Chronic Obstructive Lung Disease

- Harrison’s Principles of Internal Medicine, 17th Edition, Chapter 354
• A 67-year-old man presents with a history of dyspnea, which has progressed for the past several years.
• He began smoking cigarettes at 15 years of age and continues to smoke one pack per day. Worsening breathlessness forced him to retire as a laborer, and he has sought emergency care for what he calls bronchitis twice in the past year.
• His physical examination is notable for diminished breath sounds on auscultation, with a prolonged expiratory phase.
• Spirometry reveals severe airflow obstruction (ratio of forced expiratory volume in 1 second [FEV1] to forced vital capacity [FVC], 0.43; FEV1, 34% of the predicted value).

• How should this case be managed?
A 57-year-old patient who smokes cigarettes presents with chronic productive cough and persistent progressive exercise limitation that is a result of breathlessness.

For this patient, which of the following statements is true?

- A. Significant airway obstruction occurs in only 10% to 15% of people who smoke
- B. The best tool for assessing the severity of obstruction is the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC)
- C. Chronic bronchitis is a clinical diagnosis defined as the presence of cough and sputum production on most days for at least 3 consecutive months in a year
- D. Measurement of lung volumes in patients with chronic airway obstruction (CAO) uniformly reveals an increased residual volume and a decreased functional residual capacity (FRC)

Answer: A
A 53-year-old man presents to establish primary care. He has a history of COPD and a 60 pack-year history of cigarette smoking. Currently, he smokes one pack of cigarettes a week. His COPD is currently managed with PRN albuterol administered with a metered-dose inhaler (MDI); a long-acting beta₂ agonist; and an inhaled corticosteroid. The patient experiences dyspnea with moderate exertion; otherwise, he is functional. The results of a complete blood count (CBC) and serum chemistry are unremarkable. Pulse oximetry is significant for an O₂ saturation of 96% on room air with no change after climbing and descending two flights of stairs. The patient says he would like to change his medications to nebulized bronchodilators. He also wonders which intervention is most likely to alter the natural history of his COPD.

For this patient, which of the following statements is true?

- A. Long-term administration of oxygen will favorably alter the natural history of this patient’s disease
- B. Probably the single most important intervention is to help this patient quit smoking
- C. Physical training programs have been shown to significantly increase the exercise capacity of patients with even far-advanced chronic bronchitis and emphysema; such programs lead to objective improvements in lung function, as measured by FEV₁
- D. Nebulized bronchodilators are generally of greater benefit than MDIs

(Answer: B—)
A 62-year-old man with a history of COPD (FEV₁, 38%) presents with worsening dyspnea, which now occurs at rest; purulent sputum; and wheezing of 6 days’ duration. He has increased the use of his inhalers without experiencing an improvement of symptoms. He denies having fever, chills, or pleuritic chest pain. A chest x-ray does not demonstrate an acute process. The patient is admitted for treatment of an acute exacerbation of COPD.

Which of the following statements regarding the management of acute exacerbations of COPD is true?

- A. The duration of symptoms and the risk of serious deterioration in lung function can be reduced by at least a 14- to 21-day course of broad-spectrum antibiotics
- B. The bronchodilator of choice in exacerbations of COPD is an anticholinergic such as ipratropium
- C. Oxygen supplementation should be adjusted to maintain oxygen saturation at 95% or greater
- D. In patients already receiving theophylline, measurement of the theophylline level is indicated because acute illness and some of the medications used to treat exacerbations can precipitate theophylline toxicity; however, there are no data that show that the addition of theophylline is beneficial for exacerbations of COPD

Answer: D—
14. A 67-year-old man with a history of emphysema presents with a complaint of worsening dyspnea and cough that is productive of yellow-colored sputum. On pulmonary function testing, his FEV\(_1\) is 45%. Arterial blood gas measurements were performed several months ago. The baseline value for P\(_a\)O\(_2\) was 53 mm Hg, and the carbon dioxide tension (P\(_{CO_2}\)) on room air was normal.

There is evidence showing improved survival for which of the following interventions (in addition to smoking cessation)?

- A. Use of broad-spectrum antibiotics
- B. Use of corticosteroids
- C. Home oxygen therapy
- D. Lung volume reduction surgery
- E. Bronchodilator therapy

**Answer:** A—
A 37-year-old woman is referred to you for evaluation of dyspnea, purulent cough, and recurrent pneumonia. The patient has a childhood history of recurrent pneumonia. She has no known contacts with persons with tuberculosis, and a test for the presence of purified protein derivative (PPD) is negative. She has smoked a pack of cigarettes each day for 15 years. Pulmonary function tests were interpreted as indicating mild airflow obstruction.

Which of the following features does NOT favor a diagnosis of bronchiectasis over a diagnosis of emphysematous lung disease in this patient?

