ATS Core Curriculum 2016

Part IV. Adult Pulmonary Medicine Core Curriculum

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Gaëtane C. Michaud[1], Colleen L. Channick[2], Anica C. Law[2], Jessica B. McCannon[2], MaryEllen Antkowiak[3], Garth Garrison[3], David Sayah[4], Richard H. Huynh[4], Anna K. Brady[5], Rosemary Adamson[5], Hilary DuBrock[6], Praveen Akuthota[6], Chad Marion[7], Charles Dela Cruz[7], James A. Town[5], Başak Çoruh[5], and Carey C. Thomson[8]

[1]Pulmonary, Critical Care and Sleep Medicine, New York University School of Medicine, New York, New York; [2]Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [3]Pulmonary and Critical Care Medicine, University of Vermont College of Medicine, Burlington, Vermont; [4]Pulmonary and Critical Care Medicine, University of California, Los Angeles, Los Angeles, California; [5]Pulmonary and Critical Care Medicine, University of Washington, Seattle, Washington; [6]Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [7]Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine, New Haven, Connecticut; and [8]Pulmonary and Critical Care Medicine, Mount Auburn Hospital, Harvard Medical School, Boston, Massachusetts

ORCID ID: 0000-0001-7021-8273 (D.S.).

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Chronic Obstructive Pulmonary Disease Pathophysiology

Anica C. Law and Jessica B. McCannon

Epidemiology

The World Health Organization projects that the total number of deaths from chronic obstructive pulmonary disease (COPD) will increase by more than 30% in the next 10 years, to become the third leading cause of death worldwide by 2030 (1). Understanding its pathogenesis and various forms may lead to better diagnosis and management.

Pathogenesis

We have come to understand more about the pathogenesis of COPD. Genomic studies have identified genes associated with nicotine addiction and lung function (2). These genetic factors act in concert with toxic environmental factors to amplify immune responses, which cause damage to the airways. The microbiome of the lungs (the sum of all bacteria, viruses, and fungi present at one time, as detected by their DNA) is different in different states of disease. Microbial diversity is less in advanced emphysema with destructive effects on bronchioles, alveoli, and structural tissue (3). Although differences have been identified, their importance in COPD pathophysiology is unknown. Several humoral and cellular-mediated immune responses may contribute to the pathogenesis in COPD. B cell–activating factor is increased in the blood and bronchioloalveolar lavage, and T lymphocytes (predominantly $CD8^+$ cells) are increased in the sputum, bronchial glands, and the circulation (4, 5). In addition, cytokines, including IL-8, IL-1, IL-6, and tumor necrosis factor (TNF)-α, appear to perpetuate tissue damage such as subepithelial fibrosis and increased collagen deposition (6). Systemic inflammation,

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Correspondence and requests for reprints should be addressed to Gaëtane Michaud, M.D., M.S., 531 First Avenue, Suite 5D, New York, NY 10016. E-mail: gaetanemichaud@yahoo.ca

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Table 1. Combined assessment of chronic obstructive pulmonary disease

Patient Type	Characteristic	Severity of Airflow Limitation, Using Spirometry	Risk of Exacerbation: Number of Annual Exacerbations	Modified Medical Research Council Breathlessness Scale	COPD Assessment Test
A	Low risk Fewer symptoms	GOLD 1–2	⩽1	0–1	<10
B	Low risk More symptoms	GOLD 1–2	⩽1	⩾2	⩾10
C	High risk Fewer symptoms	GOLD 3–4	⩾2	0–1	<10
D	High risk More symptoms	GOLD 3–4	⩾2	⩾2	⩾10

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.
Adapted by permission Reference 3.

manifested as elevations in C-reactive protein, fibrinogen, and leukocytosis, occurs in COPD and is associated with an increased risk of exacerbations and other systemic disorders (7).

