for arterial measurements, and a venous PCO_2 of >45 mmHg may serve as a screening test but cannot substitute for the ABG evaluation of respiratory function (Kelly et al. 2002a).

— *Complete blood count (CBC)* is not required routinely but may be appropriate in patients who have fever or purulent sputum. Keep in mind that modest leukocytosis is common in asthma exacerbations and that corticosteroid treatment causes a further outpouring of polymorphonuclear leukocytes within 1–2 hours of administration.

— Measure *serum theophylline concentration* in patients who have taken *theophylline* before presentation.

— It may be prudent to measure *serum electrolytes* in patients who have been taking diuretics regularly and in patients who have coexistent cardiovascular disease, because frequent SABA administration can cause transient decreases in serum potassium, magnesium, and phosphate.

— *Chest radiography* is not recommended for routine assessment but should be obtained for patients suspected of a complicating cardiopulmonary process, such as congestive heart failure, or another pulmonary process such as pneumothorax, pneumomediastinum, pneumonia, or lobar atelectasis.

— *Electrocardiograms* are not required routinely, but a baseline electrocardiogram and continual monitoring of cardiac rhythm are appropriate in patients older than 50 years of age and in those who have coexistent heart disease or chronic obstructive pulmonary

disease (COPD). The electrocardiogram may show a pattern of right ventricular strain that reverses promptly with treatment of airflow obstruction.

- **Assessment considerations unique to children and infants are as follows:**

  — It is often difficult for physicians and parents to determine the severity of the airway obstruction in infants and small children who have asthma. However, using a combination of the subjective and objective parameters in figure 5–3 permits a fairly accurate assessment to guide initial therapy. Many of these parameters have not been studied systematically, so they serve only as general guides.

  — The differences in the anatomy and physiology of the lungs of infants place them at greater risk for respiratory failure. These differences include greater peripheral airway resistance, fewer collateral channels of ventilation, further extension of airway smooth muscle into the peripheral airways, less elastic recoil, and mechanical disadvantage of the diaphragm. Viral infections, particularly respiratory syncytial virus (RSV), are the most common cause of acute wheezing illness in infants. The edematous inflammatory response in the airways leads to air trapping and hyperinflation, atelectasis, increased respiratory rate, and wheezing. This sequence of changes can rapidly progress to respiratory failure, and close monitoring is critical.

  — It is particularly important to monitor SaO_2 by pulse oximetry in infants because their ventilation/perfusion characteristics lead them to become hypoxemic more readily than adults. SaO_2 should be normal for altitude (>95 percent at sea level). Decreased SaO_2 is often an early sign of severe airway obstruction, and an SaO_2 <92 percent of room air 1 hour after initial treatment is a good predictor of the need for hospitalization in small infants (Connett and Lenney 1993; Geelhoed et al. 1994; Sole et al. 1999).

  — Capillary or ABG measurements should be performed on infants suspected of respiratory failure. PCO_2 is the best measurement of ventilation in infants, as it is in adults. Children who have a normal PCO_2 but are in obvious respiratory distress are at high risk for respiratory failure.

  — After initial treatment is begun, it is important to consider possible coexisting conditions, as is done in adults. In infants, considerations should include RSV infection, foreign body aspiration, history of bronchopulmonary dysplasia (prematurity) or cystic fibrosis.

TREATMENT

The Expert Panel recommends as initial treatments: oxygen for most patients, SABA for all patients; adding multiple doses of ipratropium bromide for ED patients who have severe exacerbations (but ipratropium bromide is not recommended during hospitalization); and systemic corticosteroids for most patients. For severe exacerbations unresponsive to the initial treatments, adjunct treatments (magnesium sulfate or heliox) merit consideration to decrease the likelihood of intubation. (See the following discussion for evidence levels.)

The Expert Panel does not recommend: methylxanthines, antibiotics (except as needed for comorbid conditions), aggressive hydration, chest physical therapy, mucolytics, or sedation. (For evidence levels, see the following discussion.)

In the ED and hospital, tailor the intensity of treatment and surveillance to the severity of the exacerbation. The primary therapies—the administration of oxygen, SABA, and systemic corticosteroids—are constant, but the dose and frequency with which they are given and the frequency with which the patient's response is assessed may vary. Thus, for patients presenting with a severe exacerbation, give SABA therapy at the higher dose plus ipratropium bromide (figure 5–5) either repeatedly (three treatments in the first hour) or continuously (by nebulization) (Evidence A). Give systemic corticosteroids immediately, and watch closely for signs of worsening airflow obstruction or fatigue. For patients who have mild exacerbations, give SABA therapy and assess the patient's response before deciding whether additional therapy is necessary. When SaO_2 monitoring is not available, give supplemental oxygen to patients who have significant hypoxemia and to patients who have FEV_1 or PEF <40 percent of predicted.

The Expert Panel recommends the following treatments:

- **Oxygen is recommended for most patients (EPR—2 1997).** Administer supplemental oxygen (by nasal cannulae or mask, whichever is best tolerated) to maintain an SaO_2 >90 percent (>95 percent in pregnant women and in patients who have coexistent heart disease). Monitor SaO_2 until a clear response to bronchodilator therapy has occurred.

- **SABA treatment is recommended for all patients (Evidence A)** (For recommended doses, see figure 5–5.).

  — The repetitive or continuous administration of SABAs is the most effective means of reversing airflow obstruction (Camargo et al. 2003b; Karpel et al. 1997; McFadden 2003; Travers et al. 2001).

  — In the ED, three treatments of SABA spaced every 20–30 minutes can be given safely as initial therapy. Thereafter, the frequency of administration varies according to the improvement in airflow obstruction and associated symptoms and the occurrence of side effects. Continuous administration of SABA may be more effective in more severely obstructed patients (Camargo et al. 2003b; Papo et al. 1993).

  — Because of the risk of cardiotoxicity, use only selective SABA (albuterol, levalbuterol, pirbuterol) in high doses.

  — In mild or moderate exacerbations, equivalent bronchodilation can be achieved either by high doses (4–12 puffs) of a SABA by MDI with a valved holding chamber (VHC) in infants, children, and adults under the supervision of trained personnel or by nebulizer therapy (Cates et al. 2003; Dolovich et al. 2005). However, nebulizer therapy may be preferred for patients who are unable to cooperate effectively in using an MDI because of their age, agitation, or severity of the exacerbation.

  — The onset of action for SABAs is less than 5 minutes; repetitive administration produces incremental bronchodilation. In about 60–70 percent of patients, response to the initial three doses in the ED will be sufficient to discharge them, and most patients will have a significant response after the first dose (Karpel et al. 1997; Rodrigo and Rodrigo 1998b; Strauss et al. 1997).

— Duration of action of bronchodilation from SABAs in severe asthma exacerbations is not precisely known, but duration can be significantly shorter than that observed in stable asthma.

— A recent meta-analysis of six trials suggests that the use of nebulized magnesium sulfate in combination with SABAs may result in further improvements in pulmonary function (Blitz et al. 2005), but further research is needed.

■ **Inhaled ipratropium bromide.**

— ***In the ED: recommended* (Evidence A).** Adding multiple high doses of ipratropium bromide (0.5 mg nebulizer solution or 8 puffs by MDI in adults; 0.25–0.5 mg nebulizer solution or 4–8 puffs by MDI in children) to a selective SABA produces additional bronchodilation, resulting in fewer hospital admissions, particularly in patients who have severe airflow obstruction (Plotnick and Ducharme 2000; Rodrigo and Castro-Rodriguez 2005).

— ***In the hospital: not recommended* (Evidence A).** Two controlled clinical trials failed to detect a significant benefit from the addition of ipratropium to treatment after hospitalization for severe acute asthma (Craven et al. 2001; Goggin et al. 2001). Studies of hospitalized adults are not available.