- A. Chronic cough and dyspnea without purulent sputum production
- B. Tramlines noted on plain chest radiographs
- C. Clinical improvement from broad-spectrum antibiotics and drainage
- D. Massive hemoptysis
- E. Clubbing of the digits

*Answer: A—*
A 53-year-old man with a 60-pack-year history of cigarette smoking presents with complaints of productive cough and dypsnea. He reports that for the past 3 months, he has been treated for bronchitis with antibiotics, but his symptoms have not resolved. Over the past several weeks, he has experienced progressive dypsnea on exertion. He denies having any chest discomfort or any other significant medical history. Currently, he is not taking any medications. His lung examination shows wheezing that resolves with expectoration of phlegm. Chest x-ray shows hyperinflation. Initial pulmonary function tests show the patient's FEV₁ to be 55% of the predicted value. Arterial blood gas measurements are as follows: $P_{aO_2}$, 75 mm Hg; alveolar carbon dioxide tension ($P_{ACO_2}$), 55 mm Hg.

Which of the following is NOT true for this patient?

- A. If this patient continues to smoke, his FEV₁ value will continue to decrease two to three times faster than normal
- B. If this patient stops smoking, the rate of decline in expiratory flow reverts to that of nonsmokers, and there may be a slight improvement in FEV₁ during the first year
- C. This patient would be expected to have evidence of extensive panacinar emphysema
- D. This patient would be expected to have increased RV, increased FRC, and normal or increased total lung capacity (TLC)
- E. This patient is at risk for right-sided heart failure

Answer: C—
A 43-year-old female patient with chronic bronchitis associated with a 40-pack-year history of cigarette smoking presents for a routine appointment. Although she has a productive cough on a daily basis, she denies having any dypsnea and is currently not taking any medication.

Which of the following measures will most alter the natural progression of this patient's disease?

- A. Daily bronchodilator use alone
- B. Daily corticosteroid use alone
- C. Daily prophylactic antibiotic
- D. Daily pulmonary rehabilitation
- E. Smoking cessation

Answer: E—
Definition

• A disease state characterized by airflow limitation that is not fully reversible

• Conditions include:
  – Emphysema: anatomically defined condition characterized by destruction and enlargement of the lung alveoli
  – Chronic bronchitis: clinically defined condition with chronic cough and phlegm
  – Small-airways disease: condition in which small bronchioles are narrowed
Figure 1. Pathophysiological Features of Airflow Obstruction in Chronic Obstructive Pulmonary Disease (COPD).
Epidemiology

• Fourth leading cause of death in the U.S.
• Affects > 16 million persons in the U.S.
• Global Initiative for Chronic Obstructive Lung Disease (GOLD) estimates suggest that chronic obstructive lung disease (COLD) will increase from the sixth to the third most common cause of death worldwide by 2020.
Epidemiology

• >70% of COLD-related health care expenditures go to emergency department visits and hospital care (> $10 billion annually in the U.S.).
Epidemiology

Sex

• Higher prevalence in men, probably secondary to smoking
• Prevalence of COLD among women is increasing as the gender gap in smoking rates has diminished.
Epidemiology

Age

• Higher prevalence with increasing age
  – Dose–response relationship between cigarette smoking intensity and decreased pulmonary function
Risk Factors

Smoking (see Figure 1)
1. Cigarette smoking is a major risk factor.
2. Cigar and pipe smoking
   - Evidence less compelling; likely related to lower dose of inhaled tobacco by-products
3. Passive (secondhand) smoking
   - Associated with reductions in pulmonary function
   - Its status as a risk factor for COLD remains uncertain
• Airway hyperresponsiveness
• Respiratory infections
  – Risk factor for exacerbations
  – The association of adult and childhood respiratory infections with development and progression of COLD remains unproven.
• Occupational exposures to dust and fumes (e.g., cadmium)
  – Likely risk factors
  – The magnitude of these effects appears substantially less important than the effect of cigarette smoking.

• Ambient air pollution
  – The relationship of air pollution to COLD remains unproven.
Genetic factors

- $\alpha_1$ antitrypsin ($\alpha_1$AT) deficiency
- Common M allele: normal levels
- S allele: slightly reduced levels
- Z allele: markedly reduced levels
- Null allele: absence of $\alpha_1$AT (rare)
- Lowest levels of $\alpha_1$AT are associated with incidence of COLD; $\alpha_1$AT deficiency interacts with cigarette smoking to increase risk.
Distributions of forced expiratory volume in 1 s (FEV1) values in a general population sample, stratified by pack-years of smoking.
Etiology
COLD

– Causal relationship between cigarette smoking and development of COLD has been proven: however, the response varies considerably among individuals.
COLD exacerbation