Diagnosis

Spirometric evidence of obstruction is required to diagnose COPD. In the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, the severity of COPD is determined primarily by the impairment in FEV_1. However, more recent guidelines incorporate measures of symptom severity and frequency of exacerbation (as assessed by the modified Medical Research Council [mMRC] dyspnea scale or the COPD Assessment Tool [CAT]) to stage disease severity and guide therapy (GOLD A–D) (Table 1) (3). Beyond the well-accepted COPD subtypes chronic bronchitis and emphysema, there is now growing appreciation of the heterogeneity of the disease and its progression, as well as the impact of comorbidities. It has been recognized that COPD may manifest as several distinct clinical phenotypes including (*1*) alpha-1 antitrypsin deficiency associated with response to repletion therapy, (*2*) upper lobe emphysema with poor postrehabilitation exercise tolerance associated with mortality benefit from lung volume reduction, and (*3*) the frequent exacerbator in whom benefit is realized with antiinflammatory therapy. Specific radiologic phenotypes have been well described and delineated by the Fleischner Society, including centrilobular, panlobular, and paraseptal patterns (8). Further longitudinal studies are required to validate these disease phenotypes and to determine therapeutic strategies.

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Pharmacologic and Nonpharmacologic Management of COPD

MaryEllen Antkowiak and Garth Garrison

The goals of outpatient COPD management include improving functional status, reducing the frequency of infectious exacerbations, slowing the decline in lung function, and reducing mortality.

Nonpharmacologic Management

Regardless of GOLD stage, all patients with COPD should be counseled about smoking cessation, as this intervention has been shown to slow lung function decline and improve mortality (1). Supplemental oxygen decreases mortality in patients with hypoxemia, right heart failure, or polycythemia and its use should be strongly encouraged (1). In addition, all patients should receive yearly influenza vaccinations and pneumococcal polysaccharide vaccine. Patients greater than 65 years of age or with other risk factors for severe pneumococcal disease should also receive the pneumococcal conjugate vaccine (1). Patients with moderate to severe COPD should all be referred to a pulmonary rehabilitation program; this is associated with improvements in exercise

Table 2. Updates in pharmacologic and nonpharmacologic treatment of chronic obstructive pulmonary disease

Pharmacologic	Nonpharmacologic
LABA or LAMA for first-line bronchodilator therapy to prevent acute exacerbations	Patients >65 yr or with risk factors for severe pneumococcal disease should receive pneumococcal conjugate vaccine
Inhaled corticosteroid to reduce exacerbations	Endobronchial lung volume reduction: emerging data suggest improvement in functional capacity and quality of life
Macrolide use has been associated with a significant decrease in the rate of exacerbations	
For moderate-to-severe persistent disease, can consider phosphodiesterase-4 inhibition	Surgical lung volume reduction and transplantation should be considered in appropriate patients

Definition of abbreviations: LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.
Data from References 3, 5, and 9.

capacity, dyspnea, and quality of life, and with reduced hospital admissions (2).

Pharmacologic Management

Bronchodilators. Bronchodilators remain the first-line therapy for patients with COPD. The choice of bronchodilator is guided by symptoms and degree of airflow limitation. Patients with minimal symptoms and mildly reduced airflow may be treated with intermittent short-acting bronchodilators alone. In general, these medications are well tolerated and have few side effects. Multiple studies have demonstrated reduced symptoms and exacerbation rates, and potentially slower rate of lung function decline with the use of long-acting bronchodilator therapy (1, 3, 4). Although some data suggest a benefit of long-acting anticholinergics over long-acting β-agonists in terms of reducing exacerbations, these data are controversial and most guidelines do not recommend one class over the other (1, 3, 4).

Inhaled corticosteroids. Inhaled corticosteroids (ICS) are recommended for patients with moderate to severe COPD and who have persistent symptoms or exacerbations despite long-acting bronchodilator therapy. ICS are generally well tolerated, with common side effects being dysphonia and oral candidiasis. ICS therapy may decrease rates of COPD exacerbations. Although earlier studies raised concern for a link between ICS and pneumonia, multiple subsequent studies have not supported this association (1, 3, 4).

Other pharmacologic options. For patients with moderate to severe COPD and refractory symptoms additional pharmacologic therapies are available. Phosphodiesterase-4 inhibitors have both bronchodilator and antiinflammatory properties. They have been shown to reduce exacerbation frequency and to increase FEV_1 in patients with moderate to severe COPD. Their use may be limited by gastrointestinal and psychiatric side effects (5). Chronic macrolide antibiotic therapy has also been associated with a significant decrease in the rate of exacerbations (6). There has been concern about the risk of cardiac arrhythmias with this therapy, but the magnitude of this risk is unclear (7). Patients should be monitored carefully for other adverse effects including hearing loss. Although no longer used as a first-line therapy because of its narrow therapeutic range and lower efficacy, low-dose theophylline may be considered for patients who remain symptomatic despite optimal inhaled therapy (3).

