Approach to Internal Medicine

A Resource Book for Clinical Practice

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Fifth Edition

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PULMONARY MEDICINE

Ashley-Mae E. Gillson

Asthma

2020 Global Initiative for Asthma Guidelines
FitzGerald et al. *Can J Respir Crit Care Sleep Med* 2017;1(4)
Lougheed et al. *Can Respir J* 2012;19(2)

DIFFERENTIAL DIAGNOSIS OF WHEEZING

EXTRATHORACIC AIRWAY OBSTRUCTION

- **OROPHARYNX**—enlarged tonsils, retropharyngeal abscess, obesity, post-nasal drip
- **LARYNX**—laryngeal edema, laryngostenosis, laryngocele, epiglottitis, anaphylaxis, severe laryngopharyngeal reflux, laryngospasm
- **VOCAL CORDS**—vocal cord dysfunction, paralysis, hematoma, tumor, cricoarytenoid arthritis

INTRATHORACIC AIRWAY OBSTRUCTION

- **TRACHEAL OBSTRUCTION**—tracheal/subglottic stenosis, tracheomalacia, tracheobronchitis (herpetic, fungal), malignancy, benign tumor, aspiration, foreign body
- **TRACHEAL COMPRESSION**—goiter, right-sided aortic arch
- **LOWER AIRWAY OBSTRUCTION**—asthma, COPD, bronchiolitis, bronchiectasis, carcinoid tumor, aspiration, malignancy
- **PARENCHYMA**—pulmonary edema
- **VASCULAR**—pulmonary embolism

PATHOPHYSIOLOGY

DEFINITION OF ASTHMA—heterogeneous disease, characterized by chronic airway inflammation with variable expiratory airflow limitation, which may later become persistent

CLINICAL PHENOTYPES OF ASTHMA

- **ALLERGIC ASTHMA**—most recognized; often starts in childhood and associated with a past or family history of allergic disease such as eczema, allergic rhinitis, or food/drug allergy; induced sputum eosinophils often increased; responds well to inhaled corticosteroid (ICS) treatment

PATHOPHYSIOLOGY (CONT'D)

- **NON-ALLERGIC ASTHMA**—asthma not associated with allergy. Sputum analysis may be neutrophilic, eosinophilic, or paucigranulocytic; lower short-term response rate to ICS
- **ADULT-ONSET ASTHMA**—often non-allergic, more frequently in women; often requires higher doses of ICS or is relatively refractory to corticosteroid treatment. Occupational asthma must be ruled out
- **ASTHMA WITH PERSISTENT AIRFLOW LIMITATION**—patients with longstanding asthma develop incompletely reversible airflow limitation thought to be due to airway wall remodeling
- **ASTHMA WITH OBESITY**—prominent respiratory symptoms and little eosinophilic airway inflammation

EXACERBATORS OF ASTHMA

- **INFECTIONS**—viral, bacterial, fungal
- **OUTDOORS**—respirable particulates, ozone, sulfur dioxide, cold air, humidity, smoking
- **INDOORS**—smoke, dust mites, air conditioners, humidity, perfumes, scents, mold, animal dander
- **NON-ADHERENCE**
- **INCORRECT INHALER TECHNIQUE**
- **MAJOR PSYCHOLOGICAL OR SOCIOECONOMIC PROBLEMS**

RISK FACTORS FOR ASTHMA EXACERBATIONS—>1 exacerbation in previous year, socioeconomic status, poor adherence, incorrect inhaler technique, low lung function, smoking, eosinophilia

CLINICAL FEATURES

HISTORY—history of asthma and any life-threatening exacerbations, number of ER visits/hospital admissions in the last 6 months (or ever),

D. Hui et al. (eds.), *Approach to Internal Medicine*,
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CLINICAL FEATURES (CONT'D)

any ICU admissions, previous prednisone use, triggers for attacks, usual peak expiratory flow rate, change in peak flow rates, wheezing, cough, dyspnea, decreased function, exercise limitation, nocturnal symptoms, absenteeism from work/school, postnasal drip, recurrent sinusitis, GERD, past medical history, medication history, psychosocial issues, occupational and work environment, home environment (pets, heating source, filter changes, mold)