■ **Systemic corticosteroids are recommended for most patients** (For recommended doses, See figure 5–5.):

— ***In the ED:* Give systemic corticosteroids to patients who have moderate or severe exacerbations and patients who do not respond completely to initial SABA therapy (Evidence A).** These medications speed the resolution of airflow obstruction and reduce the rate of relapse and may reduce hospitalizations (Edmonds et al. 2003; Rowe et al. 2001; Rowe et al. 2004).

♦ **Oral administration of prednisone has been shown to have effects equivalent to those of intravenous methylprednisolone (Evidence A) (Harrison et al. 1986; Ratto et al. 1988) and, in the opinion of the Expert Panel, is usually preferred because it is less invasive.**

♦ **Give a 5- to 10-day course following ED discharge to prevent early relapse (EPR—2 1997).**

♦ **Intramuscular depot injections of corticosteroids may be considered as an alternative to oral corticosteroids for patients who are at high risk of nonadherence (Evidence D).** Intramuscular depot injections may be as effective as oral corticosteroids for preventing relapse after discharge from the ED (Lahn et al. 2004; Rowe et al. 2001; Schuckman et al. 1998).

♦ **Give supplemental doses of oral corticosteroids to patients who take them regularly, even if the exacerbation is mild (Evidence D).**

— ***In the hospital:* Give systemic corticosteroids to patients who are admitted to the hospital (Evidence A),** because oral systemic corticosteroids speed the resolution of asthma exacerbations (Manser et al. 2001; Smith et al. 2003).

- **High doses of an ICS may be considered in the ED, although current evidence is insufficient to permit conclusions about using ICSs rather than oral systemic corticosteroids in the ED (Evidence B).** (See Evidence Table 17, Increasing the Dose of Inhaled Corticosteroids.) Although simply doubling the dose of the ICS that a patient is taking for long-term therapy at the onset of an exacerbation does not appear to be effective (FitzGerald et al. 2004; Garrett et al. 1998; Harrison et al. 2004; Rice-McDonald et al. 2005), there is increasing evidence that multiple high doses of an ICS (6 mg flunisolide over 3 hours) (Rodrigo and Rodrigo 1998a) or 3 mg fluticasone/hour for 3 hours (Rodrigo 2005) are beneficial when initiated in adults early in the ED (See Evidence Table 17.). The data on ICS use in children are inconsistent (Rowe et al. 2004). This may be a result of the inconsistency of dosing. One trial reporting greater efficacy for oral corticosteroids used a single high dose of an ICS (2 mg fluticasone) (Schuh et al. 2000), whereas a trial giving multiple doses of budesonide (1.2 mg total) reported increased efficacy for the inhaled route (Singhi et al. 1999). The level of acute asthma severity also may explain apparent discrepancies found in the literature. Although the data are suggestive, a meta-analysis concluded that evidence was insufficient for firm conclusions (Edmonds et al. 2003). Further investigations with greater attention to dosing and acute asthma severity level are required.

- **For severe exacerbations unresponsive to the initial treatments listed above, whether given before arrival at the acute care setting or in the ED, adjunct treatments may be considered to decrease the likelihood of intubation: intravenous magnesium or heliox may be useful (Evidence B).** These therapies are discussed below, in the subsection on "Impending Respiratory Failure."

The following treatments are NOT recommended:

- **Methylxanthines are not recommended (Evidence A).** (See Evidence Table 18, IV Aminophylline.)

  — ***In the ED:*** Theophylline/aminophylline is not recommended because it appears to provide no additional benefit to optimal SABA therapy and increases the frequency of adverse effects (Parameswaran et al. 2000).

  — If patients are currently taking a theophylline-containing preparation, determine serum theophylline concentration to prevent theophylline toxicity.

  — ***In the hospital:*** Therapy with oral or intravenous methylxanthines does not improve lung function or other outcomes in hospitalized adults (Parameswaran et al. 2000). Most studies show no benefit, but increased toxicity, with theophylline in children who are hospitalized with severe asthma (Mitra et al. 2005). The meta-analysis, however, reported that those patients receiving intravenous aminophylline had a small (8–9 percent) but significant greater improvement in percent predicted FEV_1. This difference was due to the weight of one study (Yung and South 1998), and this difference in lung function did not result in significant differences in length of stay, ICU admission or stay, or symptoms; however, significantly greater numbers of patients in the theophylline group had therapy discontinued due to adverse effects.

- **Antibiotics are not generally recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions (Evidence B).** Bacterial, *Chlamydia,* or *Mycoplasma* infections infrequently contribute to exacerbations of asthma;

therefore, the use of antibiotics is generally reserved for patients who have fever and purulent sputum and for patients who have evidence of pneumonia (EPR—Update 2002). When the presence of bacterial sinusitis is strongly suspected, treat with antibiotics.

- **Aggressive hydration is not recommended for older children and adults but may be indicated for some infants and young children (Evidence D).** Intravenous or oral administration of large volumes of fluids does *not* play a role in the management of severe asthma exacerbations. Some infants and young children may become dehydrated, however, as a result of increased respiratory rate and decreased oral intake. In these patients, clinicians should make an assessment of fluid status (urine output, urine specific gravity, mucus membrane moisture, electrolytes) and provide appropriate corrections. The placement of intravenous lines is not without complication, and the emotional impact of this procedure may prove counterproductive. Oral routes of hydration are preferable except in very severe exacerbations with the possibility of endotracheal intubation.

- **Chest physical therapy is not generally recommended (Evidence D).** For most exacerbations, chest physiotherapy is not beneficial and is unnecessarily stressful for the breathless asthma patient. Because mucus plugging is a major contributing cause of fatal asthma (Kuyper et al. 2003), further studies are needed on the role of improved airway clearance in near-fatal exacerbations.

- **Mucolytics are not recommended (Evidence C).** Avoid mucolytic agents (e.g., acetylcysteine, potassium iodide) because they may worsen cough or airflow obstruction.

- **Sedation is not generally recommended (Evidence D).** Anxiolytic and hypnotic drugs are contraindicated in severely ill asthma patients because of their respiratory depressant effect. In asthmatic patients who have severe emotional impact, and possible comorbid anxiety disorder, therapy should stay focused on the asthma exacerbation; the benefit of short-acting sedatives is not known.

REPEAT ASSESSMENT

The Expert Panel recommends that repeat assessment of patients who have severe exacerbations be made after the initial dose of a SABA and that repeat assessment of all patients be made after three doses of a SABA (60–90 minutes after initiating treatment) (Evidence A).

The response to initial treatment in the ED is a better predictor of the need for hospitalization than is the severity of an exacerbation on presentation (Cham et al. 2002; Chey et al. 1999; Gorelick et al. 2004b; Karras et al. 2000; Kelly et al. 2002b and 2004; McCarren et al. 2000; Rodrigo and Rodrigo 1993, 1998c; Smith et al. 2002). The elements to be evaluated include the patient's subjective response, physical findings, FEV_1 or PEF, and measurement of pulse oximetry or ABG (if the patient meets the criteria described in the earlier discussion of laboratory studies).

HOSPITALIZATION

The Expert Panel recommends that the decision to hospitalize a patient be based on duration and severity of symptoms, severity of airflow obstruction, response to ED treatment (See earlier section on monitoring in "Treatment Goals."), course and severity of prior exacerbations, medication use at the time of the exacerbation, access to medical

care and medications, adequacy of support and home conditions, and presence of psychiatric illness (Evidence C) (Pollack et al. 2002; Weber et al. 2002.).

In general, the principles of care in the hospital and recommendation for treatment resemble those for care in the ED and involve both treatment (with oxygen, aerosolized SABA, and systemic corticosteroids and, perhaps, adjunct therapies) and frequent assessment, including clinical assessment of respiratory distress and fatigue as well as objective measurement of airflow (PEF or FEV_1) and oxygen saturation (EPR—2 1997).

