Approach to Internal Medicine

A Resource Book for Clinical Practice

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Fifth Edition

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Acute Dyspnea

2015 ACCP/CTS Guideline Prevention of Acute Exacerbations of COPD

DIFFERENTIAL DIAGNOSIS

RESPIRATORY

- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, infectious exacerbation of bronchiectasis, foreign body obstruction
- **PARENCHYMA**—pneumonia, cryptogenic organizing pneumonia (COP), ARDS, acute exacerbation of interstitial lung disease
- **VASCULAR**—pulmonary embolism, pulmonary hypertension
- **PLEURAL**—pneumothorax, pleural effusion

CARDIAC

- **MYOCARDIAL**—HF exacerbation, myocardial infarction
- **VALVULAR**—aortic stenosis, acute aortic regurgitation, mitral stenosis, endocarditis
- **PERICARDIAL**—pericardial effusion, tamponade

SYSTEMIC—sepsis, metabolic acidosis, anemia, cachexia

OTHERS—neuromuscular, psychogenic, anxiety

PATHOPHYSIOLOGY

PRECIPITANTS OF COPD EXACERBATION—infections, lifestyle/environmental (10% [cigarette smoke, dust, pollutants, cold air]), non-adherence to medications, pulmonary embolism, pulmonary edema, pneumothorax, progression of COPD

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THE CLINICAL EXAMINATION PREDICT AIRFLOW LIMITATION?

	LR+	LR–
History		
Smoking >40 pack-years	*12*	*0.63*
Smoking ever	1.8	0.16
Sputum >1/4 cup	4	0.84
Chronic bronchitis symptoms	3	0.78
Wheezing	3.8	0.66
Any exertional dyspnea	2.2	0.83
Coughing	1.8	0.69
Any dyspnea	1.2	0.55

CLINICAL FEATURES (CONT'D)

	LR+	LR–
Physical		
Barrel chest	10	0.90
Decreased cardiac dullness	10	0.88
Match test	7.1	0.43
Rhonchi	5.9	0.95
Hyperresonance	4.8	0.73
FEV1 >9 s	4.8	–
FEV1 6–9 s	2.7	–
FEV1 <6 s	0.45	–
Subxiphoid cardiac apical impulse	4.6	0.94
Wheezing	*4.4*	*0.88*
Maximum laryngeal height ≤ 4 cm	*4.2*	*0.70*
Pulsus paradoxus (>15 mmHg)	3.7	0.62
Decreased breath sounds	*2.6*	*0.66*
Accessory muscle use	–	0.70
Clinical Judgement		
Overall Clinical Prediction of Moderate-Severe Disease	*5.6*	–
Overall Clinical Prediction of Mild Disease	*2.3*	–

APPROACH—"No single item or combination of items from the clinical examination rules out airflow limitation." The best findings associated with increased likelihood of airflow limitation are objective wheezing, FEV1 >9 s, positive match test, barrel chest, hyperresonance, and subxiphoid cardiac impulse. "Three findings predict the likelihood of airflow limitation in men: years of cigarette smoking, subjective wheezing and either objective wheezing or peak expiratory flow rate."

Holleman et al. *JAMA* 1995;273(4)

UPDATE—multivariate 'Rule In' Obstructive Disease Model (history of obstructive airways disease, smoking >40 pack-years, age ≥45, and laryngeal height ≤4 cm) has posterior odds of disease of 220. Multivariate 'Rule Out' Obstructive Disease Model (smoking <30 years, no wheezing symptoms, and no auscultated wheezing) has posterior odds of disease of 0.02

Simel et al. *The Rational Clinical Examination*. McGraw-Hill, 2009

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, troponin/CK, Ca, Mg, PO_4
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S/fungal, nasopharyngeal swab for viral studies
- **IMAGING**—CXR
- **ECG**—left atrial enlargement, atrial fibrillation, sinus tachycardia
- **SPIROMETRY/PFT**—FEV1/FVC <0.7, may be partially reversible. Severity based on FEV1
- **ABG**—if acute respiratory distress

SPECIAL

- **BNP**—if suspect HF
- **D-DIMER, CT CHEST**—if suspect PE
- **ECHOCARDIOGRAM**

DIAGNOSTIC & PROGNOSTIC ISSUES

DIAGNOSIS OF COPD—should be considered in patients at risk of developing disease; smoking history is most important risk factor; increased risk in patients with past history of asthma or severe childhood respiratory disease, exposed to passive smoke or biomass fuel; spirometry is essential for diagnosis (fixed post-bronchodilator FEV1/FVC ratio <0.70 or less than the lower limit of normal)