Surgical Options

For patients with advanced COPD failing medical therapy, surgical options exist. Lung volume reduction surgery reduces hyperinflation and has been demonstrated to decrease mortality and to improve exercise capacity in highly selected patients with severe COPD (8). Several promising bronchoscopic techniques to reduce hyperinflation are under investigation. Among these, endobronchial valves and coils currently appear to be the most promising as they have been shown to improved lung function, quality of life, and functional status in small randomized controlled trials (9, 10). Patients with end-stage disease may be candidates for lung transplantation, and therefore consultation should be considered when appropriate.

A summary of pharmacologic and nonpharmacologic management of COPD is shown in Table 2.

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Interstitial Lung Disease: Therapeutic Options

David Sayah and Richard H. Huynh

The interstitial lung diseases (ILDs) are a heterogeneous group of disorders that include idiopathic pulmonary fibrosis (IPF), connective tissue disease–associated ILD (CTD-ILD), and several others. Treatment options are specific to the underlying disease (Table 3).

Antifibrotic Agents

Two oral antifibrotic agents, pirfenidone and nintedanib, are the first medications with clear, although modest, efficacy in IPF. Both agents are approved by the U.S. Food and Drug Administration for IPF treatment. Updated expert consensus IPF treatment guidelines include a conditional recommendation for either pirfenidone or nintedanib (1).

Pirfenidone has pleiotropic antifibrotic effects; however, its specific molecular targets are unknown (2). Three prior randomized controlled trials of pirfenidone in IPF resulted in inconsistent findings (3, 4). In a fourth, pirfenidone reduced the rate of decline in FVC and in exercise capacity. Pooled analysis of the studies suggests a possible mortality benefit (5). Common adverse effects, although rarely serious, included nausea, vomiting, abdominal discomfort, photosensitivity, and rash (3–5).

Nintedanib inhibits several tyrosine kinases implicated in the pathogenesis of IPF (6, 7). In paired randomized controlled trials, nintedanib, like pirfenidone, reduced the rate of FVC decline in IPF (8). Diarrhea and nausea were frequent side effects, although rarely resulting in drug discontinuation. Given concerns about increased myocardial infarction risk with nintedanib, caution is advised in patients at high cardiovascular risk.

Table 3. Updates in interstitial lung diseases

Idiopathic pulmonary fibrosis
Pirfenidone and nintedanib approved for IPF treatment
No comparative data demonstrating superiority of one oral agent over another
No safety or efficacy data available regarding combination of pirfenidone and nintedanib
Lung transplantation consideration recommended at diagnosis of IPF
Other interstitial lung diseases
Limited data suggest that immunosuppressive therapy has a role in CTD-ILD, but unclear benefit in other non-IPF ILDs
Transplantation important consideration, but extra-pulmonary manifestations in CTD-ILD many limit candidacy

Definition of abbreviations: CTD-ILD = connective tissue disease–associated interstitial lung disease; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis.
Data from References 1–5, 9, 10, and 13.

No comparative efficacy data exist to guide selection of one antifibrotic agent over another. Frequent hepatic monitoring is recommended with both medications. No data exist to support combination therapy, or treatment of other non-IPF ILDs with these agents.

Immunosuppressive Agents

With the exception of scleroderma-related ILD, no high-quality randomized controlled trials have studied the treatment of CTD-ILD. Experience-based practice and limited data suggest that immunosuppressive therapy, including glucocorticoids, mycophenolate, and/or azathioprine, has a role in the management of CTD-ILD (9).

In contrast, combination immunosuppressive therapy for IPF with prednisone, azathioprine, and *N*-acetylcysteine in the PANTHER-IPF (Prednisone, Azathioprine, and *N*-Acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis) trial led to excess mortality and other serious adverse events (10). Immunosuppressive medications should not be used in the treatment of patients with IPF (1).