IMPENDING RESPIRATORY FAILURE

The Expert Panel recommends that intubation not be delayed once it is deemed necessary; exactly when to intubate is based on clinical judgment (Evidence D). Most patients respond well to therapy. However, a small minority will show signs of worsening ventilation, whether from worsening airflow obstruction, worsening respiratory muscle fatigue, or a combination of the two. Signs of impending respiratory failure include inability to speak, altered mental status, intercostal retraction (Cham et al. 2002), worsening fatigue, and a PCO_2 of ≥42 mmHg. Because respiratory failure can progress rapidly and can be difficult to reverse, early recognition and treatment are critically important.

The Expert Panel recommends that adjunct treatments such as magnesium sulfate or heliox may be considered to avoid intubation, but intubation should not be delayed once it is deemed necessary (Evidence B). Because intubation of a severely ill asthma patient is difficult and associated with complications, additional treatments are sometimes attempted.

- **Intravenous magnesium sulfate. Consider intravenous magnesium sulfate in patients who have life-threatening exacerbations and in those whose exacerbations remain in the severe category after 1 hour of intensive conventional therapy (Evidence B).** (See Evidence Table 19, Magnesium Sulfate.) Meta-analyses of studies of both children and adults (Cheuk et al. 2005; Rowe et al. 2000) show that intravenous magnesium sulfate (2 grams in adults and 25–75 mg/kg up to 2 grams in children) added to conventional therapy reduces hospitalization rates in ED patients who present with severe asthma exacerbations (PEF <40 percent). However, not all individual studies have found positive results (Boonyavorakul et al. 2000; Porter et al. 2001; Scarfone et al. 2000). The treatment has no apparent value in patients who have exacerbations of lesser severity, and one study (Silverman et al. 2002) found that intravenous magnesium sulfate improved pulmonary function only in patients whose initial FEV_1 was <25 percent predicted, and the treatment did not improve hospital admission rates.

- **Heliox. Consider heliox-driven albuterol nebulization for patients who have life-threatening exacerbations and for those patients whose exacerbations remain in the severe category after 1 hour of intensive conventional therapy (Evidence B).** (See Evidence Table 20, Heliox.)

  Because of helium's low density, a mixture of helium and oxygen (heliox) could improve gas exchange in patients who have airway obstruction (Gupta and Cheifetz 2005). However, a meta-analysis of six studies (four in adults, two in pediatric patients) performed between 1996 and 2002 did not find a statistically significant improvement in pulmonary function or other measured outcomes in patients receiving heliox compared to oxygen or air (Ho et al. 2003). Likewise, a more recent study did not demonstrate a statistically significant benefit in children who had moderately severe asthma and received standard initial therapy followed

by continuous albuterol nebulization with heliox compared to air/oxygen (Rivera et al. 2006). In contrast, another recent study (Kim et al. 2005) did report a significant improvement in pulmonary index and a trend toward reduced hospitalizations in children who had moderate-to-severe exacerbations and received heliox-driven albuterol nebulization compared to children who received oxygen-driven nebulization. Other investigators recently described two randomized controlled trials (RCTs) of adults that demonstrated more rapid and greater improvements in peak flow and dyspnea scores in patients who presented with severe exacerbations and received initial treatment with heliox versus oxygen-driven albuterol therapy (Lee et al. 2005). The discrepancy in findings may result from small sample sizes. More importantly, however, some studies have neglected to account for the different effect of heliox versus oxygen (or room air) on respirable mass (Hess et al. 1999). For example, failure to increase the gas flow rate for those on heliox greatly complicates interpretation (and synthesis) of the literature.

- **Other adjunct therapies to avoid intubation include intravenous beta$_2$-agonists, intravenous leukotriene receptor antagonists (LTRAs), and noninvasive ventilation; however, insufficient data are available to make recommendations regarding these possible adjunct therapies (Evidence D).**

  — Intravenous beta$_2$-agonists remain a largely unproven treatment. Current evidence does not suggest an improved benefit from intravenous beta$_2$-agonists compared to aerosol administration (Travers et al. 2001), but data are sparse (Browne et al. 1997) on the benefit of adding an intravenous beta$_2$-agonist to high-dose nebulized therapy. Nevertheless, the Expert Panel does not recommend use of intravenous isoproterenol in the treatment of asthma because of the danger of myocardial toxicity (Evidence B) (Maguire et al. 1991).

  — Intravenous LTRAs could provide another pathway to rapid bronchodilation during impending respiratory failure. A randomized trial of intravenous montelukast in moderate and severe exacerbations demonstrated significant improvement in pulmonary function within 10 minutes of administration (Camargo et al. 2003a). The oral formulation LTRA would not be expected to provide benefit for at least 90 minutes (Dockhorn et al. 2000).

  — Noninvasive ventilation is another experimental approach for treatment of respiratory failure due to severe asthma exacerbation, but data are very limited (Ram et al. 2005).

  — Review of other experimental adjunct therapies is beyond the scope of this report.

The Expert Panel recommends the following actions regarding intubation:

- **Patients who present with apnea or coma should be intubated immediately (EPR—2 1997).** There are no other absolute indications for endotracheal intubation, but persistent or increasing hypercapnia, exhaustion, and depression of mental status strongly suggest the need for ventilatory support (Evidence D).

- **Intubate semielectively, before the crisis of respiratory arrest, because intubation is difficult in patients who have asthma (EPR—2 1997).**

- **Intubation should be performed by a physician who has extensive experience in intubation and airway management (EPR—2 1997).**
  - Because intubation should not be delayed once it is deemed necessary, it is often performed in the ED or inpatient ward, and the patient is subsequently transferred to an ICU appropriate to the patient's age.
  - Children who are intubated for asthma should be admitted to a pediatric ICU or transferred to a facility that has such a unit.
  - Even without intubation, patients who have severe exacerbations and are slow to respond to therapy may benefit from admission to an ICU, where they can be monitored closely and intubated if it is indicated.
  - Despite theoretical benefits from using ketamine as a premedication for intubation, clinical trials in nonintubated patients who have severe exacerbations have not shown clinical benefit (Allen and Macias 2005; Howton et al. 1996). Studies of intubated patients are not available.
  - Although many issues require consideration at the time of intubation, clinicians should pay close attention to maintaining or replacing intravascular volume, because hypotension commonly accompanies the initiation of positive pressure ventilation.
- **"Permissive hypercapnia" or "controlled hypoventilation" is the recommended ventilator strategy (Evidence C).** Permissive hypercapnia provides adequate oxygenation and ventilation while minimizing high airway pressures and barotrauma (Darioli and Perret 1984; Menitove and Goldring 1983; Tuxen 1994). It involves administration of as high a fraction of inspired oxygen as is necessary to maintain adequate arterial oxygenation, acceptance of hypercapnia, and treatment of respiratory acidosis with intravenous sodium bicarbonate. Adjustments are made to the tidal volume, ventilator rate, and inspiration-to-expiration ratio to minimize airway pressures. Consultation with or comanagement by physicians who have expertise in ventilator management is appropriate, because mechanical ventilation of patients who have severe refractory asthma is complicated and fraught with risk. Continuation of a SABA in ventilated patients is recommended, although no RCTs provide evidence for or against this practice (Dhand and Tobin 1997; Jones et al. 2001). This ventilator strategy is not uniformly successful in critically ill asthma patients, and additional therapies are being evaluated. Their review is beyond the scope of this report.

PATIENT DISCHARGE

The Expert Panel recommends that clinicians, before patients' discharge from the ED or hospital, provide patients with necessary medications and education on how to use them, a referral for a followup appointment, and instruction in an ED asthma discharge plan for recognizing and managing relapse of the exacerbation or recurrence of airflow obstruction (Evidence B).