GOLD CLASSIFICATION FOR COPD—all have FEV1/FVC <0.7. Severity of airflow limitation based on post-bronchodilator FEV1

- **STAGE 1** (mild)—FEV1 ≥ 80% predicted
- **STAGE 2** (moderate)—FEV1 50–79% predicted
- **STAGE 3** (severe)—FEV1 30–49% predicted
- **STAGE 4** (very severe)—FEV1 <30% predicted

MODIFIED MEDICAL RESEARCH COUNCIL (mMRC) DYSPNEA SCALE

- **0**—no breathlessness except on strenuous exercise
- **1**—short of breath when hurrying or walking up a slight hill
- **2**—walks slower than people of same age on level because of breathlessness or has to stop when walking at own pace
- **3**—stops for breath after walking 100m or after a few minutes
- **4**—too dyspneic to leave house; breathless when dressing

COPD ASSESSMENT TEST—a validated patient-reported outcome that consists of 8 items (cough, phlegm, chest tightness, shortness of breath on exertion, activity level, confidence to leave home, sleep, energy), each rated using a 6-point numeric rating scale from 0 to 5, with a higher total score indicating greater symptom burden

GOLD ABCD GRADING—assessment for initiation of COPD therapy

DIAGNOSTIC & PROGNOSTIC ISSUES (CONT'D)

Exacerbations/ Hospitalizations	Assess symptoms mMRC 0–1; CAT<10	mMRC ≥2; CAT ≥10
0–1 exacerbations without hospitalization	Gold A	Gold B
≥2 exacerbations or ≥1 hospitalization	Gold C	Gold D

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 Report

PROGNOSIS OF PATIENTS WITH ACUTE EXACERBATION OF COPD—in-hospital mortality 5–10%

BODE INDEX

- **BMI**—0 points = >21, 1 point = ≤21
- **OBSTRUCTION** (post-bronchodilator FEV1)—0 points = ≥65% predicted, 1 point = 50–64%, 2 points = 36–49%, 3 points = ≤35%
- **DISTANCE WALKED IN 6 MIN**—0 points = ≥350 m, 1 point = 250–349 m, 2 points = 150–249 m, 3 points = ≤149 m
- **EXERCISE MMRC DYSPNEA SCALE**—0 points = 0–1, 1 point = 2, 2 points = 3, 3 points = 4
- **SCORING**—total BODE score calculated as sum of all points. Relative risk for death (any cause) is increased by 34% per one-point increase in BODE score. Relative risk for death (from respiratory failure, pneumonia, or pulmonary embolism) is increased by 62% per one-point increase in BODE score

Celli et al. *NEJM* 2004;350:(10)

ACUTE MANAGEMENT

ABC—O_2 to keep sat >90%, or 88–92% if CO_2 retainer, IV

BRONCHODILATORS—***salbutamol*** 100 µg MDI 2 puffs q4h ATC + q1h PRN and ***ipratropium*** 20 µg MDI 2 puffs q4h ATC

STEROIDS—***prednisone*** 40–60 mg PO daily × 5–14 days (tapering dose not always necessary) or ***methylprednisolone*** 60–125 mg IV q6–12 h (inpatient)

ANTIBIOTICS—give if any two of the following criteria are met: ↑ sputum purulence, ↑ dyspnea or ↑ sputum volume. Other considerations include the need for non-invasive mechanical ventilation and "at risk" for poor outcomes (substantial comorbidities, severe COPD, frequent exacerbations >3/year, recent antibiotics within 3 months); choices depend on clinical circumstance (*levofloxacin* 500 mg PO daily × 5–7 days [or 750 mg PO daily × 5

ACUTE MANAGEMENT (CONT'D)

days if no renal disease], *doxycycline* 100 mg PO BID × 5–7 days, *amoxicillin* 500 mg PO BID × 5–7 days, *cefuroxime* 250–500 mg PO BID × 5–7 days, *ceftriaxone* 1g IV × 5–7 days, or *azithromycin* 500 mg PO × 1 day then 250 mg PO daily × 4 days)

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

OTHERS—DVT prophylaxis (*unfractionated heparin* 5000 U SC q8–12 h, *enoxaparin* 40 mg SC q24h, *dalteparin* 5000 U SC q24h, *tinzaparin* 75 IU/kg SC q24h), physiotherapy

LONG-TERM MANAGEMENT

EDUCATION—**smoking cessation** (see p. 490). Disease-specific self-management program. **Inhaler technique** education and review

VACCINATIONS—influenza vaccine annually and pneumococcal vaccine booster every 5 years

REHABILITATION—**education** and **exercise training** (increases quality of life and exercise tolerance); **pulmonary rehabilitation** associated with ↓ risk of recurrent exacerbation in patients with moderate to very severe COPD and recent AECOPD (<4 weeks)