– Bacterial infections
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Moraxella catarrhalis*
  - *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* (5–10% of exacerbations)

– Viral infections (one-third)

– No specific precipitant identified (20–35%)
Associated Conditions

- Lung cancer
- Asthma
Symptoms & Signs

• 3 most common:
  – Cough
  – Sputum production
  – Exertional dyspnea, frequently of long duration
Additional signs and symptoms

- Dyspnea at rest
- Prolonged expiratory phase and/or expiratory wheezing on lung examination
- Decreased breath sounds
- Barrel chest
- Large lung volumes and poor diaphragmatic excursion, as assessed by percussion
- Use of accessory muscles of respiration
- Pursed lip breathing (predominantly emphysema)
- Characteristic "tripod" sitting position to facilitate the actions of the sternocleidomastoid, scalene, and intercostal muscles
- Cyanosis, visible in lips and nail beds
Systemic wasting
- Significant weight loss
- Bitemporal wasting
- Diffuse loss of subcutaneous adipose tissue

Paradoxical respiration
- Inward movement of the rib cage with inspiration (Hoover's sign) in some patients

"Pink puffers" are patients with predominant emphysema—no cyanosis or edema, with decreased breath sounds.

"Blue bloaters" are patients with predominant bronchitis—cyanosis and edema.
- Most patients have elements of each.
Advanced disease: signs of cor pulmonale

- Elevated jugular venous distention
- Right ventricular heave
- Third heart sound
- Hepatic congestion
- Ascites
- Peripheral edema
<table>
<thead>
<tr>
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<th>Differential Diagnosis</th>
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<tbody>
<tr>
<td>1</td>
<td>Congestive heart failure</td>
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<td>2</td>
<td>Asthma</td>
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<tr>
<td>3</td>
<td>Bronchiectasis</td>
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<tr>
<td>4</td>
<td>Obliterative bronchiolitis</td>
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<td>5</td>
<td>Pneumonia</td>
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<td>6</td>
<td>Tuberculosis</td>
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<td>7</td>
<td>Atelectasis</td>
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<tr>
<td>8</td>
<td>Pneumothorax</td>
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<tr>
<td>9</td>
<td>Pulmonary embolism</td>
</tr>
</tbody>
</table>
Considerations

1. COLD is present only if chronic airflow obstruction occurs.
   - Chronic bronchitis without chronic airflow obstruction is not COLD.

2. Asthma
   - Reduced forced expiratory volume in 1 second (FEV1) in COLD seldom shows large responses (>30%) to inhaled bronchodilators, although improvements up to 15% are common.
   - Asthma patients can also develop chronic (not fully reversible) airflow obstruction.
Considerations

3. Problems other than COLD should be suspected when hypoxemia is difficult to correct with modest levels of supplemental oxygen.

4. Lung cancer
   - Clubbing of the digits is not a sign of COLD.
   - In patients with COLD, development of lung cancer is the most likely explanation for newly developed clubbing.
Diagnostic Approach

Initial assessment

1. History and physical examination (Signs & Symptoms)
2. Pulmonary function testing to assess airflow obstruction
3. Radiographic studies
Assessment of exacerbation

1. History
   - Fever
   - Change in quantity and character of sputum
   - Ill contacts
   - Associated symptoms
   - Frequency and severity of prior exacerbations
Assessment of exacerbation

2. Physical examination
   - Tachycardia
   - Tachypnea
   - Chest examination
     - Focal findings
     - Air movement
     - Symmetry
     - Presence or absence of wheezing
     - Paradoxical movement of abdominal wall
     - Use of accessory muscles
   - Perioral or peripheral cyanosis
   - Ability to speak in complete sentences
   - Mental status
3. Radiographic studies
   - Chest radiography focal findings (pneumonia, atelectasis)

4. Arterial blood gases
   - Hypoxemia
   - Hypercapnia

5. Hospitalization recommended for:
   - Respiratory acidosis and hypercarbia
   - Significant hypoxemia
   - Severe underlying disease
   - Living situation not conducive to careful observation and delivery of prescribed treatment
Laboratory Tests

ABG and oximetry

• Although not sensitive, they may demonstrate resting or exertional hypoxemia.

• Blood gases provide additional information about alveolar ventilation and acid–base status by measuring arterial PCO 2 and pH.