The Expert Panel recommends the following actions for discharging patients from the ED:

- **Release of the patient from the ED depends on the patient's response to treatment (EPR—2 1997).**

  — In general, discharge is appropriate if FEV_1 or PEF has returned to ≥70 percent of predicted or personal best and symptoms are minimal or absent. Patients who have an incomplete response to therapy (FEV_1 or PEF 50–69 percent of predicted or personal best) and with mild symptoms should be assessed individually for their suitability for discharge home, with consideration given to factors listed in figure 5–2a (Evidence C).

  — The Expert Panel's opinion is that patients who have a rapid response should be observed for 30–60 minutes after the most recent dose of bronchodilator to ensure their stability of response before discharge to home.

  — Extended treatment and observation in a holding area, clinical decision unit, or overnight unit to determine the need for hospitalization may be appropriate, provided there is sufficient monitoring and nursing care (McCarren et al. 2000).

- **Prescribe sufficient medications for the patient to continue treatment after discharge.**

  — **Patients given systemic corticosteroids should continue oral systemic corticosteroids for 3–10 days (Evidence A).** The need for further corticosteroid therapy should be assessed at a followup visit. For corticosteroid courses of less than 1 week, there is no need to taper the dose. For 10-day courses, there remains no need to taper if patients are concurrently taking ICSs (O'Driscoll et al. 1993).

  — **Consider initiating an ICS at discharge, in addition to oral systemic corticosteroids (Evidence B).** A retrospective review of a large patient database found a significant reduction in the risk of subsequent ED visits among patients using ICS therapy after ED discharge (Sin and Man 2002). A clinical RCT comparing ED patients discharged with and without ICSs demonstrated that ICSs added to oral systemic corticosteroids halved patients' risk of relapse events (Rowe et al. 1999). A Cochrane review (Edmonds et al. 2000) noted that two other relapse trials did not report similar benefit, but the review found that the combined estimate of the three available trials had borderline statistical significance (odds ratio 0.68; 95 percent CI 0.46 to 1.02). The Expert Panel concludes that initiating ICS therapy (e.g., providing a 1–2 month supply) at discharge from ED should be considered, given the potential for ICSs is to reduce subsequent ED visits, the strong evidence that long-term-control ICS therapy reduces exacerbations in patients who have persistent asthma, and the opinion of the Expert Panel that the initiation (and continuation) of ICS therapy at ED discharge can be an important effort to bridge the gap between emergency and primary care for asthma. Patients already taking ICS therapy should continue it following discharge.

- **Emphasize the need for continual, regular care in an outpatient setting, and refer the patient for a followup asthma care appointment (either primary care provider (PCP) or asthma specialist) within 1–4 weeks (Evidence B). If appropriate, consider referral to an asthma self-management education program (Evidence B).** A visit to the ED is often an indication of inadequate long-term management of asthma or inadequate plans for handling exacerbations. Having fewer general practice contacts in the previous year has

been independently associated with an increased risk of fatal asthma (Sturdy et al. 2005), and an observational study found that having followup appointments within 30 days of an asthma-related ED visit was associated with a reduced 90-day readmission rate (Sin et al. 2002). Likewise, referral of patients in the ED to an asthma specialist for consultation was associated with a reduced rate of subsequent ED visits (Zeiger et al. 1991). These results contrast, however, with two recent randomized trials that found that facilitated referral of ED patients to the PCP did not alter long-term asthma outcomes (Baren et al. 2006; Smith et al. 2004). Although the evidence from RCTs regarding optimal referral practice is limited (e.g., PCP or asthma specialist), the ED and hospital staff should notify the patient's health care professional (or provide a referral to one if the patient does not name a source of asthma care) and encourage the patient to contact his/her health care provider (e.g., by telephone) for asthma-related problems during the first 3–5 days after ED or hospital discharge. The ED and hospital staff should instruct the patient to seek a followup medical appointment within 1–4 weeks. Whenever possible, the ED should schedule such an appointment before the patient is discharged, because this action will increase the likelihood that the patient actually receives an appointment and attends the followup (Baren et al. 2006; Zorc et al. 2003). At the followup appointment, the health care provider should try to ascertain the cause of the exacerbation and institute appropriate, specific, preventative therapy if possible. The followup visit should also include a detailed review of the patient's medications, inhaler and peak flow meter technique, and development of a comprehensive written asthma action plan that will help prevent subsequent exacerbations and urgent or emergency care visits (See section 3, "Component 2: Education for a Partnership in Asthma Care," figures 3–10a, b, and c; 3–11; and 3–14.). If appropriate, consider referring the patient to an asthma self-management education program.

- **Review discharge medications with the patient and provide patient education on correct use of an inhaler (Evidence B)** (See section 3, "Component 2: Education for a Partnership in Asthma Care," figures 3–12 and 3–14.).

- **Give the patient an ED asthma discharge plan with instruction for medications prescribed at discharge and for increasing medications or seeking medical care if asthma should worsen (Evidence B).** Although evidence from RCTs is limited, for many patients, a thoughtful, asthma-oriented ED discharge plan will suffice. If local staff and resources permit, however, the provision of a more detailed plan may be appropriate, especially for patients who had severe exacerbations or who do not have regular asthma care. See figure 5–7 for a sample ED asthma discharge plan and "Component 2: Education for a Partnership in Asthma Care."

- **Consider issuing a peak flow meter and giving appropriate education on how to measure and record PEF to patients who have difficulty perceiving airflow obstruction or symptoms of worsening asthma (Evidence D).** Studies document that some patients are unable to perceive signs of deterioration that would indicate a need to increase medication (Hardie et al. 2002; Kikuchi et al. 1994). These "poor perceivers" may particularly benefit from action plans based on peak flow monitoring, because this tool may prevent delays in treating exacerbations. Although clinical trials have not yet evaluated issuing peak flow meters at discharge from ED, it is the opinion of the Expert Panel that this approach warrants consideration. See "Component 1: Measures of Asthma Assessment and Monitoring" and "Component 2: Education for a Partnership in Asthma Care" for discussions of the advantages and disadvantages of peak flow monitoring.

FIGURE 5–7. EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN

EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN

Name: _____ was seen by **Dr.**_____ on ___/___/___

- Take your prescribed medications as directed—do not delay!
- Asthma attacks like this one can be prevented with a long-term treatment plan.
- Even when you feel well, you may need daily medicine to keep your asthma in good control and prevent attacks.
- Visit your doctor or other health care provider as soon as you can to discuss how to control your asthma and to develop *your own* action plan.

Your followup appointment with _____ is on: ___/___/___. **Tel:** _____

YOUR MEDICINE FOR THIS ASTHMA ATTACK IS:

Medication	Amount	Doses per day, for # days
Prednisone/prednisolone (oral corticosteroid)		_____ a day for _____ days Take the entire prescription, even when you start to feel better.
Inhaled albuterol		_____ puffs every 4 to 6 hours if you have symptoms, for _____days

YOUR DAILY MEDICINE FOR LONG-TERM CONTROL AND PREVENTING ATTACKS IS:

Medication	Amount	Doses per day
Inhaled corticosteroids		

YOUR QUICK-RELIEF MEDICINE WHEN YOU HAVE SYMPTOMS IS:

Medication	Amount	Number of doses/day
Inhaled albuterol		

ASK YOURSELF 2 TO 3 TIMES PER DAY, EVERY DAY, FOR AT LEAST 1 WEEK:

"How good is my asthma compared to when I left the hospital?"

If you feel much better:	**If you feel better, but still need your quick-relief inhaler often:**	**If you feel about the same:**	**If you feel worse:**
• Take your daily long-term control medicine.	• Take your daily long-term-control medicine. • See your doctor as soon as possible.	• Use your quick-relief inhaler. • Take your daily long-term control medicine. • See your doctor as soon as possible—don't delay.	• Use your quick-relief inhaler. • Take your daily long-term control medicine. • Immediately go to the emergency department or call 9–1–1.

