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ATS Core Curriculum 2020

Adult Pulmonary Medicine

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ABSTRACT

The American Thoracic Society Core Curriculum updates clinicians annually in adult and pediatric pulmonary disease, medical critical care, and sleep medicine in a 3- to 4-year recurring cycle of topics. The topics of the 2020 Pulmonary Core Curriculum include pulmonary vascular disease (submassive pulmonary embolism, chronic thromboembolic pulmonary hypertension, and pulmonary hypertension) and pulmonary infections (community-acquired pneumonia, pulmonary nontuberculous mycobacteria, opportunistic infections in immunocompromised hosts, and coronavirus disease [COVID-19]).

Keywords:
submassive pulmonary embolism; nontuberculous mycobacteria; COVID-19; community-acquired pneumonia; pulmonary hypertension

KEY POINTS

- Risk stratification and treatment (particularly reperfusion therapies) for submassive pulmonary embolism involve a complex decision-making process that can be best accomplished with involvement of a multidisciplinary pulmonary embolism response team.
- Echocardiography is the recommended screening test for pulmonary hypertension. To confirm a diagnosis of pulmonary hypertension, right heart catheterization is required, with guidelines now recommending a mean pulmonary arterial pressure cutoff of >20 mm Hg to make a diagnosis of pulmonary hypertension.
- The treatments available for chronic thromboembolic pulmonary hypertension have expanded to include medical, surgical, and percutaneous options. Thus, selection of the most appropriate treatment strategy requires multidisciplinary assessment by a center with chronic thromboembolic pulmonary hypertension expertise.
- Recent updates in the guidelines for diagnosis and treatment of community-acquired pneumonia have downplayed the role of sputum cultures and procalcitonin in nonsevere community-acquired pneumonia.
- The nodular–bronchiectatic phenotype of nontuberculous mycobacterial pulmonary disease is commonly seen in tall, thin postmenopausal women without significant smoking history, and the fibrocavitary phenotype predominantly affects elderly male smokers with underlying tobacco-related lung disease. Treatment of *Mycobacterium avium* complex pulmonary disease should be continued for 12 months beyond negative culture conversion.
- Opportunistic infections in the immunocompromised host carry high morbidity and mortality. Culture confirmation and histopathologic confirmation are often the gold-standard diagnostics tools but lack sensitivity. Laboratory tests (polymerase chain reaction [PCR] assays, antigen testing, and serology) in conjunction with compatible clinical and radiologic findings are alternative tools that can rapidly and accurately aid in the diagnosis.
- The test currently recommended for the diagnosis of coronavirus disease (COVID-19) is the nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription PCR. Treatment focuses on supportive care, with close monitoring for rapidly increasing oxygen demands and impending respiratory failure. Although there are no randomized controlled trials of ventilator management of severe COVID-19, use of strategies beneficial in other causes of acute respiratory distress syndrome is recommended. COVID-19–specific therapies are under intense investigation with preliminary data emerging.

SUBMASSIVE PULMONARY EMBOLISM

Rami Alashram and Parth Rali

Pulmonary embolism is the third most common cause of death in hospitalized patients, with a presentation that ranges from no symptoms to sudden death (1). In the absence of hypotension, pulmonary embolism with objective evidence of right ventricular dysfunction noted on computed tomographic (CT) pulmonary angiography (CTPA) or transthoracic echocardiography and/or because of cardiac biomarker elevation (BNP [brain natriuretic peptide], NT-proBNP [N-terminal pro-BNP], or troponin) is termed *submassive with right ventricular strain* by the American Heart Association or *intermediate risk* by the European Society of Cardiology (2, 3). In addition, the European Society of Cardiology incorporates the Pulmonary Embolism Severity Index (PESI) or the simplified PESI,

validated prognostic scores, into pulmonary embolism classification and further subclassifies *intermediate-risk* pulmonary embolism into two categories: *intermediate–low risk* and *intermediate–high risk* (2) (Table 1).

The clinical course of submassive pulmonary embolism is highly variable. A subset of patients will progress to high-risk (massive) pulmonary embolism (pulmonary embolism with hypotension) (2, 3). An elevated PESI or simplified PESI score, severe pulmonary embolism–related functional impairment, and signs of reduced end-organ perfusion (e.g., increased lactate or renal impairment) are associated with an increased risk of hemodynamic deterioration (1).