  - Change in pH with PCO 2 is 0.08 units/10 mmHg acutely and 0.03 units/10 mmHg in the chronic state.
  - Arterial pH allows classification of ventilatory failure, defined as PCO 2 > 45 mmHg, into an acute or chronic condition.
Laboratory Tests

1. Elevated hematocrit suggests chronic hypoxemia.
2. Serum level of α1AT should be measured in some patients.
   - Presenting at ≤ 50 years of age
   - Strong family history
   - Predominant basilar disease
   - Minimal smoking history
   - Definitive diagnosis of α1AT deficiency requires PI type determination.
     - Typically performed by isoelectric focusing of serum, which reflects the genotype at the PI locus for the common alleles and many of the rare PI alleles
     - Molecular genotyping can be performed for the common PI alleles (M, S, and Z).
3. Sputum gram stain and culture (for COLD exacerbation)
Imaging

• Chest radiography
  – Emphysema: obvious bullae, paucity of parenchymal markings, or hyperlucency
  – Hyperinflation: increased lung volumes, flattening of diaphragm
    – Does not indicate chronicity of changes

• Chest CT
  – Definitive test for establishing the diagnosis of emphysema, but not necessary to make the diagnosis
Diagnostic Procedures

Pulmonary function tests/spirometry
- Chronically reduced ratio of FEV1 to forced vital capacity (FVC)
  - In contrast to asthma, the reduced FEV1 in COLD seldom shows large responses (>30%) to inhaled bronchodilators, although improvements up to 15% are common.
- Reduction in forced expiratory flow rates
- Increases in residual volume
- Increases in ratio of residual volume to total lung capacity
- Increased total lung capacity (late in the disease)
- Diffusion capacity may be decreased in patients with emphysema.

Electrocardiography
- may detect signs of ventricular hypertroph
Classification

- GOLD stage
- Classification based on pathologic type
GOLD stage

0
- Severity: at risk
- Symptoms: chronic cough, sputum production
- Spirometry: normal

I
- Severity: mild
- Symptoms: with or without chronic cough or sputum production
- Spirometry: FEV1:FVC < 0.7 and FEV1 \geq 80\% predicted

II
- Severity: moderate
- Symptoms: with or without chronic cough or sputum production
- Spirometry: FEV1:FVC < 0.7 and FEV1 50–80\% predicted

III
- Severity: severe
- Symptoms: with or without chronic cough or sputum production
- Spirometry: FEV1:FVC < 0.7 and FEV1 30–50\% predicted

IV
- Severity: very severe
- Symptoms: with or without chronic cough or sputum production
- Spirometry:
  - FEV1:FVC < 0.7 and FEV1 < 30\% predicted or
  - FEV1 < 50\% predicted with respiratory failure or signs of right heart failure
Classification based on pathologic type

**Centriacinar emphysema**
- Type most frequently associated with cigarette smoking
- Most prominent in upper lobes and superior segment of the lower lobes of the lungs

**Panacinar emphysema**
- Usually observed in patients with α1AT deficiency
- Most prominent in lower lobes
Treatment Approach
General

– Institute therapy after assessment of symptoms, potential risks, costs, and benefits.
– Only 2 interventions have been demonstrated to influence the natural history.
  □ Smoking cessation
  □ Oxygen therapy in chronically hypoxemic patients
– All other current therapies are directed at improving symptoms and decreasing frequency and severity of exacerbations.
– Therapeutic response should determine continuation of treatment.
Exacerbation

- Assess the severity of both the acute and chronic components of the patient’s illness.
- Attempt to identify and treat the precipitant of the exacerbation.
Specific Treatments
Stable-phase COLD, pharmacotherapy

Oxygen

1. Supplemental O2 is the only therapy demonstrated to decrease mortality.
2. In resting hypoxemia (resting O2 saturation < 88% or < 90% with signs of pulmonary hypertension or right heart failure), the use of O2 has been demonstrated to significantly affect mortality.
3. Supplemental O2 is commonly prescribed for patients with exertional hypoxemia or nocturnal hypoxemia.
   - The rationale for supplemental O2 in these settings is physiologically sound, but benefits are not well substantiated.
Specific Treatments
Stable-phase COLD, pharmacotherapy

Bronchodilators

– Used to treat symptoms
– The inhaled route is preferred.
– Side effects are less than with parenteral delivery.
– Theophylline: various dosages and preparations; typical dose 300–600 mg/d, adjusted based on levels
Specific Treatments
Stable-phase COLD, pharmacotherapy

Anticholinergic agents

- Trial of inhaled anticholinergics is recommended in symptomatic patients.
- Side effects are minor.
- Improve symptoms and produce acute improvement in FEV
- Do not influence rate of decline in lung function
- Ipratropium bromide (short-acting anticholinergic) (Atrovent)
  - Inhaled: 30-min onset of action; 4-h duration
  - Atrovent: metered-dose inhaler; 18 µg per inhalation; 1–2 inhalations qid
Specific Treatments
Stable-phase COLD, pharmacotherapy

• Tiotropium (long-acting anticholinergic) (Spiriva)
  □ Spiriva: powder via handihaler; 18 μg per inhalation; 1 inhalation qd