YOUR ASTHMA IS UNDER CONTROL WHEN YOU:

① Can be active daily and sleep through the night.	② Need fewer than 4 doses of quick-relief medicine in a week.	③ Are free of shortness of breath, wheeze, and cough.	④ Achieve an acceptable "peak flow" (discuss with your health care provider).

Reprinted by permission from Carlos Camargo, M.D., Principal Investigator of Agency for Health Care Research and Quality. Grant No. R13H31094.

Source: Camargo CA Jr, Emond SD, Boulet L, Gibson PG, Kolbe J, Wagner CW, Brenner BE. Emergency Department—Asthma Action Plan. Developed at "Asthma Education in the Adult Emergency Department: A Multidisciplinary Consensus Conference," New York Academy of Medicine, New York, NY; 2001 April 1–5. Boston, MA: Massachusetts General Hospital, 2001. 2 pp.

FIGURE 5–7b. EMERGENCY DEPARTMENT—ASTHMA DISCHARGE PLAN: HOW TO USE YOUR METERED-DOSE INHALER

Using an inhaler seems simple, but most patients do not use it the right way. When you use your inhaler the wrong way, less medicine gets to your lungs.

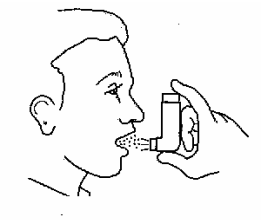
For the next few days, read these steps aloud as you do them or ask someone to read them to you. Ask your doctor, nurse, other health care provider, or pharmacist to check how well you are using your inhaler.

Use your inhaler in one of the three ways pictured below. A or B are best, but C can be used if you have trouble with A and B. Your doctor may give you other types of inhalers.

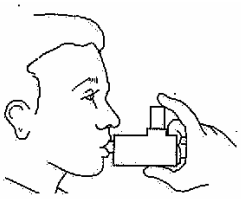
Steps for Using Your Inhaler

Getting ready	1. Take off the cap and shake the inhaler. 2. Breathe out all the way. 3. Hold your inhaler the way your doctor said (A, B, or C below).
Breathe in slowly	4. As you start breathing in slowly through your mouth, press down on the inhaler one time. (If you use a holding chamber, first press down on the inhaler. Within 5 seconds, begin to breathe in slowly.) 5. Keep breathing in slowly, as deeply as you can.
Hold your breath	6. Hold your breath as you count to 10 slowly, if you can. 7. For inhaled quick-relief medicine (short-acting beta$_2$-agonists), wait about 15–30 seconds between puffs. There is no need to wait between puffs for other medicines.

L. Hold inhaler 1 to 2 inches in front of your mouth (about the width of two fingers).



M. Use a spacer/holding chamber. These come in many shapes and can be useful to any patient.



N. Put the inhaler in your mouth. Do not use for steroids.

Clean your inhaler as needed, and know when to replace your inhaler. For instructions, read the package insert or talk to your doctor, other health care provider, or pharmacist.

The Expert Panel recommends the following actions for discharging patients from the hospital:

- **Prior to discharge, adjust the patient's medication to an outpatient regimen (EPR—2 1997).** During the first 24 hours after this medication adjustment, observe the patient for possible deterioration.

- **Discharge medications should include a SABA and sufficient oral systemic corticosteroids to complete the course of therapy (Evidence A) and instructions to continue long-term control therapy until the followup appointment (Evidence B). Consider initiating ICS therapy for patients who did not use an ICS prior to the hospital admission (Evidence B).** If the decision is made to start the patient on an ICS, the ICS should be started before the course of oral corticosteroids is completed, because their onset of action is gradual (Kraan et al. 1988). Starting the ICS therapy before discharge gives the patient additional time to learn and demonstrate appropriate technique.

- **Provide patient education:**

  — **Review patient understanding of the causes of asthma exacerbations, the purposes and correct uses of treatment (including inhaler technique), and the actions to be taken for worsening symptoms or peak flow measures (Evidence B) (See "Component 2: Education for a Partnership in Asthma Care.").** An exacerbation severe enough to require hospitalization may reflect a failure of the patient's self-management, particularly in patients who have low levels of health literacy (Paasche-Orlow et al. 2005). Some studies report that 35 percent of adult patients presenting to the ED are current smokers (Silverman et al. 2003). It would be appropriate to query patients hospitalized for asthma about their smoking status and encourage smoking cessation along with their asthma discharge plan. Hospitalized patients may be particularly receptive to information and advice about their illness (See "Component 2: Education for a Partnership in Asthma Care.").

  — **Educate patients about their discharge medications and the importance of taking medications as prescribed and attending their followup visit (Evidence B).** Low levels of adherence to asthma medications are common, even in patients recently hospitalized for severe asthma exacerbations (Krishnan et al. 2004).

  — **Referral to an asthma specialist should be considered for patients who have a history of life-threatening exacerbations or multiple hospitalizations (Evidence B)** (Harish et al. 2001; Mahr and Evans 1993; Mayo et al. 1990; Sperber et al. 1995).

  — **Consider issuing a peak flow meter and giving appropriate education on peak flow monitoring to patients who are ≥5 years of age (and parents) who have a history of severe exacerbations or who have moderate or severe persistent asthma (Evidence B) and those who poorly perceive airflow obstruction or worsening asthma (Evidence D).**

- **Review or develop a written plan for managing either relapse of the exacerbation of recurrent symptoms or exacerbations (Evidence B).** The plan should describe the signs, symptoms, and/or peak flow values that should prompt increases in self-medication, contact with a health care provider, or return for emergency care. The plan given at discharge from the ED may be quite simple (e.g., instructions for discharge medications and returning for care if asthma worsens; see figure 5–7). The preparation for discharge from the hospital should be more complete (See figure 5–8.). A detailed written asthma action plan for comprehensive long-term management and handling of exacerbations should be developed by the regular provider at a followup visit (See figure 3–10a, b, and c; "Component 2: Education for a Partnership in Asthma Care.").

FIGURE 5–8. CHECKLIST FOR HOSPITAL DISCHARGE OF PATIENTS WHO HAVE ASTHMA

Intervention	Dose/Timing	Education/Advice	M.D./R.N. Initials
Inhaled medications (e.g., MDI with valved holding chamber (VHC or spacer); nebulizer)	Select agent, dose, and frequency (e.g., albuterol)	■ Teach purpose ■ Teach and check technique ■ For MDIs, emphasize the importance of VHC or spacer	
SABA	2–6 puffs every 3–4 hours as needed		
Corticosteroids	Medium dose		
Oral medications	Select agent, dose, and frequency (e.g., prednisone 50 mg qd for 5 days)	■ Teach purpose ■ Teach side effects	
Peak flow meter	For selected patients: measure a.m. and p.m. PEF, and record best of three tries each time	■ Teach purpose ■ Teach technique ■ Distribute peak flow diary	
Followup visit	Make appointment for followup care with primary clinician or asthma specialist	Advise patient (or caregiver) of date, time, and location of appointment, ideally within 7 days of hospital discharge	
Action plan	Before or at discharge	Instruct patient (or caregiver) on simple plan for actions to be taken when symptoms, signs, or PEF values suggest airflow obstruction	

Key: MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting beta$_2$-agonist.

References

Abramson MJ, Bailey MJ, Couper FJ, Driver JS, Drummer OH, Forbes AB, McNeil JJ, Haydn WE; Victorian Asthma Mortality Study Group. Are asthma medications and management related to deaths from asthma? *Am J Respir Crit Care Med* 2001;163(1):12–8.

Allen JY, Macias CG. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. *Ann Emerg Med* 2005;46(1):43–50.

Banasiak NC, Meadows-Oliver M. Inpatient asthma clinical pathways for the pediatric patient: an integrative review of the literature. *Pediatr Nurs* 2004;30(6):447–50.