PHYSICAL—HR ↑, RR ↑, pulsus paradoxus, O_2 requirement, moderate-severe dyspnea, barrel chest, cyanosis, stridor, chest hyperresonance, decreased breath sounds, wheezing, forced expiratory time

TYPES OF WHEEZING—inspiratory wheeze and expiratory wheeze are classically associated with extrathoracic and intrathoracic airway obstruction, respectively. However, they are neither sensitive nor specific and cannot help to narrow differential diagnosis

INVESTIGATIONS

BASIC

- **LABS**—CBC (including eosinophils), lytes, urea, Cr, troponin/CK
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S, nasopharyngeal swab for viral studies
- **IMAGING**—CXR

SPECIAL

- **ABG**—if acute respiratory distress
- **PEAK FLOW METER**—need to compare bedside reading to patient's baseline
- **SPIROMETRY/PFT** (non-acute setting)—↑ FEV1 >12% and an absolute ↑ by 200 mL post-bronchodilator suggests asthma
- **BRONCHIAL PROVOCATION TESTING** (i.e. methacholine challenge, non-acute setting)—if diagnosis of asthma not confirmed by spirometry alone. A decrease of FEV1 >20% after methacholine challenge suggests asthma. Sens 95%
- **ALLERGY TESTING** (non-acute setting)—skin prick testing has high sensitivity, allergen serology IgE testing
- **SPUTUM EOSINOPHIL COUNTS** (non-acute setting)—performed in specialized centres for monitoring of asthma control in patients with moderate to severe asthma
- **FRACTIONAL CONCENTRATION OF EXHALED NITRIC OXIDE (FENO)**—not currently recommended for general asthma population; further studies required to determine specific patients who would benefit and frequency of testing

ACUTE MANAGEMENT

ABC—**O_2** to keep sat >92%, IV

BRONCHODILATORS—***salbutamol*** 100 µg MDI 2 puffs q6h ATC + q1h PRN and ***ipratropium*** 20 µg MDI 2 puffs q6h scheduled (frequency stated is only a guide, may increase or decrease on a case by case basis); consider asthma protocol if present in Emergency Department

STEROID—***prednisone*** 0.5–1 mg/kg PO daily × 7–14 days (may be shorter depending on response) or ***methylprednisolone*** 0.4–0.8 mg/kg IV daily (until conversion to prednisone)

OTHERS—if refractory case and life-threatening, consider IV epinephrine, IV salbutamol, theophylline, inhaled anesthetics, $MgSO_4$

RESPIRATORY SUPPORT—non-invasive ventilation, intubation and mechanical ventilation

LONG-TERM MANAGEMENT

EDUCATION—**smoking cessation** (see p. 490). **Asthma action plan. Puffer technique** education and review; consider medication adherence and cost to patient

ENVIRONMENTAL CONTROL—**avoidance** of outdoor/indoor allergens, irritants, and infections; home environment cleanliness (e.g. steam cleaning)

VACCINATIONS—influenza vaccine annually and pneumococcal vaccine every 5 years

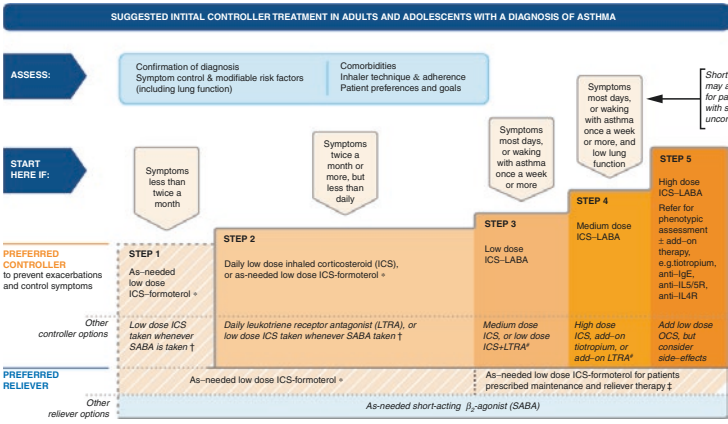
MANAGE COMORBIDITIES—obesity, GERD, allergies, rhinitis/sinusitis/nasal polyps, anxiety/depression