The primary focus of submassive pulmonary embolism management is prompt and effective anticoagulation, unless contraindicated (1, 4). Advanced therapies, including systemic

thrombolysis and catheter-based treatments (catheter-directed thrombolysis and catheter-based embolectomy), are available to treat selected patients with submassive pulmonary embolism (1, 4). These therapies have been shown to reduce clot burden, improve hemodynamics, and improve right ventricular function in the short term. However, their ability to impact short- and long-term mortality, long-term symptoms, and functional status has not been clearly established (1). Advanced therapies are not without risk, as bleeding and procedure-related complications can be fatal (1, 4). Quantifying these risks is critical during decision-making and can be achieved by using available bleeding-risk scores such as the El Registro Informatizado de Pacientes con Enfermedad TrombóEmbolica score, which assesses the risk of major bleeding during

Table 1. Definitions of submassive (intermediate-risk) pulmonary embolism according to the American Heart Association and the European Society of Cardiology guidelines

	Shock	PESI Class III–V or sPESI Score ≥ 1	RV Dysfunction on CTPA or TTE	Elevated Troponin	Elevated NT–proBNP or BNP	EKG (RV Strain Pattern)	Available Treatment Options
AHA 2011							Systemic anticoagulation
Submassive with RV strain (any one positive)	No	N/A	+	+	+	+	Low-molecular-weight heparin
							Oral anticoagulant
ESC 2019							Reperfusion therapies*
Intermediate–low risk (either one or *none* positive for RV dysfunction and elevated troponin)	No	+	±	±	N/A	N/A	Half-dose (50 mg tPA) thrombolysis
							Catheter-directed thrombolysis
Intermediate–high risk (both positive for RV dysfunction and elevated troponin)	No	+	+	+	N/A[†]	N/A	Percutaneous mechanical embolectomy
							Surgical embolectomy
							Inferior vena cava filter[‡]

Definition of abbreviations: AHA = American Heart Association; BNP = brain natriuretic peptide; CTPA = computed tomographic pulmonary angiography; EKG = electrocardiogram; ESC = European Society of Cardiology; N/A = not applicable; NT-proBNP = N-terminal pro-BNP; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified PESI; tPA = tissue plasminogen activator; TTE = transthoracic echocardiography.
*Reperfusion therapies should be considered on a case-by-case basis, and in a multidisciplinary pulmonary embolism response team setting, given very limited evidence.
[†]Elevation of NT-proBNP or BNP may provide additional prognostic information but is not used to classify pulmonary embolism as per ESC guidelines.
[‡]Use only when therapeutic anticoagulation is absolutely contraindicated.

anticoagulant therapy, and the Pulmonary Embolism–Intracranial Hemorrhage score, which assesses the risk of intracranial hemorrhage (1, 4).

Advanced therapies are most appropriate for those patients with the highest mortality risk (i.e., clinical deterioration) and are avoided in patients with an unacceptably high risk of bleeding (particularly intracranial hemorrhage). The location of the thrombus, operator expertise, and individual patient preference should also be weighed when considering advanced therapies. The extent of the thrombus by itself does not

necessarily inform the need for intervention (1, 4). Surgical embolectomy can be considered when there is an absolute contraindication to thrombolysis, failure of thrombolysis, or clot traversing the foramen ovale (4). Given uncertainty in the optimal management of some patients with life-threatening pulmonary embolism, formal multidisciplinary teams such as the pulmonary embolism response team can leverage the expertise of local clinical specialists who can provide treatment recommendations in a time-sensitive manner (1, 4).