Baren JM, Boudreaux ED, Brenner BE, Cydulka RK, Rowe BH, Clark S, Camargo CA Jr. Randomized controlled trial of emergency department interventions to improve primary care follow-up for patients with acute asthma. *Chest* 2006;129(2):257–65.

Blitz M, Blitz S, Hughes R, Diner B, Beasley R, Knopp J, Rowe BH. Aerosolized magnesium sulfate for acute asthma: a systematic review. *Chest* 2005;128(1):337–44.

Boonyavorakul C, Thakkinstian A, Charoenpan P. Intravenous magnesium sulfate in acute severe asthma. *Respirology* 2000;5(3):221–5.

Boychuk RB, Yamamoto LG, DeMesa CJ, Kiyabu KM. Correlation of initial emergency department pulse oximetry values in asthma severity classes (steps) with the risk of hospitalization. *Am J Emerg Med* 2006;24(1):48–52.

Browne GJ, Penna AS, Phung X, Soo M. Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. *Lancet* 1997;349(9048):301–5.

Camargo CA Jr. A model protocol for emergency medical services management of asthma exacerbations. *Prehosp Emerg Care* 2006;10(4):418–29.

Camargo CA Jr, Emond SD, Boulet L, Gibson PG, Kolbe J, Wagner CW, Brenner BE. Emergency Department—Asthma Action Plan. Developed at "Asthma Education in the Adult Emergency Department: A Multidisciplinary Consensus Conference," New York Academy of Medicine, New York, NY; 2001 April 1–5. Boston, MA: Massachusetts General Hospital, 2001. 2 pp.

Camargo CA Jr, Smithline HA, Malice MP, Green SA, Reiss TF. A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med* 2003a;167(4):528–33.

Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev* 2003b;(4):CD001115.

Cates CC, Bara A, Crilly JA, Rowe BH. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2003;(3):CD000052.

Cham GW, Tan WP, Earnest A, Soh CH. Clinical predictors of acute respiratory acidosis during exacerbation of asthma and chronic obstructive pulmonary disease. *Eur J Emerg Med* 2002;9(3):225–32.

Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child* 2005;90(1):74–7.

Chey T, Jalaludin B, Hanson R, Leeder S. Validation of a predictive model for asthma admission in children: how accurate is it for predicting admissions? *J Clin Epidemiol* 1999;52(12):1157–63.

Connett GJ, Lenney W. Use of pulse oximetry in the hospital management of acute asthma in childhood. *Pediatr Pulmonol* 1993;15(6):345–9.

Crago S, Coors L, Lapidus JA, Sapien R, Murphy SJ. Prehospital treatment of acute asthma in a rural state. *Ann Allergy Asthma Immunol* 1998;81(4):322–5.

Craven D, Kercsmar CM, Myers TR, O'Riordan MA, Golonka G, Moore S. Ipratropium bromide plus nebulized albuterol for the treatment of hospitalized children with acute asthma. *J Pediatr* 2001;138(1):51–8.

Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. *Am Rev Respir Dis* 1984;129(3):385–37.

Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. *Am J Respir Crit Care Med* 1997;156(1):3–10.

Diner B, Brenner B, Camargo CA Jr. Inaccuracy of "personal best" peak expiratory flow rate reported by inner-city patients with acute asthma. *J Asthma* 2001;38(2):127–32.

Dockhorn RJ, Baumgartner RA, Leff JA, Noonan M, Vandormael K, Stricker W, Weinland DE, Reiss TF. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax* 2000;55(4):260–5.

Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, Smaldone GC, Guyatt G; American College of Chest Physicians; American College of Asthma, Allergy, and Immunology. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest* 2005;127(1):335–71.

Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev* 2003;(3):CD002308.

Edmonds ML, Camargo CA Jr, Saunders LD, Brenner BE, Rowe BH. Inhaled steroids in acute asthma following emergency department discharge. *Cochrane Database Syst Rev* 2000;(3):CD002316.

EPR—2. Expert panel report 2: guidelines for the diagnosis and management of asthma (EPR—2 1997). NIH Publication No. 97-4051. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997.

EPR—Update 2002. Expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics 2002 (EPR—Update 2002). NIH Publication No. 02-5074. Bethesda, MD: U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, June 2003. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf.

Fergusson RJ, Stewart CM, Wathen CG, Moffat R, Crompton GK. Effectiveness of nebulised salbutamol administered in ambulances to patients with severe acute asthma. *Thorax* 1995;50(1):81–2.

FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004;59(7):550–6.

Foresi A, Morelli MC, Catena E. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group. *Chest* 2000;117(2):440–6.

Garrett J, Williams S, Wong C, Holdaway D. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. *Arch Dis Child* 1998;79(1):12–7.

Geelhoed GC, Landau LI, Le Souef PN. Evaluation of SaO_2 as a predictor of outcome in 280 children presenting with acute asthma. *Ann Emerg Med* 1994;23(6):1236–41.

Goggin N, Macarthur C, Parkin PC. Randomized trial of the addition of ipratropium bromide to albuterol and corticosteroid therapy in children hospitalized because of an acute asthma exacerbation. *Arch Pediatr Adolesc Med* 2001;155(12):1329–34.

Gorelick MH, Stevens MW, Schultz T, Scribano PV. Difficulty in obtaining peak expiratory flow measurements in children with acute asthma. *Pediatr Emerg Care* 2004a;20(1):22–6.

Gorelick MH, Stevens MW, Schultz TR, Scribano PV. Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. *Acad Emerg Med* 2004b;11(1):10–8.

Greenberger PA, Miller TP, Lifschultz B. Circumstances surrounding deaths from asthma in Cook County (Chicago) Illinois. *Allergy Proc* 1993;14(5):321–6.

Gupta VK, Cheifetz IM. Heliox administration in the pediatric intensive care unit: an evidence-based review. *Pediatr Crit Care Med* 2005;6(2):204–11.

Hardie GE, Gold WM, Janson S, Carrieri-Kohlman V, Boushey HA. Understanding how asthmatics perceive symptom distress during a methacholine challenge. *J Asthma* 2002;39(7):611–8.

Harish Z, Bregante AC, Morgan C, Fann CS, Callaghan CM, Witt MA, Levinson KA, Caspe WB. A comprehensive inner-city asthma program reduces hospital and emergency room utilization. *Ann Allergy Asthma Immunol* 2001;86(2):185–9.

Harrison BD, Stokes TC, Hart GJ, Vaughan DA, Ali NJ, Robinson AA. Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. *Lancet* 1986;1(8474):181–4.

Harrison TW, Oborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. *Lancet* 2004;363(9405):271–5.

Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA Jr. The effect of heliox on nebulizer function using a beta-agonist bronchodilator. *Chest* 1999;115(1):184–9.

Ho J, Bender BG, Gavin LA, O'Connor SL, Wamboldt MZ, Wamboldt FS. Relations among asthma knowledge, treatment adherence, and outcome. *J Allergy Clin Immunol* 2003;111(3):498–502.

Howton JC, Rose J, Duffy S, Zoltanski T, Levitt MA. Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. *Ann Emerg Med* 1996;27(2):170–5.

Jones A, Rowe B, Peters J, Camargo C, Hammarquist C, Rowe B. Inhaled beta-agonists for asthma in mechanically ventilated patients. *Cochrane Database Syst Rev* 2001;(4):CD001493.

Kallenbach JM, Frankel AH, Lapinsky SE, Thornton AS, Blott JA, Smith C, Feldman C, Zwi S. Determinants of near fatality in acute severe asthma. *Am J Med* 1993;95(3):265–72.

Karpel JP, Aldrich TK, Prezant DJ, Guguchev K, Gaitan-Salas A, Pathiparti R. Emergency treatment of acute asthma with albuterol metered-dose inhaler plus holding chamber: how often should treatments be administered? *Chest* 1997;112(2):348–56.