• Symptomatic benefit

• Long-acting inhaled β-agonists, such as salmeterol, have benefits similar to ipratropium bromide.
  □ More convenient than short-acting agents
Specific Treatments
Stable-phase COLD, pharmacotherapy

- Addition of a β-agonist to inhaled anticholinergic therapy provides incremental benefit.
  - Side effects
    - Tremor
    - Tachycardia

- Salmetrol (Serevent):
  - Powder via diskus; 50-μg inhalation every 12 h

- Formoterol (Foradil):
  - Powder via aerolizer; 12-μg inhalation every 12 h
Specific Treatments
Stable-phase COLD, pharmacotherapy

Albuterol (short-acting β-agonist) (Proventil HFA, Ventolin HFA, Ventolin, Proventil)
- Metered-dose inhaler (or in nebulizer solution); 180-μg inhalation every 4–6 h as needed

Combined β-agonist/anticholinergic: albuterol/ipratropium (Combivent)
- Metered-dose inhaler (also available in nebulizer solution); 120 mcg/21 μg per inhalation 1–2 inhalations qid
Specific Treatments
Stable-phase COLD, pharmacotherapy

Inhaled glucocorticoids

- Reduce frequency of exacerbations by 25–30%
- No evidence of a beneficial effect for the regular use of inhaled glucocorticoids on the rate of decline of lung function, as assessed by FEV1
- Consider a trial in patients with frequent exacerbations (≥2 per year) and those who demonstrate a significant amount of acute reversibility in response to inhaled bronchodilators.

- Side effects
  - Increased rate of oropharyngeal candidiasis
  - Increased rate of loss of bone density
Specific Treatments
Stable-phase COLD, pharmacotherapy

- Beclomethasone (QVAR):
  - Metered-dose inhaler; 40–80 μg/spray; 40–160 μg bid
- Budesonide (Pulmicort):
  - Powder via Turbuhaler; 200 μg/spray; 200 μg inhaled bid
- Fluticasone (Flovent):
  - Metered-dose inhaler; 44, 110 or 220 μg/spray; 88–440 μg inhaled bid
- Triamcinolone (Azmacort)
  - Metered-dose inhaler via built-in spacer; 100 μg/spray; 100–400 μg inhaled bid
Specific Treatments
Stable-phase COLD, pharmacotherapy

Parenteral corticosteroids

- Long-term use of oral glucocorticoids is not recommended.
- Side effects
  - Osteoporosis, fracture
  - Weight gain
  - Cataracts
  - Glucose intolerance
  - Increased risk of infection
- Patients tapered off long-term low-dose prednisone (~10 mg/d) did not experience any adverse effect on the frequency of exacerbations, quality of life, or lung function.
- On average, patients lost ~4.5 kg (~10 lb) when steroids were withdrawn.
Specific Treatments
Stable-phase COLD, pharmacotherapy

Theophylline

- Produces modest improvements in expiratory flow rates and vital capacity and a slight improvement in arterial oxygen and carbon dioxide levels in moderate to severe COPD
- Side effects
  - Nausea (common)
  - Tachycardia
  - Tremor
Specific Treatments
Stable-phase COLD, pharmacotherapy

Other agents

1. N-acetyl cysteine
   - Used for its mucolytic and antioxidant (current clinical trials) properties
2. Intravenous α1AT augmentation therapy for patients with severe α1AT deficiency
3. Antibiotics
   - Long-term suppressive or "rotating" antibiotics are not beneficial
Smoking cessation

- All patients with COLD should be strongly urged to quit and educated about the benefit of cessation and risks of continuation.
- Combining pharmacotherapy with traditional supportive approaches considerably enhances the chances of successful smoking cessation.

- Bupropion
- Nicotine replacement (gum, transdermal, inhaler, nasal spray)
- The U.S. Surgeon General recommendation is for all smokers considering quitting to be offered pharmacotherapy in the absence of any contraindication.
Specific Treatments
Stable-phase COLD, nonpharmacologic therapies

General medical care
1. Annual influenza vaccine
2. Polyvalent pneumococcal vaccine is recommended, although proof of efficacy in COLD patients is not definitive.
Table 3. Guidelines for Influenza and Pneumococcal Vaccinations in Patients with COPD.