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CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Tyler Peck and Alison Witkin

Chronic thromboembolic pulmonary hypertension (CTEPH) is the most feared long-term complication of acute pulmonary embolism. The incidence of CTEPH among survivors of pulmonary embolism is estimated to be as high as 4% (1). This syndrome is defined by the accumulation of occlusive fibrotic tissue within the pulmonary vasculature, resulting in elevations in the resting mean pulmonary artery pressure (>20 mm Hg) and an increased pulmonary vascular resistance (PVR; ≥3 Wood units

[WU]) (2). More recently, there has been increased recognition that CTEPH represents the most severe end of the spectrum of chronic pulmonary embolism. Patients with pulmonary embolism can also develop chronic thromboembolic disease (CTED), involving similar pathophysiology and symptoms without resting pulmonary hypertension. These patients may report exercise limitation owing to either exercise-induced pulmonary hypertension or increased dead-space ventilation.

Clinical Features

Dyspnea and exercise intolerance are common in both CTEPH and CTED,

although symptoms are nonspecific and may be mistaken for those of other diseases (3). As many patients with diagnosed CTEPH have not previously received a diagnosis of acute pulmonary embolism or deep vein thrombosis (DVT), it is important to maintain a high degree of clinical suspicion. Risk factors for the development of CTEPH include antiphospholipid antibody syndrome, chronic inflammatory states, splenectomy, and prior pulmonary embolism (4).

Diagnostic Testing

All patients with diagnosed pulmonary hypertension should receive screening for CTEPH, as it is the only form of pulmonary hypertension that is potentially curable without lung transplantation. The ventilation–perfusion ($\dot{V}/\dot{Q}$) lung scan is the preferred screening test. Although CTPA often shows signs of CTEPH, it is less sensitive than a $\dot{V}/\dot{Q}$ scan in detecting the vascular filling defects associated with
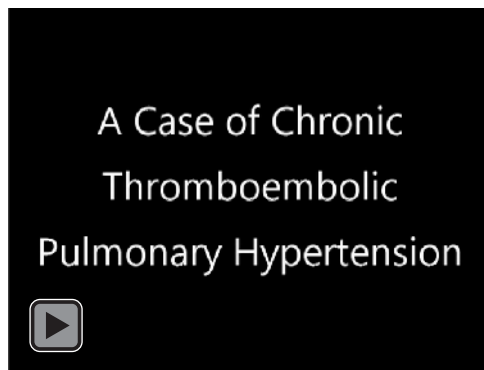
Video 1. This video shows the complementary use of ventilation–perfusion ($\dot{V}/\dot{Q}$) scan and pulmonary angiography in the diagnosis and treatment of chronic thromboembolic pulmonary hypertension. The $\dot{V}/\dot{Q}$ scan shows absent perfusion to the bilateral lower lobes. A right–heart catheterization and pulmonary angiogram is then performed (only the right side is shown), confirming complete occlusion of the descending pulmonary artery with pulmonary hypertension. The patient underwent successful pulmonary thromboendarterectomy, and the surgical specimen is shown.

CTEPH (Video 1) (5). Right-heart catheterization (RHC) is required to quantify the presence and severity of pulmonary hypertension. Pulmonary angiography is performed to define the location and severity of pulmonary vascular obstruction, an important step in assessing treatment options. For patients with CTED, exercise testing may be useful to help quantify the degree of disease and to evaluate for a pulmonary vascular cause of exercise limitation.

Treatment Options

Pulmonary thromboendarterectomy (PTE) is first-line therapy for patients with surgically accessible disease. Although invasive, PTE offers an opportunity for cure. Survival and functional status are markedly improved in appropriately selected patients (6). For patients who are not surgical candidates, either owing to comorbidities or disease location, or for those who have residual disease despite PTE, balloon pulmonary angioplasty and pharmacologic therapy are available alternatives. Balloon pulmonary angioplasty is a staged procedure and has been associated with improvements in both hemodynamics and symptoms as measured by functional class (7). Riociguat, a soluble guanylate cyclase stimulator, is currently the only U.S. Food and Drug Administration (FDA)-approved medical therapy for residual or inoperable CTEPH. All patients should be treated with indefinite anticoagulation.

Role of Multidisciplinary Care in CTEPH

As CTEPH is a rare disease with complex and invasive treatment options, it is essential that patients be evaluated at a specialized CTEPH center that can

provide multidisciplinary care (8). In such a setting, pulmonologists with expertise in pulmonary hypertension, interventional specialists (typically cardiologists or radiologists), and surgeons can review individual cases to determine the best course of treatment.