ASTHMA MEDICATIONS

- **STEP 1** (infrequent asthma symptoms <2 per month and no risk factors for exacerbations)—low dose ICS-formoterol as needed
- **STEP 2** (asthma symptoms or need for reliever ≥2x per month)—daily low dose ICS or as needed low dose ICS-formoterol; also consider daily leukotriene receptor antagonist (LTRA), which is most effective in asthma complicated with sinus disease and exercise-induced asthma, or low dose scheduled ICS plus SABA as needed (*salbutamol* 100 µg MDI 2 puffs PRN)
- **STEP 3** (asthma symptoms most days)—low dose ICS-LABA, consider increasing to medium dose ICS
- **STEP 4** (asthma symptoms most days and low lung function)—medium dose ICS-LABA, consider increasing to high dose ICS, add-on tiotropium or LTRA
- **STEP 5** (severe asthma symptoms or need for reliever most days and low lung function)—high dose ICS-LABA, consider low doses oral corticosteroids

LONG-TERM MANAGEMENT (CONT'D)

- **PHENOTYPE ASSESSMENT**—referral
- **ADD-ON THERAPY**—anti-IgE (i.e. omalizumab for refractory allergic asthma), anti-IL5/5R (i.e. SC mepolizumab or benralizumab with severe eosinophilic asthma), anti-IL4R (i.e. SC dupilumab for severe type 2 asthma, or requiring oral corticosteroids)
- **AZITHROMYCIN**—consider *azithromycin* 500 mg PO 3 ×/week (consider ototoxicity and cardiac arrhythmia; requires ECG to check for long QTc, sputum for atypical mycobacteria; treatment for at least 6 months to determine efficacy)
- **BRONCHIAL THERMOPLASTY**—severe asthma, currently should only be performed as a part of clinical study; further evidence on effectiveness and safety needed



HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta2-agonist; SLIT: sublingual immunotherapy

TREATMENT ISSUES

ASTHMA CONTROL CRITERIA

Characteristic	Frequency or value
Daytime symptoms	<4 days/week
Night-time symptoms	<1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school due to asthma	None
Need for a SABA	<4 doses/week
FEV1 or PEF	≥90% personal best
PEF diurnal variation[a]	<10–15%
Sputum eosinophils	<2–3%

[a]Diurnal variation is calculated as the difference between the highest and lowest PEF divided by the highest PEF multiplied by 100 for morning and night (determined over a 2 week period)

TREATMENT ISSUES (CONT'D)

ASSESSING ASTHMA SEVERITY

- **MILD**—well controlled with step 1 or 2 treatment (i.e. PRN ICS-formoterol alone)
- **MODERATE**—well controlled with step 3 treatment (i.e. low dose ICS-LABA)
- **SEVERE**—requires step 4 or 5 treatment (i.e. high dose ICS-LABA to prevent it from becoming uncontrolled) or asthma that remains uncontrolled

COMMON INHALED MEDICATIONS

- **SHORT-ACTING β-AGONISTS (SABA)**—*salbutamol* MDI 100 µg 1–2 puffs PRN or 2.5 mg NEB PRN, *terbutaline* 500 µg INH PRN
- **SHORT-ACTING MUSCARINIC ANTAGONISTS (SAMA)**—*ipratropium* MDI 20 µg 2 puffs QID or 500 µg NEB QID
- **LONG-ACTING β-AGONISTS (LABA)**—*formoterol* 6–24 µg INH BID, *salmeterol* diskus 50 µg 1 puff BID