In the Scleroderma Lung Study, patients with scleroderma-related ILD treated with cyclophosphamide compared with placebo had a modestly higher FVC, as well as less dyspnea and higher quality of life, establishing it as a treatment option (11). Adverse events associated with cyclophosphamide included hematuria, leukopenia, neutropenia, anemia, and pneumonia. In a follow-up study comparing mycophenolate and cyclophosphamide, both agents appeared to have comparable efficacy; however, the former was better tolerated (12).

Although immunosuppressive agents may also be beneficial in other ILDs, the paucity of currently available data supporting their use highlights the urgent need for more randomized trials.

Lung Transplantation

Lung transplantation remains an important therapeutic option for patients with IPF (13). Expert consensus guidelines recommend a discussion about lung transplantation or referral to a lung transplantation center, at the time of IPF diagnosis in appropriate patients. Lung transplantation is also an important option in other ILDs, including CTD-ILD. However, patients must be carefully selected as extrapulmonary manifestations of systemic connective tissue disease may compromise posttransplantation outcome (13).

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Sarcoidosis and Hypersensitivity Pneumonitis

Anna K. Brady and Rosemary Adamson

Etiology and Diagnosis

Sarcoidosis is a granulomatous disease of unclear etiology. Evidence suggests that both genetics and infectious agents contribute to its pathogenesis (1, 2).

The hallmark of sarcoidosis is the finding of noncaseating granulomas in affected tissues. Nevertheless, it is not always necessary to obtain a tissue biopsy as certain clinical syndromes (asymptomatic bilateral hilar lymphadenopathy, Löfgren syndrome, and Heerfordt syndrome) have been found to follow a benign clinical course (3).

When tissue diagnosis is required, biopsies should be taken from the most accessible involved organ. Given that the lungs are the most common site of involvement, bronchoscopy is often the procedure of choice. There are numerous studies indicating that endobronchial ultrasound-guided transbronchial needle aspiration provides a higher diagnostic yield than conventional needle aspiration. The highest diagnostic yield is obtained when sampling methods are combined (4).

Treatment with Glucocorticoids

Treatment is not indicated for Löfgren syndrome, asymptomatic patients with pulmonary sarcoidosis, or isolated radiographic change. If the only symptoms are cough and wheezing, inhaled corticosteroids can be used. When or whether to initiate corticosteroids for patients with reduced lung function is controversial. Some experts advocate treatment of pulmonary sarcoidosis if the FEV_1 and FVC are less than 70% predicted, there is a decrement in FVC by 10–15%, or a reduction in $D_{L_{CO}}$ (diffusing capacity of the lung for carbon monoxide) by 20% (5). Certain extrapulmonary manifestations of sarcoidosis typically merit systemic treatment with prednisone, including hypercalcemia, cardiac sarcoidosis, and neurologic sarcoidosis (6).

Cardiac Sarcoidosis

Cardiac sarcoidosis can cause conduction system disease, heart failure, and sudden death; thus, patients with sarcoidosis should be questioned about cardiac symptoms on every visit. Patients endorsing these symptoms should be thoroughly evaluated. Both cardiac magnetic resonance imaging and positron emission tomography can identify cardiac inflammation, whereas echocardiography may show less specific signs of heart failure (5). Event or Holter monitors may be used if conduction system disease is suspected. Endomyocardial biopsy is not recommended as a first-line test because it is both risky and insensitive due to patchy myocardial involvement (3, 5).

Calcium and Vitamin D Metabolism in Sarcoidosis

Active granulomas produce IFN-γ, which increases hydroxylation of 25-OH vitamin D to 1,25-OH vitamin D, the metabolically active form of the hormone. Although 25-OH vitamin D is the form of the vitamin checked before repletion in patients without sarcoidosis, 1,25-OH vitamin D more accurately reflects vitamin D activity in patients with sarcoidosis. Elevated levels of 1,25-OH vitamin D can lead to hypercalcemia by promoting intestinal calcium absorption, among other mechanisms (7).

Hypersensitivity Pneumonitis

Diagnostic usefulness of clinical factors. Diagnosing hypersensitivity pneumonitis on the basis of clinical criteria can be challenging, in part because the radiographic appearance is nonspecific and varies considerably. Lacasse and colleagues identified six clinical findings most likely to predict hypersensitivity pneumonitis (Table 4), of which exposure to a known offending antigen was the strongest predictor. If all six factors are present, the probability of the patient having hypersensitivity pneumonitis is 98% (8). The presence of immunoglobulin G antibodies (serum precipitins) to known offending antigens supports a diagnosis of hypersensitivity pneumonitis; however, their presence is neither necessary nor sufficient to make the diagnosis (8–10). Failure to identify an offending antigen is associated with a worse prognosis (9).