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UPDATES IN PULMONARY HYPERTENSION

Amita Krishnan and Matthew R. Lammi

Definition

At the 2018 sixth World Symposium on Pulmonary Hypertension, major revisions were made to the definition of pulmonary hypertension from a mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg to a new definition of >20 mm Hg. A PVR cutoff of 3 WU was also recommended to discriminate elevation of mPAP owing to precapillary pulmonary vascular disease from other causes, such as high cardiac output or elevations in pulmonary artery wedge pressure (PAWP) (1, 2).

Pulmonary hypertension is grouped into five clinical classifications on the basis of pathophysiologic mechanisms, clinical presentation, hemodynamic characteristics, and treatment. The two main modifications to group 1 pulmonary arterial hypertension (PAH) were the inclusion of the subgroups "PAH with overt features of venous/capillary involvement" and "PAH long-term responders to calcium channel blockers (CCBs)." In addition, methamphetamines and dasatinib were added as drugs that definitely cause drug-induced PAH (2).

Diagnosis

Echocardiography is the most important screening tool in patients suspected of having pulmonary hypertension on the basis of history, symptoms, physical examination findings, and biomarkers (Video 2). RHC remains the gold standard for establishing the diagnosis of pulmonary hypertension. $\dot{V}/\dot{Q}$ scanning should be performed in all patients to screen for CTEPH. Patients with scleroderma, the human immunodeficiency virus (HIV), and portal hypertension have elevated risk for developing pulmonary hypertension and require more aggressive screening (3).

Patients with idiopathic, heritable, and drug- or toxin-associated PAH should undergo acute vasoreactivity testing during RHC to predict responsiveness to CCBs. If used, adequate response should be confirmed by sustained hemodynamic improvement after 1 year of treatment.

Management of Pulmonary Hypertension

A multiparametric risk-stratification approach is recommended to assess the
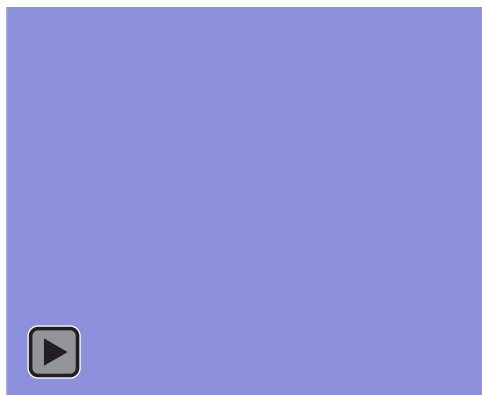
Video 2. Echocardiographic findings in pulmonary hypertension. (Clip 1) Right ventricular enlargement. (Clip 2) Straightening of the interventricular septum. (Clip 3) Tricuspid regurgitant jet velocity elevation. (Clip 4) Inferior vena cava diameter without respiratory variability. (Clip 5) Right ventricular pressure volume overload.

severity and prognosis of PAH patients and to guide treatment, both at time of diagnosis and on follow-up. With rare exception, patients who are at low/intermediate risk should initially be treated with oral combination therapy. In high-risk patients, initial combination therapy including intravenous prostacyclin analogs is recommended. If the treatment approach results in a low-risk status within 3–6 months, the regimen should be continued. If the patient is still in intermediate- or high-risk status, escalation of therapy is recommended (4).

Pulmonary hypertension is a common complication of left-heart disease (LHD) owing to an increase in left-sided filling pressures. The hemodynamic definition of pulmonary hypertension–LHD is as follows: *1*) isolated postcapillary pulmonary hypertension (PAWP > 15 mm Hg; mPAP > 20 mm Hg; PVR < 3 WU) and *2*) combined pre- and postcapillary pulmonary hypertension (PAWP > 15 mm Hg; mPAP > 20 mm Hg; PVR ≥ 3 WU]). Distinguishing between PAH and pulmonary hypertension–LHD may be difficult; therefore, determining pretest probability and evaluating hemodynamics is vital for the confirmation of any PAH diagnosis. Evidence-based guidelines recommend against using PAH-specific drugs in the treatment of pulmonary hypertension–LHD (1, 5).