LONG-TERM MANAGEMENT (CONT'D)

LONG-TERM OXYGEN THERAPY—if chronic hypoxemia

INITIAL PHARMACOLOGIC THERAPY—based on symptoms and risk of exacerbations

- **GOLD A (MINIMAL SYMPTOMS, LOW RISK OF EXACERBATION)**—short-acting bronchodilator with SABA (short-acting beta agonist) and/or SAMA (short-acting muscarinic antagonist)
- **GOLD B (MORE SYMPTOMS, LOW RISK OF EXACERBATION)**—regular treatment with long-acting bronchodilator (LAMA or LABA) plus SABA for symptom relief as needed
- **GOLD C (MINIMAL SYMPTOMS, HIGH RISK OF EXACERBATION)**—regular treatment with LAMA plus SABA for symptom relief as needed
- **GOLD D (MORE SYMPTOMS, HIGH RISK OF EXACERBATION)**—regular treatment with LAMA or combination LABA and LAMA if severe breathlessness (CAT >20); if features of asthma/COPD overlap syndrome, ICS/LABA combination may be preferred; plus SABA for symptom relief as needed

SUBSEQUENT PHARMACOLOGIC THERAPY

Current therapy	If persistent dyspnea or high COPD impact (i.e. mMRC ≥2 or CAT ≥10) with no exacerbations	If ≥1 exacerbations in past year ± persistent dyspnea or high COPD impact
SABA or SABA-SAMA PRN	Add LAMA or LABA	Add LAMA
LAMA or LABA monotherapy	Change to LAMA/LABA	LAMA/LABA if peripheral eosinophils normal LABA/ICS if LAMA contraindicated and 1 exacerbation in past year with peripheral eosinophils >300/μL or ≥2 exacerbations/1 hospitalization in past year with peripheral eosinophils ≥100/μL
LABA/ICS	LAMA/LABA/ICS or LAMA/LABA if no response to ICS or adverse effects from ICS	LAMA/LABA/ICS if prior indication for ICS LAMA/LABA if lack of response to ICS or adverse effects from ICS
LAMA/LABA	Trial of different LAMA/LABA or alternate delivery system Consider low dose theophylline, repeat pulmonary rehabilitation	LAMA/LABA/ICS or Continue LAMA/LABA and add phosphodiesterase-4 inhibitor (roflumilast 500 μg PO daily)[a] or azithromycin[b]
LAMA/LABA/ICS	Continue LAMA/LABA/ICS Consider low dose theophylline (400 mg PO daily × 3 days, then 400–600 mg PO daily, therapeutic level 10–20 μg/mL), repeat pulmonary rehabilitation Consider stopping ICS if lack of response or adverse effect to ICS	Add roflumilast[a] or azithromycin[b] Stop ICS if lack of response or adverse effect

[a]roflumilast for patients with FEV_1 <50% predicted and at least 1 hospitalization in past year

[b]azithromycin preventive therapy is more effective in patients who are not current smokers; consider development of resistant organisms such as non-Tuberculous mycobacterium

LONG-TERM MANAGEMENT (CONT'D)

INVASIVE INTERVENTIONS—if symptoms still persistent and/or decline in function, consider lung volume reduction procedures (surgery, endobronchial valves), lung transplantation

TREATMENT ISSUES

COMMON INHALED MEDICATIONS (DPI=dry powder inhaler; SMI=soft mist inhaler)

- **LAMA**—*tiotropium* DPI 18 mcg daily or SMI 2 inhalations of 2.5 mcg once daily, *glycopyrronium* DPI 50 mcg capsule once daily, *umeclidinium* DPI 62.5 mcg inhalation daily, *aclidinium* DPI 400 mcg BID
- **LABA**—*formoterol* DPI 12–24 mcg BID, *indacaterol* DPI 75 mcg daily, *salmeterol* DPI 50 mcg BID
- **LAMA/LABA COMBINATIONS**—*glycopyrrolate* 50 mcg/*indacaterol* 110 mcg 1 INH daily, *tiotropium* 2.5 mcg/*olodaterol* 2.5 mcg 2 INH daily, *umeclidinium* 62.5 mcg/*vilanterol* 25 mcg 1 INH daily
- **LAMA/LABA/ICS**—*fluticasone furoate* 100 mcg/*umeclidinium* 62.5 mcg/*vilanterol* 25 mcg 1 INH daily