TREATMENT ISSUES (CONT'D)

- **LONG-ACTING MUSCARINIC ANTAGONISTS (LAMA)**—*tiotropium* 18 μg INH daily
- **INHALED CORTICOSTEROIDS**—*beclomethasone* 125–250 μg INH BID, *budesonide* turbuhaler 200–400 μg INH BID or 0.5–1 mg NEB BID, *fluticasone* 125–250 μg INH BID, *ciclesonide* MDI 100–400 μg INH daily (only indicated for asthma at this time, not COPD), *mometasone twisthaler* 100–400 μg INH BID

ADMISSION CRITERIA

	FEV1 (L)	PEF (L/min)	PaO_2	Action
Very severe	–	–	<90% with O_2	Admit
Severe	<1.6 (<40%)	<200 (<40%)	<90%	Admit
Moderate	1.6–2.1	200–300	>90%	Admit?
Mild	>2.1 (>60%)	>300 (>60%)	>90%	Send home

DISCHARGE CRITERIA—consider discharging patient if peak flow >70% of usual (or predicted) value for at least 1 h after bronchodilator

SPECIFIC ENTITIES

EXERCISE-INDUCED ASTHMA

- **PATHOPHYSIOLOGY**—mild asthma with symptoms only during exercise due to bronchoconstriction as a result of cooling of airways associated with heat and water loss
- **DIAGNOSIS**—spirometry. Exercise or methacholine challenge may help in diagnosis
- **TREATMENTS**—prophylaxis with *salbutamol* 2 puffs MDI, given 5–10 min before exercise. Consider leukotriene antagonists or inhaled glucocorticoids if frequent use of prophylaxis

OCCUPATIONAL ASTHMA AND WORK-EXACERBATED ASTHMA

- **PATHOPHYSIOLOGY**—may be induced or aggravated by exposure to allergens or other sensitizing agents at work, or sometimes from a single, massive exposure; estimated 5–20% of new adult-onset asthma cases can be attributed to an occupational exposure

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—PEF monitoring at and away from work
- **MANAGEMENT**—refer to Occupational Medicine specialist, use strategies to limit exposure to allergen/sensitizing agent; consider changing occupations; treat asthma as per guidelines

TRIAD ASTHMA (Samter syndrome)—triad of asthma, aspirin/NSAIDs sensitivity, and nasal polyps. Cyclooxygenase inhibition → ↓ prostaglandin E_2 → ↑ leukotriene synthesis → asthma symptoms. Management includes ASA/NSAIDs avoidance and leukotriene antagonists (montelukast)

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

- **PATHOPHYSIOLOGY**—associated with asthma and cystic fibrosis. Due to colonization of the airways by *Aspergillus fumigatus*, leading to an intense, immediate hypersensitivity-type reaction in the airways
- **CLINICAL FEATURES**—history of asthma or cystic fibrosis (CF), recurrent episodes of fever, dyspnea, and productive cough (brownish sputum). Peripheral blood eosinophilia. CXR findings of patchy infiltrates and central bronchiectasis, CT chest findings of central bronchiectasis, "finger-in-glove" appearance (i.e. mucus-filled dilated bronchi)
- **DIAGNOSIS**—one predisposing condition (asthma or CF); obligatory criteria (positive *Aspergillus* extract skin test, detectable serum IgE level, elevated total serum IgE concentration); other criteria (≥2 must be present: serum antibodies to *A. fumigatus* or elevated *A. fumigatus*-specific IgG levels, radiographic pulmonary opacities consistent with ABPA, elevated eosinophil in glucocorticoid-naïve patients)
- **TREATMENTS**—systemic glucocorticoids (i.e. *prednisone* 0.5 mg/kg PO daily or equivalent × 14 days), followed by tapering over 3–4 months; consult Infectious Diseases service; consider antifungal therapy with itraconazole or voriconazole as part of initial therapy for acute ABPA, with the goal of reduction in the long-term glucocorticoid dose