Chronic lung disease is frequently complicated by pulmonary hypertension, resulting in reduced functional status and worse outcomes (6). RHC should be performed only when significant pulmonary hypertension is suspected and management

would be influenced by the RHC results (transplant referral, inclusion in clinical trials, treatment of LHD, and compassionate use of PAH therapy). Overall, PAH-targeted therapy has not shown benefit in this group (2, 4).

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COMMUNITY–ACQUIRED PNEUMONIA

Bronwyn L. Small and Kristina L. Bailey

Community-acquired pneumonia (CAP) remains a major cause of morbidity and mortality. Recently, new American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines highlighted existing evidence and recommendations for the diagnosis and treatment of CAP in adults (1). Several important updates are summarized in Table 2.

Diagnostic Considerations

The diagnosis of CAP is based on patient history, physical examination, and chest imaging. Previously, a distinction was made between pneumonia acquired as an outpatient and pneumonia acquired as an inpatient (health care–associated pneumonia) to guide evaluation and therapy. The 2019 guidelines recommend abandoning the category of health care–associated pneumonia and using local epidemiology and specific risk factors for infection with methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* to guide the diagnostic evaluation and initial treatment.

Adjunctive tests such as sputum and blood cultures, *Legionella* testing, and procalcitonin are often used clinically. Sputum and blood cultures from patients with CAP do not improve patient outcomes and often have a poor yield (1–4). Therefore, the ATS/IDSA 2019 guidelines recommend obtaining sputum and blood cultures only in hospitalized patients with severe CAP and in those empirically treated for MRSA and *P. aeruginosa*. The results of blood and sputum cultures should be used to de-escalate therapy if possible. Likewise, routine testing for *Legionella* and pneumococcal pneumonia are not recommended and should be limited to patients with severe CAP or risk factors for the infection, as randomized clinical trials have failed to show benefit to this testing

Table 2. Comparison between 2019 and 2007 ATS/IDSA CAP guidelines

	2007 Guidelines	2019 Guidelines
Diagnostic recommendations		
Use of the HCAP category	Endorsed, previously included in 2005 guidelines	Recommend abandoning this category
Sputum culture	Recommended with severe CAP	Recommended in severe CAP and for inpatients empirically treated for MRSA or *P. aeruginosa*
Blood culture	Recommended with severe CAP	Recommended in severe CAP and for inpatients empirically treated for MRSA or *P. aeruginosa*
Use of procalcitonin	Not addressed	Not recommended to determine need for antibacterial therapy
Initial treatment recommendations		
Outpatient	Macrolide as strong recommendation	No comorbidities: Amoxicillin, doxycycline, or macrolide (only if local pneumococcal resistance is <25%) With comorbidities: 1) Amoxicillin/clavulanate or cephalosporin, *and* macrolide or doxycycline *or 2*) Monotherapy with a respiratory quinolone
Inpatient	β-lactam/macrolide and β-lactam/fluoroquinolone combinations given equal weighting for severe CAP	Both accepted, but stronger evidence in favor of β-lactam/macrolide combination

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; HCAP = health care–associated pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*; *P.* = *Pseudomonas*.

(5). Procalcitonin testing is occasionally used to determine whether CAP is bacterial or viral in origin. However, an appropriate threshold for procalcitonin in bacterial pneumonia has not been determined. Therefore, use of procalcitonin as the sole metric for withholding antibiotic treatment is not recommended, and adults with clinical and radiologic features of CAP should receive appropriate initial antibiotic treatment even when procalcitonin is low (1).

Treatment Considerations

The recommendations for initial antibiotic coverage have shifted slightly in the new guidelines (1). Healthy outpatients can be treated with amoxicillin, doxycycline, or a macrolide when pneumococcal resistance is low (<25%). Outpatients with comorbidities, including heart, lung, or renal disease, should receive amoxicillin/clavulanate or a cephalosporin *and* a macrolide *or* monotherapy with a respiratory fluoroquinolone.