Diagnostic Usefulness of Bronchoscopy

Bronchoalveolar lavage is useful to evaluate for alveolitis. An increase in lymphocytes is typical, although an increase in neutrophils is seen with acute attacks. Alveolar lymphocytosis can be seen in asymptomatic individuals exposed to common

Table 4. Clinical factors most likely to predict hypersensitivity pneumonitis

Factor	Odds Ratio
Exposure to a known offending antigen	38.8
Symptoms 4–8 h after exposure	7.2
Presence of serum precipitins	5.3
Inspiratory crackles	4.5
Recurrent episodes of symptoms	3.3
Weight loss	2.0

Adapted by permission from Reference 8.

antigens, and the CD4:CD8 ratio is of limited value (10). A normal bronchoalveolar lavage cell count rules out active hypersensitivity pneumonitis, but it does not rule out the chronic form.

Transbronchial lung biopsy may show loosely formed noncaseating granulomas, although the diagnostic yield is considerably lower than for surgical lung biopsy (10). The role of newer biopsy techniques such as cryobiopsies is as yet unknown.

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Rare Lung Diseases

Hilary DuBrock and Praveen Akuthota

The rare lung diseases highlighted include rare vascular diagnoses and rare asthma-related syndromes.

Pulmonary Arteriovenous Malformations

Pulmonary arteriovenous malformations are abnormal vascular communications between the pulmonary and systemic circulation. They have an estimated prevalence of 1 in 2,600 and are most commonly associated with hereditary hemorrhagic telangiectasia (1). Patients with pulmonary arteriovenous malformations may present with dyspnea, asymptomatic hypoxemia, or complications such as cerebral abscess, stroke, and hemoptysis (1). Contrast-enhanced echocardiography is an effective screening tool, and diagnosis is made with chest computed tomography (1, 2). Current guidelines recommend embolization if technically feasible and follow-up chest computed tomography 6–12 months after embolization and every 3 years thereafter (1, 2). The literature, however, suggests alternative follow-up approaches to minimize radiation exposure (1, 3). Antibiotic prophylaxis for procedures with risk of bacteremia, filtration of peripheral intravenous lines, supplemental oxygen for hypoxemia if present, and counseling regarding avoidance of scuba diving are recommended (1, 2).

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis is a rare and progressive lung disease characterized by capillary proliferation, which can lead to dyspnea, hypoxemia, pulmonary arterial hypertension, and death (4). It is classified as World Health Organization Group 1′ pulmonary arterial hypertension (5). Radiographic features include pulmonary artery enlargement and centrilobular ground-glass opacities. Pleural effusions, mediastinal lymphadenopathy, and prominent interlobular septa have also been reported (6). The cause of pulmonary capillary hemangiomatosis is unknown, but mutations in EIF2AK4 (eukaryotic translation initiation factor 2α kinase 4) have been identified in both sporadic and familial forms (7). There are no proven effective treatments for pulmonary capillary hemangiomatosis beyond lung transplantation.

Pulmonary Sequestration

Pulmonary sequestration is a rare congenital anomaly in which nonfunctioning lung tissue is supplied by an anomalous systemic artery, most often the descending thoracic aorta (8, 9). Sequestrations are categorized as either intralobar or extralobar, with the prior representing more than 75% of cases. The sequestered lung parenchyma is excluded from the central airways. Bacteria are able to translocate via the pores of Khon, gastrointestinal tract, or other parts of the lung, particularly in intralobar sequestrations. These patients typically present with recurrent pneumonia. Pulmonary sequestration can appear mass-like, cystic, or fluid-filled on imaging. Additional abnormalities such as congenital pulmonary airway malformations can coexist. The mainstay of treatment is lobectomy or surgical resection in both symptomatic and asymptomatic patients.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis is a syndrome driven by sensitivity to *Aspergillus fumigatus* that colonizes the airways. It is almost exclusively seen in patients who have either concurrent asthma or cystic fibrosis. Other characteristic features include the following (10):

- Positive skin testing to *Aspergillus* (and/or positive serum *Aspergillus*-specific IgE)
- Marked elevations in total circulating IgE
- Precipitating serum *Aspergillus* antibodies
- Serum eosinophil count greater than 500 cells/μl

Radiographic features may include central bronchiectasis, mucus plugging, atelectasis, and peripheral infiltrates. Corticosteroids remain the mainstay of treatment, but azole antifungal agents are effective in reducing the need for corticosteroids.