<table>
<thead>
<tr>
<th>Category</th>
<th>Inactivated Influenza Vaccine</th>
<th>Polysaccharide Pneumococcal Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target group</td>
<td>All patients with COPD, except those who are hypersensitive to any component of vaccine, particularly eggs</td>
<td>All patients with COPD, except those who are hypersensitive to any component of vaccine</td>
</tr>
<tr>
<td>Frequency</td>
<td>Annually, preferably before influenza season or at any time throughout season</td>
<td>For patients &lt;65 yr of age, once or twice in lifetime; for patients ≥65 yr of age, one-time revaccination if vaccinated ≥5 yr earlier and &lt;65 yr of age at time of primary vaccination</td>
</tr>
<tr>
<td>Evidence of efficacy in COPD</td>
<td>Data from a meta-analysis of a limited number of trials indicate substantial reduction in influenza-related respiratory illnesses, large cohort study showed significant association between vaccination and reductions in hospitalizations for pneumonia and influenza and in risk of death during influenza season in persons with chronic lung disease.</td>
<td>Data from a meta-analysis of a limited number of trials showed no benefit in reducing COPD exacerbations; one large cohort study showed significant association between vaccination and reductions in hospitalizations for pneumonia and in risk of death in persons with chronic lung disease, but another study did not.</td>
</tr>
</tbody>
</table>

* Adapted from the Advisory Committee on Immunization Practices: Recommended Adult Immunization Schedule, 2009.
Specific Treatments
Stable-phase COLD, nonpharmacologic therapies

**Pulmonary rehabilitation**
- Improves health-related quality of life, dyspnea, and exercise capacity
- Rates of hospitalization are reduced over 6 to 12 months.
Specific Treatments
Stable-phase COLD, nonpharmacologic therapies

Lung volume reduction surgery
Produces symptomatic and functional benefit in selected patients
- Emphysema
- Predominant upper lobe involvement

Contraindications
- Significant pleural disease (pulmonary artery systolic pressure >45 mm Hg)
- Extreme deconditioning
- Congestive heart failure
- Other severe comorbid conditions
- FEV1 < 20% of predicted and diffusely distributed emphysema on CT or diffusing capacity for CO <20% of predicted (due to increased mortality)
Specific Treatments
Stable-phase COLD, nonpharmacologic therapies

Lung transplantation

- COLD is the leading indication.
- Candidates
  - ≤65 years
  - Severe disability despite maximal medical therapy
  - No comorbid conditions, such as liver, renal, or cardiac disease
  - Anatomic distribution of emphysema and presence of pulmonary hypertension are not contraindications.
- Unresolved issues include whether single- or double-lung transplantation is preferred.
<table>
<thead>
<tr>
<th>Category</th>
<th>GOLD</th>
<th>American Thoracic Society–European Respiratory Society</th>
<th>American College of Physicians</th>
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<tbody>
<tr>
<td>Indications for spirometry</td>
<td>Presence of chronic respiratory symptoms; in the absence of symptoms, history of exposure to risk factors (e.g., cigarette smoking or occupational exposure)</td>
<td>Presence of chronic respiratory symptoms; in the absence of symptoms, history of exposure to risk factors (e.g., cigarette smoking or occupational exposure)</td>
<td>Presence of chronic respiratory symptoms, particularly dyspnea</td>
</tr>
<tr>
<td>Indications for treatment</td>
<td>(\text{FEV}_1: \text{FVC} &lt; 0.70), with any symptoms</td>
<td>(\text{FEV}_1: \text{FVC} &lt; 0.70), with any symptoms</td>
<td>Chronic respiratory symptoms and (\text{FEV}_1 &lt; 60%) of predicted value</td>
</tr>
<tr>
<td>Medications recommended</td>
<td>Short-acting bronchodilator for GOLD stages 1 to 4; add LABA, LAAC, or both for GOLD stages 2 to 4; add inhaled corticosteroid for GOLD stages 3 to 4, if patient is prone to exacerbations</td>
<td>Short-acting bronchodilator for intermittent symptoms; add LABA or LAAC for persistent symptoms; if LABA or LAAC alone shows limited benefit, combine LABA or LAAC with inhaled corticosteroid</td>
<td>Monotherapy with LABA, LAAC, or inhaled corticosteroid for all symptomatic patients with (\text{FEV}_1 &lt; 60%) of predicted value; consider combined therapy for the same patients; use of short-acting bronchodilators not addressed</td>
</tr>
<tr>
<td>Candidates for pulmonary</td>
<td>Patients with GOLD stages 2 to 4</td>
<td>All patients with dyspnea and exercise limitation in addition to COPD</td>
<td>Symptomatic patients with (\text{FEV}_1 &lt; 50%) of predicted value</td>
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<td>rehabilitation</td>
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<td>Indications for long-term</td>
<td>Chronic hypoxemia with (\text{PaO}_2 \leq 55 \text{ mm Hg}) or (\text{SaO}_2 \leq 88%) or chronic hypoxemia with (\text{PaO}_2) of 55 to 60 mm Hg in presence of right-sided heart failure or polycythemia</td>
<td>Chronic hypoxemia with (\text{PaO}_2 \leq 55 \text{ mm Hg})</td>
<td>Chronic hypoxemia with (\text{PaO}_2 \leq 55 \text{ mm Hg})</td>
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<td>oxygen therapy</td>
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\(^a\) \(\text{FEV}_1\) denotes forced expiratory volume in 1 second, \(\text{FVC}\) forced vital capacity, \(\text{GOLD}\) the Global Initiative for Chronic Obstructive Lung Disease, \(\text{LAAC}\) long-acting anticholinergic, \(\text{LABA}\) long-acting \(\beta_2\)-adrenergic agonist, \(\text{PaO}_2\) partial pressure of oxygen in arterial blood, and \(\text{SaO}_2\) arterial oxygen saturation.