Initial inpatient management depends on CAP severity and the presence of risk factors for MRSA and *P. aeruginosa*. Initial therapy for inpatients with nonsevere CAP is the same as for outpatients with comorbidities unless there is a history of previous infection with MRSA or *P. aeruginosa*, in which case coverage for that organism should be added. Inpatients with nonsevere CAP and risk factors for MRSA or *P. aeruginosa* should be cultured, and coverage should be added if cultures are positive. For inpatients

with severe pneumonia, a β-lactam plus a macrolide or a β-lactam plus a respiratory fluoroquinolone may be initiated with additional coverage for MRSA or *P. aeruginosa* if there is previous infection with or risk factors for these organisms.

In the 2019 ATS/IDSA CAP guideline, the routine use of corticosteroids is not recommended; however, it may be considered in patients with refractory septic shock (1).

New guidelines for CAP recommend shifting our focus toward which pathogens to target in therapy, and the guidelines delineate treatment and investigational recommendations primarily on the basis of severe and nonsevere CAP.

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PULMONARY NONTUBERCULOUS MYCOBACTERIA

Rebecca Kapolka and Colin Swenson

Nontuberculous mycobacteria (NTM) are a group of ubiquitous environmental organisms found mainly in water and soil. Of the over 200 known species of NTM, only a fraction are considered human pathogens (1). Human exposure may occur through the municipal water supply, recreational water activities, and gardening (1). NTM are opportunistic pathogens with variable mechanisms of pathogenicity. Common host risk factors include underlying structural lung disease, thoracic skeletal abnormalities, low body weight, gastroesophageal reflux disease, and chronic aspiration (2).

The prevalence of NTM pulmonary disease (NTM-PD) is increasing worldwide because of improved microbiologic culture techniques, increased clinician awareness, increased use of radiographic imaging, and more specific diagnostic criteria (3).

NTM clinical isolates are differentiated into two main groups by their rates of growth: slow growers, such as *Mycobacterium avium* complex (MAC), appear on growth media *after* 7 days; and rapid growers, such as *M. abscessus* complex, are isolated within 7 days of culture (3). The most common clinically encountered slow-growing species are *avium*, *intracellulare*, and *chimaera*, and *M. kansasii*. The most common rapidly

growing clinical isolates include *M. abscessus* complex (which includes *abscessus*, *bolletii*, and *massiliense*), *M. chelonae*, and *M. fortuitum* (3).

The most common clinical manifestations of NTM-PD are cough, fatigue, malaise, dyspnea, weight loss, subjective fever, and sputum production that may be accompanied by hemoptysis (4). There are two primary disease phenotypes in NTM-PD. The nodular–bronchiectatic phenotype is commonly seen in tall, thin, postmenopausal women without significant smoking history, although nonsmoking males increasingly compose part of this disease cohort. Radiographically, the phenotype is characterized by centrilobular pulmonary nodules, tree-in-bud opacities, and/or cylindrical bronchiectasis, often within the same lobe (4) (Figure 1). The fibrocavitary disease phenotype is more commonly seen in older male smokers with underlying chronic lung disease, most commonly emphysema. Chest imaging typically shows an upper-lobe thick-walled cavitary lesion, which may have an appearance similar to that of active pulmonary tuberculosis (Figure 2). Although most cases with these patterns are caused by MAC, both slow and rapid growers may have similar presentations.

Figure 1. Chest computed tomographic image of the nodular–bronchiectatic phenotype of nontuberculous mycobacterial pulmonary disease showing centrilobular pulmonary nodules, tree-in-bud opacities, and cylindrical bronchiectasis.
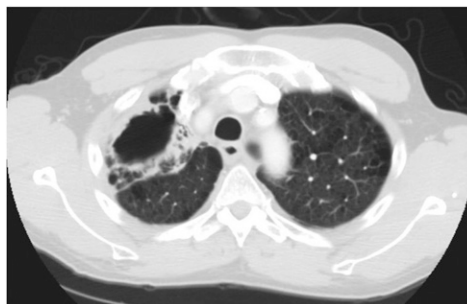
Figure 2. Chest computed tomographic image of the fibrocavitary disease phenotype of nontuberculous mycobacterial pulmonary disease with an upper-lobe thick-walled cavitary lesion.