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis, previously known as Churg-Strauss syndrome, is a multisystem disorder characterized by high-grade peripheral eosinophilia with vasculitic features (11, 12). Although eosinophilic granulomatosis with polyangiitis is categorized as a small-vessel anti-neutrophil cytoplasmic antibody–associated vasculitis, the presence of anti-neutrophil cytoplasmic antibody is variable and pathological evidence of vasculitis may not be obtainable. Asthma and sinusitis are prominent characteristic features of eosinophilic granulomatosis with polyangiitis. Mononeuritis multiplex is often seen. Other end-organ manifestations may include cardiac, gastrointestinal, renal, and dermatologic disease. Corticosteroids are usually necessary for both initial and maintenance therapy, although cytotoxic agents are often necessary as well. A trial of an anti–IL-5 monoclonal antibody is ongoing (NCT02020889; access at https://clinicaltrials.gov/).

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Hospital-acquired and Ventilator-associated Pneumonia

Chad Marion and Charles Dela Cruz

Clinical Definition and Diagnosis

Hospital-acquired pneumonia and ventilator-associated pneumonia are the most common nosocomial infections resulting in increased intensive care unit mortality. Ventilator-associated pneumonia is a type of hospital-acquired pneumonia that develops more than 48–72 hours after endotracheal intubation. Unfortunately, there is no "gold standard" to define either entity, thus rendering diagnosis difficult. The diagnosis is usually defined by clinical, radiographic, and microbiological criteria (Table 5) (1). However, these are nonspecific and subjective, with substantial interobserver variability. Biomarker studies exist, but none are adequately validated for clinical use.

Multidrug Resistance: Risk factors

Multidrug-resistant gram-negative bacilli are an important cause of hospital-acquired and ventilator-associated pneumonia. It is defined as resistance to at least two antibiotics typically used to treat the infection (2). Extensively drug-resistant gram-negative bacilli show resistance to all commonly used systemic antibiotics with the exception of colistin, tigecycline, and aminoglycosides. Mechanical ventilation is one of the most significant risk factors for hospital-acquired and ventilator-associated pneumonia, with intubation increasing the risk by 6- to 21-fold. Of patients hospitalized for pneumonia, 51% have one risk factor on admission for acquiring a multidrug-resistant bacteria. Hospitalization within 90 days and residency in a nursing facility are independent predictors for resistant organisms and in-hospital mortality (3).

Treatments for Multidrug-Resistant Organisms

Antimicrobial selection should be based on risk of multidrug-resistant organisms, recent antibiotic use, local flora, comorbidities, and available culture data. The American Thoracic Society/Infectious Diseases Society of America guidelines recommend initial empiric therapy with an antipseudomonal β-lactam plus either an antipseudomonal fluoroquinolone or aminoglycoside plus coverage for methicillin-resistant *Staphylococcus aureus* with linezolid or vancomycin (4). Adherence to guidelines resulted in more appropriate treatment and a trend toward better clinical

Table 5. Diagnostic criteria for hospital- and ventilator-acquired pneumonia

Imaging	Signs and Symptoms	Laboratory
Two or more serial chest radiographs with at least one of the following: • New infiltrate • Consolidation • Cavitary lesion	At least one of the following: • Fever (>38.0°C or >100.4°F) • Leukopenia or leukocytosis • Altered mental status in adults > 70 yr old And at least one of the following: • New purulent sputum, change in character of sputum or more frequent suctioning requirements • New onset or worsening cough, dyspnea or tachypnea • New rales or rhonchi on physical examination • Increased oxygen requirements	At least one of the following: • Positive growth in blood culture not due to other source • Positive growth in pleural fluid • Positive quantitative culture from minibronchoalveolar lavage or bronchoscopy • >5% BAL-obtained cells containing intracellular bacteria by microscopy • Positive lung tissue culture

Definition of abbreviation: BAL = bronchoalveolar lavage.

response for patients presenting late (≥5 d) or having multidrug resistance risk factors, although it did not affect mortality (5). Late-onset hospital-acquired or ventilator-associated pneumonia is associated with multidrug-resistant pathogens including those with extended-spectrum β-lactamase activity. It is recommended to narrow and deescalate therapy when possible to mitigate risk of further resistance.