\(\uparrow\) Data are from the Global Initiative for Chronic Obstructive Lung Disease.\(^9\)

\(\downarrow\) Data are from Celli and MacNee.\(^15\)

\(\uparrow\) Data are from Qaseem et al.\(^54\)

GOLD identifies four stages of COPD, with 1 indicating mild COPD and 4 indicating very severe COPD.
Specific Treatments

Exacerbations of COLD

**Bronchodilators**

- Inhaled β-agonist, often with addition of an anticholinergic agent
- Frequency of administration depends on severity of disease.
- Initial treatment with nebulized therapy is common; it is often easier to administer in older patients or those in respiratory distress.
- Conversion to metered-dose inhalers is effective and allows an easier transition to outpatient care.
- Methylxanthines (e.g., theophylline) can be added to this regimen, although proof of efficacy is lacking; serum levels should be monitored to minimize toxicity.
Specific Treatments

Exacerbations of COLD

Antibiotics

• Choice should be based on local patterns of antibiotic susceptibility of pathogens and the patient’s clinical condition.
Specific Treatments
Exacerbations of COLD

Glucocorticoids

- Have been demonstrated to reduce the length of hospital stay, hasten recovery, and reduce the chance of subsequent exacerbation or relapse for up to 6 months.
- GOLD guidelines recommend 30–40 mg of oral prednisolone or its equivalent for 10–14 days.
- 2 weeks of glucocorticoid therapy produces benefit indistinguishable from 8 weeks of therapy.
- Side effects: hyperglycemia, particularly with preexisting diagnosis of diabetes.
Specific Treatments

Exacerbations of COLD

Oxygen

Supplemental O2 should be supplied to keep arterial saturation ≥90%.
Specific Treatments

Exacerbations of COLD
Mechanical ventilatory support

Noninvasive positive pressure ventilation
in patients with respiratory failure
(PaCO\(_2\) > 45 mmHg)

- Significantly reduces:
  - Mortality
  - Need for intubation
  - Complications of therapy
  - Length of hospital stay

- Contraindications
  - Cardiovascular instability
  - Impaired mental status or inability to cooperate
  - Copious secretions or inability to clear secretions
  - Craniofacial abnormalities or trauma precluding effective fitting of mask
  - Extreme obesity
Specific Treatments
Exacerbations of COLD

Invasive (conventional) mechanical ventilation via endotracheal tube

- **Indications**
  - Severe respiratory distress despite initial therapy
  - Life-threatening hypoxemia
  - Severe hypercapnia and/or acidosis
  - Markedly impaired mental status
  - Respiratory arrest
  - Hemodynamic instability
  - Other complications

- **Goal:** correct the aforementioned conditions

- For patients ≥ 65 years of age admitted to the intensive care unit for treatment, mortality doubles over the next year to 60%, regardless of whether mechanical ventilation was required.
Specific Treatments

Exacerbations of COLD

Monitoring

• Symptom assessment
• Pulse oximetry
• Serial pulmonary function tests
Specific Treatments
Exacerbations of COLD

Complications

• Cor pulmonale
  Right ventricular hypertrophy and failure induced by hypoxia

• Spontaneous pneumothorax occurs in a small proportion of emphysematous patients.
Prognosis

• The principal determinant of morbidity in COLD is the degree of airway obstruction.
  – Patients who continue to smoke cigarettes experience a yearly decrease in FEV1 of 80–100 mL.
  – Even for patients who quit smoking, the FEV1 decreases by 30 mL per year.