Karras DJ, Sammon ME, Terregino CA, Lopez BL, Griswold SK, Arnold GK. Clinically meaningful changes in quantitative measures of asthma severity. *Acad Emerg Med* 2000;7(4):327–34.

Keahey L, Bulloch B, Becker AB, Pollack CV Jr, Clark S, Camargo CA Jr. Initial oxygen saturation as a predictor of admission in children presenting to the emergency department with acute asthma. *Ann Emerg Med* 2002;40(3):300–7.

Kelly AM, Kerr D, Powell C. Is severity assessment after one hour of treatment better for predicting the need for admission in acute asthma? *Respir Med* 2004;98(8):777–81.

Kelly AM, Kyle E, McAlpine R. Venous pCO(2) and pH can be used to screen for significant hypercarbia in emergency patients with acute respiratory disease. *J Emerg Med* 2002a;22(1):15–9.

Kelly AM, Powell C, Kerr D. Patients with a longer duration of symptoms of acute asthma are more likely to require admission to hospital. *Emerg Med (Fremantle)* 2002b;14(2):142–5.

Keogh KA, Macarthur C, Parkin PC, Stephens D, Arseneault R, Tennis O, Bacal L, Schuh S. Predictors of hospitalization in children with acute asthma. *J Pediatr* 2001;139(2):273–7.

Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato K, Takishima T. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Engl J Med* 1994;330(19):1329–34.

Kim IK, Phrampus E, Venkataraman S, Pitetti R, Saville A, Corcoran T, Gracely E, Funt N, Thompson A. Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: a randomized, controlled trial. *Pediatrics* 2005;116(5):1127–33.

Knapp B, Wood C. The prehospital administration of intravenous methylprednisolone lowers hospital admission rates for moderate to severe asthma. *Prehosp Emerg Care* 2003;7(4):423–6.

Kraan J, Koeter GH, van der Mark TW, Boorsma M, Kukler J, Sluiter HJ, De Vries K. Dosage and time effects of inhaled budesonide on bronchial hyperreactivity. *Am Rev Respir Dis* 1988;137(1):44–8.

Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, Hill P, Rand CS. Corticosteroid use after hospital discharge among high-risk adults with asthma. *Am J Respir Crit Care Med* 2004;170(12):1281–15.

Krishnan V, Diette GB, Rand CS, Bilderback AL, Merriman B, Hansel NN, Krishnan JA. Mortality in patients hospitalized for asthma exacerbations in the United States. *Am J Respir Crit Care Med* 2006;174(6):633–8.

Kuyper LM, Pare PD, Hogg JC, Lambert RK, Ionescu D, Woods R, Bai TR. Characterization of airway plugging in fatal asthma. *Am J Med* 2003;115(1):6–11.

Lahn M, Bijur P, Gallagher EJ. Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department. *Chest* 2004;126(2):362–8.

Lee DL, Hsu CW, Lee H, Chang HW, Huang YC. Beneficial effects of albuterol therapy driven by heliox versus by oxygen in severe asthma exacerbation. *Acad Emerg Med* 2005;12(9):820–7.

Maguire JF, O'Rourke PP, Colan SD, Geha RS, Crone R. Cardiotoxicity during treatment of severe childhood asthma. *Pediatrics* 1991;88(6):1180–6.

Mahr TA, Evans R III. Allergist influence on asthma care. *Ann Allergy* 1993;71(2):115–20.

Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database Syst Rev* 2001;(1):CD001740.

Markenson D, Foltin G, Tunik M, Cooper A, Treiber M, Caravaglia K. Albuterol sulfate administration by EMT-basics: results of a demonstration project. *Prehosp Emerg Care* 2004;8(1):34–40.

Mayo PH, Richman J, Harris HW. Results of a program to reduce admissions for adult asthma. *Ann Intern Med* 1990;112(11):864–71.

McCarren M, Zalenski RJ, McDermott M, Kaur K. Predicting recovery from acute asthma in an emergency diagnostic and treatment unit. *Acad Emerg Med* 2000;7(1):28–35.

McFadden ER Jr. The chronicity of acute attacks of asthma—mechanical and therapeutic implications. *J Allergy Clin Immunol* 1975;56(1):18–26.

McFadden ER Jr. Acute severe asthma. *Am J Respir Crit Care Med* 2003;168(7):740–759.

Menitove SM, Goldring RM. Combined ventilator and bicarbonate strategy in the management of status asthmaticus. *Am J Med* 1983;74(5):898–901.

Mitra A, Bassler D, Goodman K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. *Cochrane Database Syst Rev* 2005;(2):CD001276. Review.

O'Driscoll BR, Kalra S, Wilson M, Pickering CA, Carroll KB, Woodcock AA. Double-blind trial of steroid tapering in acute asthma. *Lancet* 1993;341(8841):324–7.

O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, Sachs MI. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991;324(6):359–63.

Paasche-Orlow MK, Riekert KA, Bilderback A, Chanmugam A, Hill P, Rand CS, Brancati FL, Krishnan JA. Tailored education may reduce health literacy disparities in asthma self-management. *Am J Respir Crit Care Med* 2005;172(8):980–6. Epub August 2005.

Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. *Crit Care Med* 1993;21(10):1479–86.

Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta$_2$-agonists in adults with acute asthma. *Cochrane Database Syst Rev* 2000;(4):CD002742.

Plotnick LH, Ducharme FM. Combined inhaled anticholinergics and beta$_2$-agonists for initial treatment of acute asthma in children. *Cochrane Database Syst Rev* 2000;(4):CD000060.

Pollack CV Jr, Pollack ES, Baren JM, Smith SR, Woodruff PG, Clark S, Camargo CA Jr; Multicenter Airway Research Collaboration Investigators. A prospective multicenter study of patient factors associated with hospital admission from the emergency department among children with acute asthma. *Arch Pediatr Adolesc Med* 2002;156(9):934–40.

Porter RS, Nester, Braitman LE, Geary U, Dalsey WC. Intravenous magnesium is ineffective in adult asthma, a randomized trial. *Eur J Emerg Med* 2001;8(1):9–15.

Rachelefsky G. Treating exacerbations of asthma in children: the role of systemic corticosteroids. *Pediatrics* 2003;112(2):382–97.

Radeos MS, Camargo CA Jr. Predicted peak expiratory flow: differences across formulae in the literature. *Am J Emerg Med* 2004;22(7):516–21.

Ram FS, Wellington S, Rowe BH, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev* 2005;(1):CD004360.

Ratto D, Alfaro C, Sipsey J, Glovsky MM, Sharma OP. Are intravenous corticosteroids required in status asthmaticus? *JAMA* 1988;260(4):527–9.

Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A. Differences between asthma exacerbations and poor asthma control. *Lancet* 1999;353(9150):364–9.

Rice-McDonald G, Bowler S, Staines G, Mitchell C. Doubling daily inhaled corticosteroid dose is ineffective in mild to moderately severe attacks of asthma in adults. *Intern Med J* 2005;35(12):693–8.

Richmond NJ, Silverman R, Kusick M, Matallana L, Winokur J. Out-of-hospital administration of albuterol for asthma by basic life support providers. *Acad Emerg Med* 2005;12(5):396–403.

Ritz T, Steptoe A, Dewilde S, Costa M. Emotions and stress increase respiratory resistance in asthma. *Psychosom Med* 2000;62(3):401–12.

Rivera ML, Kim TY, Stewart GM, Minasyan L, Brown L. Albuterol nebulized in heliox in the initial ED treatment of pediatric asthma: a blinded, randomized controlled trial. *Am J Emerg Med* 2006;24(1):38–42.

Rodrigo C, Rodrigo G. Salbutamol treatment of acute severe asthma in the ED: MDI versus hand-held nebulizer. *Am J Emerg Med* 1998a;16(7):637–42.

Rodrigo C, Rodrigo G. Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. *Chest* 1998b;113(3):593–8.