FACTORS FOR IMPENDING INTUBATION—cardiac or respiratory failure, hemodynamic instability, markedly elevated respiratory rate (>35/min), fatigue and labored respiration, use of accessory muscles, worsening hypercapnia, acidosis (especially lactic), stridor (impending upper airway obstruction), agonal breathing (impending respiratory arrest)

LIFE-PROLONGING MEASURES FOR COPD—smoking cessation, supplemental O_2, lung transplant

INDICATIONS FOR SUPPLEMENTAL HOME O_2—ABG done at room air. PaO_2 <55 mmHg alone or PaO_2 <60 mmHg in the presence of bilateral ankle edema, cor pulmonale, or hematocrit >56%

SPECIFIC ENTITIES

α1-ANTITRYPSIN DEFICIENCY

- **PATHOPHYSIOLOGY**—production of an abnormal protease inhibitor (homozygous ZZ) with impaired transport out of the liver. Serum level is only 10–15% of normal → increased protease activity leads to emphysema and cirrhosis (10%)
- **DIAGNOSIS**—α1-antitrypsin levels; targeted testing should be considered in patients with COPD diagnosed before 65 years of age or with a smoking history of <20 pack years
- **TREATMENTS**—similar to COPD, α1-antitrypsin replacement

SPECIFIC ENTITIES (CONT'D)

ASTHMA AND COPD OVERLAP SYNDROME (ACOS)

- **DIAGNOSIS**—patients with clinical features of both asthma and COPD. Airflow limitation not fully reversible, FEV1/FVC ratio <0.7 or <LLN and bronchodilator increase in FEV1 >12% and 400 mL; history of atopy or allergies; exposure to risk factors (i.e. >10 pack year smoking or equivalent, indoor/outdoor air pollutant exposure)
- **TREATMENTS**—similar to COPD and asthma

BRONCHIOLITIS OBLITERANS

- **PATHOPHYSIOLOGY**—severe inflammation of bronchioles → airflow obstruction. Very different from bronchiolitis obliterans organizing pneumonia (BOOP)/cryptogenic organizing pneumonia (COP), a parenchymal lung disorder
- **CAUSES**—infection (viral, *Mycoplasma*), inflammatory (ulcerative colitis, rheumatoid arthritis), transplant (bone marrow, lung), toxic fumes, idiopathic
- **TREATMENTS**—bronchiolitis obliterans (with an organizing intraluminal exudate and proliferative granulation tissue polyp) is usually steroid responsive. Constrictive bronchiolitis (late, fibrotic, concentric) is not responsive to glucocorticoids

BRONCHIECTASIS

- **PATHOPHYSIOLOGY**—airway obstruction, destruction, altered immunity → ↑ cellular and mediator inflammatory response → ↑ elastase, sputum production → recurrent infections → vicious cycle → permanent dilatation of bronchi. Major types of bronchiectasis include
  - **CYLINDRICAL OR TUBULAR BRONCHIECTASIS**—dilated airways alone, sometimes represents residual effect of pneumonia and may resolve
  - **VARICOSE BRONCHIECTASIS**—focal constrictive areas along the dilated airways
  - **SACCULAR OR CYSTIC BRONCHIECTASIS**—most severe form. Progressive dilatation of the airways, resulting in large cysts or saccules
- **CAUSES**
  - **FOCAL**—broncholith, post-infectious, tumor, extrinsic lymph node compression, post-lobar resection, recurrent aspiration
  - **DIFFUSE**
    - **POST-INFECTIOUS**—bacterial (*Pseudomonas, Haemophilus*), mycobacterium, fungal, viral (adenovirus, measles, influenza, HIV)

SPECIFIC ENTITIES (CONT'D)

- **IMMUNODEFICIENCY**—cancer, chemotherapy, hypogammaglobulinemia, immunosuppression, sequelae of toxic inhalation or aspiration of foreign body
- **INTERSTITIAL LUNG DISEASE**—traction bronchiectasis
- **INFLAMMATORY**—RA, SLE, Sjögren syndrome, relapsing polychondritis, IBD
- **INHERITED**—α1-antitrypsin deficiency, cystic fibrosis, primary ciliary dyskinesia (Kartagener syndrome, Young syndrome), tracheobronchomegaly (Mounier–Kuhn syndrome), cartilage deficiency (Williams–Campbell syndrome), Marfan syndrome

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—high-resolution CT chest (signet ring sign), PFT (obstruction ± reversibility)
- **TREATMENTS**—exercises, chest physiotherapy, and bronchodilators similar to COPD; however, if reversible, inhaled corticosteroids should be given early. Ensure adequate systemic hydration. Effective treatment of exacerbations

Related Topics
Cryptogenic Organizing Pneumonia (p. 21)
Pulmonary Function Tests (p. 25)
Smoking (p. 490)