• Median survival for severe disease (FEV1 < 1 L) is 4 years.
Prevention

• Smoking prevention or cessation
• Prevention of exacerbations
  – Long-term suppressive antibiotics are not beneficial.
  – Inhalation glucocorticoids should be considered in patients with frequent exacerbations or in patients with an asthmatic component.
• Vaccination against influenza and pneumococcal infection
PEARL

Dyspnea with arm work, especially above the shoulder, is particularly common and severe in COLD.
## Table 3. Risk classification and suggested antimicrobial therapy [1, 3]

<table>
<thead>
<tr>
<th>Group</th>
<th>Basic Clinical State</th>
<th>Symptoms and Risk Factors</th>
<th>Probable Pathogens</th>
<th>First Choice</th>
<th>Alternatives for Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Acute tracheobronchitis</td>
<td>Cough &amp; sputum without previous pulmonary disease</td>
<td>Usually viral</td>
<td>None unless symptoms persist for &gt; 7 to 10 days</td>
<td>Macrolide or tetracycline</td>
</tr>
<tr>
<td>I</td>
<td>Chronic bronchitis without risk factors (Simple)</td>
<td>Increased cough and sputum, sputum purulence, and increased dyspnea</td>
<td>H. influenzae, Haemophilus spp., M. catarrhalis, S. pneumoniae, Amoxicillin, doxycycline, trimethoprim/sulphamethoxazole</td>
<td>Second generation macrolide, second or third generation cephalosporin, inhibitor</td>
<td>Fluoroquinolone, β-lactam/β-lactamase</td>
</tr>
<tr>
<td>II</td>
<td>Chronic bronchitis with risk factors (Complicated)</td>
<td>As in class I plus (at least one of): • FEV1 &lt; 50% predicted • ≥ 4 exacerbations/year • Age &gt; 65 years • Significant co-morbidity (especially heart disease) • Use of home oxygen • Chronic oral steroid use • Antibiotic use in the past 3 months</td>
<td>As in class I plus • Klebsiella spp. + other Gram-negatives • Increased probability of β-lactam resistance</td>
<td>Fluoroquinolone, β-lactam/β-lactamase inhibitor</td>
<td>may require parenteral therapy consider referral to a specialist or hospital</td>
</tr>
<tr>
<td>III</td>
<td>Chronic supplicative bronchitis</td>
<td>• As in class II with constant purulent sputum; • Some have bronchiectasis • FEV1, usually &lt; 35% predicted or • Multiple risk factors (e.g. frequent exacerbations and FEV1 &lt; 50%</td>
<td>As in class II plus <em>Pseudomonas aeruginosa</em> and multi-resistant Enterobacteriaceae</td>
<td>Ambulatory patients: tailor treatment to airway pathogen <em>P. aeruginosa</em> common (ciprofloxacin); Hospitalized patients: parenteral therapy usually required.</td>
<td></td>
</tr>
</tbody>
</table>


Summary of Evidence Regarding Antibiotic Therapy
for Acute Exacerbations of Chronic Bronchitis (Table 3)

1. Antimicrobial therapy is warranted for patients with an acute exacerbation of chronic bronchitis if they fall into the Anthonisen type I or type II categories (Level A evidence, 2 randomized, large scale double-blind trials, 1 meta-analysis).

2. Antimicrobial therapy is not warranted for patients with a type III exacerbation (Level A evidence).

3. Patients can be stratified according to their risk of treatment failure (Level C, D evidence).

4. A high-risk group of patients can be identified on clinical grounds and the major clinical features are significant impairment of lung function (FEV₁ ≤50% predicted), frequent exacerbations (> 4/year), long duration of disease, significant co-morbidity, advanced age, malnutrition, and chronic oral corticosteroid use. (Level C evidence)

5. Risk group 0 patients (acute tracheobronchitis) should not be treated with antibiotics unless symptoms persist beyond 7 to 10 days (Level A evidence).

6. For risk group 0 patients with persistent symptoms, a macrolide or tetracycline is recommended since Mycoplasma pneumoniae, Chlamydia pneumoniae, or Bordetella pertussis may be pathogens (Level C evidence).

7. Although resistant H. influenzae and M. catarrhalis may be pathogens, traditional first-line agents (aminopenicillins, doxycycline, trimethaprim-sulphamethoxazole) continue to be efficacious and are recommended for patients without risk factors for treatment failure (Level B evidence). Second generation macrolides and some second and third generation cephalosporins (cefuroxime, cefprozil, cefixime) may be better choices given concerns regarding emerging antimicrobial resistance (Level C evidence).

8. There are no data to demonstrate that, among Group I patients (low risk for treatment failure), that there is any clinical or economic benefit derived from using more potent, broader spectrum agents (Level A evidence).

9. Broad-spectrum potent agents such as fluoroquinolones or amoxicillin/clavulanate are recommended for group II patients (Level C evidence).

10. There is some evidence that fluoroquinolones perform better than other agents for group II patients (Level B evidence).

11. Group III patients at risk for Pseudomonas aeruginosa infection (frequent antimicrobials, structural lung damage, and chronic corticosteroids) should be treated with an anti-pseudomonal agent (ciprofloxacin). Alternative agents currently must be given parenterally (Level C evidence).

12. Patients presenting with a relapse or recurrence of acute exacerbation of chronic bronchitis, within 3 months of previous antibiotic therapy, should be treated with a different class of antibiotics (Level C evidence).