

Chronic Obstructive Lung Disease

(See also *Harrison's Principles of Internal Medicine*, 17th Edition, Chapter 354)

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

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.
- >70% of COLD-related health care expenditures go to emergency department visits and hospital care (>\$10 billion annually in the U.S.).
- 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.
- Age
 - Higher prevalence with increasing age
 - Dose-response relationship between cigarette smoking intensity and decreased pulmonary function

Risk Factors

- Smoking (see Figure 1)
 - Cigarette smoking is a major risk factor.
 - Cigar and pipe smoking
 - Evidence less compelling; likely related to lower dose of inhaled tobacco by-products
 - 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
 - α_1 antitrypsin (α_1 AT) deficiency
 - Common M allele: normal levels
 - S allele: slightly reduced levels
 - Z allele: markedly reduced levels
 - Null allele: absence of α_1 AT (rare)
 - Lowest levels of α_1 AT are associated with incidence of COLD; α_1 AT deficiency interacts with cigarette smoking to increase risk.
- Genetic factors probably contribute to the level of pulmonary function achieved during growth and to the rate of decline in response to smoking and other environmental factors.

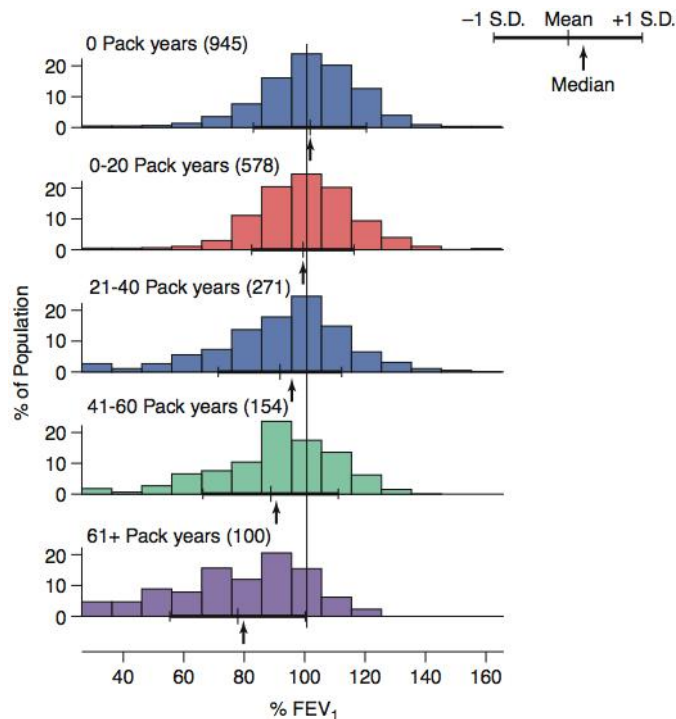


Figure 1: Distributions of forced expiratory volume in 1 s (FEV_1) values in a general population sample, stratified by pack-years of smoking. Means, medians, and ± 1 standard deviation of percent predicted FEV_1 are shown for each smoking group. Although a dose-response relationship between smoking intensity and FEV_1 was found, marked variability in pulmonary function was observed among subjects with similar smoking histories. (From Burrows *et al*, with permission.)

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

Differential Diagnosis

- Differential diagnosis
 - Congestive heart failure
 - Asthma
 - Bronchiectasis
 - Obliterative bronchiolitis
 - Pneumonia
 - Tuberculosis
 - Atelectasis
 - Pneumothorax
 - Pulmonary embolism
- Considerations
 - COLD is present only if chronic airflow obstruction occurs.
 - Chronic bronchitis without chronic airflow obstruction is not COLD.
 - 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.
 - Problems other than COLD should be suspected when hypoxemia is difficult to correct with modest levels of supplemental oxygen.
 - 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
 - History and physical examination (see Signs & Symptoms)
 - Pulmonary function testing to assess airflow obstruction
 - Radiographic studies
- Assessment of exacerbation
 - History
 - Fever
 - Change in quantity and character of sputum
 - Ill contacts
 - Associated symptoms
 - Frequency and severity of prior exacerbations
 - 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
- Radiographic studies
 - Chest radiography focal findings (pneumonia, atelectasis)
- Arterial blood gases
 - Hypoxemia (see below)
 - Hypercapnia (see below)
- 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

- Arterial blood gases 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.
- Elevated hematocrit suggests chronic hypoxemia.
- Serum level of α_1AT should be measured in some patients.
 - Presenting at ≤ 50 years of age
 - Strong family history
 - Predominant basilar disease
 - Minimal smoking history
 - Definitive diagnosis of α_1AT 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).
- 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 hypertrophy.