Clinical Tool for Antibiotic Stewardship

Several clinical scoring systems and biomarkers have been established to diagnose hospital-acquired and ventilator-associated pneumonia including the pneumonia severity index, clinical pulmonary infection score, CURB-65, procalcitonin, and C-reactive protein (CRP). Unfortunately, clinical scoring systems and inflammatory biomarkers are nonspecific; however, they may play a role in excluding hospital-acquired and ventilator-associated pneumonia (6). Microbiological data in addition to a clinical pulmonary infection score are referred to as a modified clinical pulmonary infection score. A modified clinical pulmonary infection score greater than 6 improves the diagnostic accuracy for ventilator-associated pneumonia but has not been studied in hospital-acquired pneumonia (7). A serial modified clinical pulmonary infection score of 6 or less predicts low risk of hospital-acquired and ventilator-associated pneumonia (sensitivity, 100%; specificity, 83%) and the ability to safely narrow antibiotics after 3 days of treatment. In high-risk patients, a lack of clinical pulmonary infection score improvement by Day 3 is 100% sensitive and 83% specific for antibiotic failure, and therefore its role in these high-risk patients remains unclear (8).

Table 6. Recommendations to reduce risk of ventilator-associated pneumonia

- Minimizing sedation
- Optimizing physical condition
- Elevation of head of bed
- Subglottic drainage to minimize secretion pooling above endotracheal tube cuff
- Maintenance of ventilator circuits
- Use of oropharyngeal antiseptic such as chlorhexidine
- Selective decontamination of aerodigestive tract with antibiotics

Prevention of Ventilator-Associated Pneumonia

Evidence-based prevention strategies should be implemented. One of the primary prevention strategies for ventilator-associated pneumonia is avoidance of mechanical ventilation. Noninvasive positive ventilation (NIPPV) strategies are an attractive alternative for patients with exacerbations of chronic obstructive pulmonary disease or acute hypoxemic respiratory failure secondary to congestive heart failure as they are associated with a reduction in ventilator-associated pneumonia risk, shortened mechanical ventilation duration, decreased length of stay, and lower mortality rates. Caution is needed, however, when considering NIPPV use (9). There has been an increase in the use of high-flow oxygen through nasal cannula (HFNC) for patients with hypoxemia. A trial showed a benefit from HFNC use in nonhypercapnic patients with acute hypoxemic respiratory failure. *Post-hoc* analysis showed that for patients with severe initial hypoxemia (ratio of Pa_{O_2} to fraction of inspired oxygen, <200 mm Hg), the intubation rate was significantly lower among patients who received HFNC versus standard care or NIPPV (10). Recommendations by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America to reduce the risk of ventilator-associated pneumonia are outlined in Table 6 (11). Although evidence for the impact of ventilator-associated pneumonia prevention bundles is still limited, preventive measures to enhance care and minimize pneumonia in the hospital setting remain essential.

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Opportunistic Pulmonary Infections in Patients with HIV and Patients without HIV

James A. Town and Başak Çoruh

In immunocompromised patients, the severity, duration, and nature of an immunologic deficit impact the risk for opportunistic infections (Table 7) and guide antimicrobial prophylaxis. Bacterial pneumonia remains the most common lung infection in immunocompromised hosts and produces more severe effects than in the immunocompetent host (1). This section provides an overview of several of the most common opportunistic infections identified in this patient population.

Viruses

Patients with impaired adaptive immunity are at risk for viral opportunistic infections from reactivation or primary infection. Even mildly pathogenic viruses can cause severe disease in the immunocompromised host. Cytomegalovirus (CMV) rarely causes pneumonia in patients infected with human immunodeficiency virus (HIV) but may reactivate in the setting of other opportunistic infections, notably *Pneumocystis jirovecii* (2). Treatment should target the primary opportunistic infections, with CMV treatment (e.g., ganciclovir) reserved for patients without clinical improvement or no other cause of pneumonia. In contrast, CMV is a leading cause of pneumonia in solid organ transplant and hematopoietic stem cell transplant recipients (3, 4). Viral cytopathologic effect or tissue invasion are more specific for infection than serum or bronchoalveolar lavage nucleic acid amplification (5).