Rodrigo G, Rodrigo C. Assessment of the patient with acute asthma in the emergency department. A factor analytic study. *Chest* 1993;104(5):1325–8.

Rodrigo G, Rodrigo C. Early prediction of poor response in acute asthma patients in the emergency department. *Chest* 1998c;114(4):1016–21.

Rodrigo GJ. Comparison of inhaled fluticasone with intravenous hydrocortisone in the treatment of adult acute asthma. *Am J Respir Crit Care Med* 2005;171(11):1231–6. Epub March 2005.

Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005;60(9):740–6. Epub July 2005. Erratum in: *Thorax* 2006;61(3):274 and *Thorax* 2006;61(5):458.

Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. *Chest* 2004;125(3):1081–102.

Rowe BH, Bota GW, Fabris L, Therrien SA, Milner RA, Jacono J. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: a randomized controlled trial. *JAMA* 1999;281(22):2119–26.

Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA Jr. Intravenous magnesium sulfate treatment for acute asthma in the emergency department: a systematic review of the literature. *Ann Emerg Med* 2000;36(3):181–90.

Rowe BH, Edmonds ML, Spooner CH, Camargo CA Jr. Evidence-based treatments for acute asthma. *Respir Care* 2001;46(12):1380–1390. Discussion 1390–1.

Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA Jr. Corticosteroid therapy for acute asthma. *Respir Med* 2004;98(4):275–84.

Scarfone RJ, Loiselle JM, Joffe MD, Mull CC, Stiller S, Thompson K, Gracely EJ. A randomized trial of magnesium in the emergency department treatment of children with asthma. *Ann Emerg Med* 2000;36(6):572–8.

Schuckman H, DeJulius DP, Blanda M, Gerson LW, DeJulius AJ, Rajaratnam M. Comparison of intramuscular triamcinolone and oral prednisone in the outpatient treatment of acute asthma: a randomized controlled trial. *Ann Emerg Med* 1998;31(3):333–8.

Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arseneault R, Alothman G, Tennis O, Canny G. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. *N Engl J Med* 2000;343(10):689–94.

Shim CS, Williams MH Jr. Evaluation of the severity of asthma: patients versus physicians. *Am J Med* 1980;68(1):11–3.

Silverman RA, Boudreaux ED, Woodruff PG, Clark S, Camargo CA Jr. Cigarette smoking among asthmatic adults presenting to 64 emergency departments. *Chest* 2003;123(5):1472–9.

Silverman RA, Osborn H, Runge J, Gallagher EJ, Chiang W, Feldman J, Gaeta T, Freeman K, Levin B, Mancherje N, et al.; Acute Asthma/Magnesium Study Group. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest* 2002;122(2):489–97.

Sin DD, Bell NR, Svenson LW, Man SF. The impact of follow-up physician visits on emergency readmissions for patients with asthma and chronic obstructive pulmonary disease: a population-based study. *Am J Med* 2002;112(2):120–5.

Sin DD, Man SF. Low-dose inhaled corticosteroid therapy and risk of emergency department visits for asthma. *Arch Intern Med* 2002;162(14):1591–5.

Singhi S, Banerjee S, Nanjundaswamy H. Inhaled budesonide in acute asthma. *J Paediatr Child Health* 1999;35(5):483–7.

Sly RM, Badiei B, Faciane J. Comparison of subcutaneous terbutaline with epinephrine in the treatment of asthma in children. *J Allergy Clin Immunol* 1977;59(2):128–35.

Smith M, Iqbal S, Elliott TM, Everard M, Rowe BH. Corticosteroids for hospitalised children with acute asthma. *Cochrane Database Syst Rev* 2003;(1):CD002886.

Smith PR, Heurich AE, Leffler CT, Henis MM, Lyons HA. A comparative study of subcutaneously administered terbutaline and epinephrine in the treatment of acute bronchial asthma. *Chest* 1977;71(2):129–34.

Smith SR, Baty JD, Hodge D III. Validation of the pulmonary score: an asthma severity score for children. *Acad Emerg Med* 2002;9(2):99–104.

Smith SR, Jaffe DM, Fisher EB Jr, Trinkaus KM, Highstein G, Strunk RC. Improving follow-up for children with asthma after an acute Emergency Department visit. *J Pediatr* 2004;145(6):772–7. Erratum in: *J Pediatr* 2005;146(3):413.

Sole D, Komatsu MK, Carvalho KV, Naspitz CK. Pulse oximetry in the evaluation of the severity of acute asthma and/or wheezing in children. *J Asthma* 1999;36(4):327–33.

Sperber K, Ibrahim H, Hoffman B, Eisenmesser B, Hsu H, Corn B. Effectiveness of a specialized asthma clinic in reducing asthma morbidity in an inner-city minority population. *J Asthma* 1995;32(5):335–43.

Stead L, Whiteside T. Evaluation of a new EMS asthma protocol in New York City: a preliminary report. *Prehosp Emerg Care* 1999;3(4):338–42.

Strauss L, Hejal R, Galan G, Dixon L, McFadden ER Jr. Observations on the effects of aerosolized albuterol in acute asthma. *Am J Respir Crit Care Med* 1997;155(2):454–458.

Strunk RC, Mrazek DA. Deaths from asthma in childhood: can they be predicted? *N Engl Reg Allergy Proc* 1986;7(5):454–61.

Sturdy PM, Butland BK, Anderson HR, Ayres JG, Bland JM, Harrison BD, Peckitt C, Victor CR; National Asthma Campaign Mortality and Severe Morbidity Group. Deaths certified as asthma and use of medical services: a national case-control study. *Thorax* 2005;60(11):909–15. Epub July 2005.

Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockroft D, Blais L, McNutt M, Buist AS, Spitzer WO. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;149(3 Pt 1):604–10.

Travers A, Jones AP, Kelly K, Barker SJ, Camargo CA, Rowe BH. Intravenous beta$_2$-agonists for acute asthma in the emergency department. *Cochrane Database Syst Rev* 2001;(2):CD002988.

Tuxen DV. Permissive hypercapnic ventilation. *Am J Respir Crit Care Med* 1994;150(3):870–4.

von Leupoldt A, Dahme B. Emotions and airway resistance in asthma: study with whole body plethysmography. *Psychophysiology* 2005;42(1):92–7.

Weber EJ, Silverman RA, Callaham ML, Pollack CV Jr, Woodruff PG, Clark S, Camargo CA Jr. A prospective multicenter study of factors associated with hospital admission among adults with acute asthma. *Am J Med* 2002;113(5):371–8.

Wright RO, Santucci KA, Jay GD, Steele DW. Evaluation of pre- and posttreatment pulse oximetry in acute childhood asthma. *Acad Emerg Med* 1997;4(2):114–7.

Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. *Arch Dis Child* 1998;79(5):405–10.

Zeiger RS, Heller S, Mellon MH, Wald J, Falkoff R, Schatz M. Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits. *J Allergy Clin Immunol* 1991;87(6):1160–8. Erratum in: *J Allergy Clin Immunol* 1992;90(2):278.

Zorc JJ, Scarfone RJ, Li Y, Hong T, Harmelin M, Grunstein L, Andre JB. Scheduled follow-up after a pediatric emergency department visit for asthma: a randomized trial. *Pediatrics* 2003;111(3):495–502.

For More Information

The National Heart, Lung, and Blood Institute (NHLBI) Health Information Center is a service of the NHLBI of the National Institutes of Health. The NHLBI Health Information Center provides information to health professionals, patients, and the public about the treatment, diagnosis, and prevention of heart, lung, and blood diseases and sleep disorders. For more information, contact:

NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Phone: 301-592-8573
TTY: 240-629-3255
Fax: 301-592-8563
Web site: http://www.nhlbi.nih.gov

NIH Publication No. 07-4051
Originally Printed July 1997
Revised June 2002, August 2007