Classification

- 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 ≥ 80% predicted
 - IIA
 - 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
 - Supplemental O₂ is the only therapy demonstrated to decrease mortality.
 - 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.
 - 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.
- 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
- Anticholinergic agents
 - Trial of inhaled anticholinergics is recommended in symptomatic patients.
 - Side effects are minor.
 - Improve symptoms and produce acute improvement in FEV₁
 - 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
 - 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
 - Addition of a β-agonist to inhaled anticholinergic therapy provides incremental benefit.
 - Side effects
 - Tremor
 - Tachycardia
 - Salmeterol (Serevent):
 - Powder via diskus; 50-µg inhalation every 12 h
 - Formoterol (Foradil):
 - Powder via aerolizer; 12-µg inhalation every 12 h

- Albuterol (short-acting β -agonist) (Proventil HFA, Ventolin HFA, Ventolin, Proventil)
 - Metered-dose inhaler (or in nebulizer solution); 180- μ g 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 μ g per inhalation 1–2 inhalations qid
- 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
 - Beclomethasone (QVAR):
 - Metered-dose inhaler; 40–80 μ g/spray; 40–160 μ g bid
 - Budesonide (Pulmicort):
 - Powder via Turbuhaler; 200 μ g/spray; 200 μ g inhaled bid
 - Fluticasone (Flovent):
 - Metered-dose inhaler; 44, 110 or 220 μ g/spray; 88–440 μ g inhaled bid
 - Triamcinolone (Azmacort)
 - Metered-dose inhaler via built-in spacer; 100 μ g/spray; 100–400 μ g inhaled bid
- 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.
- 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
- Other agents
 - N-acetyl cysteine
 - Used for its mucolytic and antioxidant (current clinical trials) properties
 - Intravenous α_1 AT augmentation therapy for patients with severe α_1 AT deficiency
 - Antibiotics
 - Long-term suppressive or "rotating" antibiotics are not beneficial.

Stable-phase COLD, nonpharmacologic therapies

- 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.
- General medical care
 - Annual influenza vaccine
 - Polyvalent pneumococcal vaccine is recommended, although proof of efficacy in COLD patients is not definitive.
- Pulmonary rehabilitation
 - Improves health-related quality of life, dyspnea, and exercise capacity
 - Rates of hospitalization are reduced over 6 to 12 months.
- 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
 - $FEV_1 < 20\%$ of predicted and diffusely distributed emphysema on CT or diffusing capacity for CO <20% of predicted (due to increased mortality)
- 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.

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.

- Antibiotics
 - Choice should be based on local patterns of antibiotic susceptibility of pathogens and the patient's clinical condition.
- 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
- Oxygen
 - Supplemental O₂ should be supplied to keep arterial saturation ≥90%.
- Mechanical ventilatory support
 - Noninvasive positive pressure ventilation in patients with respiratory failure (PaCO₂ > 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
 - 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.

Monitoring

- Symptom assessment
- Pulse oximetry
- Serial pulmonary function tests

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

ICD-9-CM

- 496.00 Chronic airway obstruction, not elsewhere classified (includes COPD, unspecified)

See Also

- Approach to Weight Loss
- Asthma
- Cor Pulmonale
- Cough
- Dyspnea
- Lung Cancer, General
- Pulmonary Arterial Hypertension, Secondary
- Pulmonary Function Tests
- Respiratory Failure

Internet Sites

- Professionals
 - Home
 - Global Initiative for Chronic Obstructive Lung Disease
 - Standards for Diagnosis and Management of COPD
 - American Thoracic Society and European Respiratory Society
- Patients
 - Tobacco cessation
 - U.S. Surgeon General
 - COPD
 - Medline Plus

General Bibliography

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PEARL

- Dyspnea with arm work, especially above the shoulder, is particularly common and severe in COLD.