Fungi

Risk factors for invasive aspergillosis and other fungal pneumonias include solid organ transplant, stem cell transplantation, high-dose corticosteroids, neutropenia, and congenital immunodeficiencies (e.g., chronic granulomatous disease, severe combined immunodeficiency), whereas patients with HIV are less susceptible to invasive aspergillosis (1). This infection can be diagnosed on the basis of radiographic features, host risk factors, and mycological evidence; "probable" or "possible" invasive aspergillosis may still warrant empiric therapy. Bronchoalveolar lavage galactomannan is the most sensitive test for pulmonary disease, but serum galactomannan positivity can obviate the need for bronchoscopy. Voriconazole is preferred over amphotericin for treatment and patients should be monitored for clinical improvement and drug toxicity (6).

Parasites

Reactivation of previously acquired parasites is a risk in organ transplant recipients; serologic screening is undertaken before transplantation. Patients with HIV incur higher risk for parasites and require prophylaxis with decreasing $CD4^+$ T-cell counts. *Strongyloides stercoralis*, a tropical and subtropical nematode, can persist asymptomatically for decades and manifest as a fatal hyperinfection syndrome during immunosuppression. Ivermectin is effective therapy, but is approved only in oral form.

Toxoplasma gondii causes encephalitis in patients with HIV, but may also result in severe pneumonitis. This disease is rare in non-HIV immunocompromised patients. Most prophylaxis regimens against *Pneumocystis* protects against *Toxoplasma*. Pyrimethamine, sulfadiazine, and leucovorin are first-line therapy for encephalitis and pneumonitis, but other options exist if medications are not tolerated or intravenous delivery is required (7).

Mycobacteria

Mycobacterial infections, both tuberculous and nontuberculous, range from hematogenous to acute and chronic pulmonary infections arising from primary exposure or reactivation. Tuberculosis affects up to one-third of the world's population and is a potentially devastating copathogen with HIV. Patients taking TNF-α inhibitors or other immunosuppressants are also at risk for reactivation.

Tuberculous pleuritis is characterized by a lymphocytic effusion with a high protein concentration and few (<5%) mesothelial cells. Pleural fluid culture and polymerase chain reaction have low yield, but granulomatous inflammation on pleural biopsy is highly sensitive in combination with acid-fast staining and culture. Sputum examination, often overlooked in tuberculous pleuritis, is easily available and potentially useful.

Table 7. Association of immunologic deficit and potential opportunistic infections

Immunologic Defense	Example of Immunologic Deficit	Opportunistic Infection
Physical defenses	Impaired cough/mucociliary function after lung transplantation	Bacteria
Innate immunity	Severe combined immunodeficiency	*Staphylococcus aureus*
	Chronic granulomatous disease	*Pseudomonas aeruginosa*
	Neutropenia	Invasive fungi
Adaptive immunity: humoral	Solid organ transplantation	*Streptococcus pneumoniae*
	Stem cell transplant	*Haemophilus influenzae*
	Asplenia	*Mycoplasma* spp.
Adaptive immunity: cellular	HIV	Cytomegalovirus
	Solid organ transplant	*Pneumocystis jirovecii*
	Stem cell transplant	Fungi
	Severe combined immunodeficiency	Mycobacteria
	Common variable immunodeficiency	

Definition of abbreviation: HIV = human immunodeficiency virus.
Chemotherapies, hematologic malignancies, biologic agents (e.g., tumor necrosis factor-α inhibitors), and corticosteroids can cause immune dysfunction across multiple arms of the immune system.

GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA), an automated nucleic acid amplification test with high sensitivity for detecting *Mycobacterium tuberculosis* in pulmonary specimens, can simultaneously identify rifampin resistance but is insensitive for pleural disease (8). In contrast, adenosine deaminase has high sensitivity for tuberculous pleuritis in populations with at least moderate pretest probability (8). ■

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