Not all NTM pulmonary infections are symptomatic, and not all require antibiotic treatment. The 2007 ATS and IDSA guidelines have outlined three main criteria for the diagnosis of NTM-PD: clinical symptoms of pulmonary disease, radiographic findings suggestive of NTM infection, and microbiologic data from either two positive sputum cultures, one positive bronchoscopic culture, or lung tissue with a positive culture for NTM and granulomatous inflammation (5). All three criteria are required to establish a diagnosis of NTM-PD and help distinguish clinically active disease from indolent infection or asymptomatic colonization (5).

Before initiating treatment for NTM-PD, it is important to optimize therapy of any underlying pulmonary comorbidities (e.g., airway clearance for bronchiectasis or bronchodilators for obstructive diseases). For patients with nodular–bronchiectatic MAC-PD, the current guidelines recommend a thrice-weekly regimen of a macrolide (typically azithromycin), ethambutol, and a rifamycin (typically rifampin). For patients with fibrocavitary disease or more severe nodular–bronchiectatic disease, a daily regimen including a macrolide, ethambutol, and a rifamycin, with

consideration of a thrice-weekly intravenous aminoglycoside, is recommended. It is important to avoid macrolide monotherapy, as this therapy may promote macrolide resistance (6).

Sputum acid-fast bacillus cultures should be monitored every 1–3 months while on treatment, and therapy is continued for 12 months after sputum culture conversion (7).

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APPROACH TO THE DIAGNOSIS OF OPPORTUNISTIC FUNGAL INFECTIONS IN IMMUNOCOMPROMISED HOSTS

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Immunocompromised hosts are susceptible to life-threating pathogens that typically cause minimal or no disease in normal hosts (1). Infections owing to these pathogens are termed "opportunistic infections".

Patients at Risk for Opportunistic Infections

Risk of opportunistic infections is determined by host risk factors, including environmental exposure (occupation, home environment, travel, and hobbies) and type and degree of immunodeficiency (1). Defects can affect humoral immunity (B cell–mediated), cell-mediated immunity (T cell–mediated), or neutrophil function (2). Non-HIV cases of acquired immunodeficiency may result from medications, solid-organ transplant or bone marrow transplant, malignancy, autoimmune disease, or structural lung disease (2).

Clinical Syndrome and Diagnostic Approach of Common Opportunistic Infections

Bacteria, viruses, and fungi can cause opportunistic infections. Herein, we focus on fungal pathogens, including *Aspergillus* species, *Cryptococcus* species, and *Pneumocystis jirovecii* (Table 3). *Aspergillus*

Table 3. Common opportunistic fungal infections: clinical presentation and diagnostic tests

Pathogen	Host Risk Factors	Clinical Presentation	Common Diagnostic Tests
Aspergillus species	Invasive pulmonary aspergillosis	Invasive pulmonary aspergillosis	• Culture from sterile site: gold standard/low sensitivity
	• Impaired cellular immunity	• Fever, cough, pleuritic chest pain, hemoptysis, and nodular or ground–glass infiltrate on chest imaging	• Histology: gold standard/invasive
	• Neutropenia		• Serum or BAL galactomannan: less invasive and rapid turnaround; antifungal therapy may reduce sensitivity, false positives in mucositis, cross–react with Histoplasma and other fungi
	• Bone marrow transplant		• Serum or BAL *Aspergillus* PCR: less invasive and rapid turnaround; lack of standard technique, contamination, and inability to distinguish colonization from infection
	• Solid-organ transplant		
	• Chronic high–dose corticosteroids		
	Tracheobronchitis	Tracheobronchitis	
	• Lung transplant	• Ulceration/eschar at airway anastomosis	
C. neoformans	• Impaired cellular immunity	• Cough, fever, headache ± meningismus, pulmonary nodules, and lymphadenopathy	• Culture/India–ink stain from BAL or CSF: gold standard
	• Chronic high–dose corticosteroids	• Lumbar puncture should be completed to evaluate for CNS disease	• Antigen testing on serum, BAL, or CSF
	• Sarcoidosis		• β-1,3-D-glucan (Fungitell): characteristically negative
	• Exposure to pigeons		
P. jirovecii	• Impaired cellular immunity ± lung disease	• Nonproductive cough, fever, severe hypoxemic respiratory failure, and diffuse ground–glass or cystic lesions on chest imaging	• Direct visualization: gold standard/requires trained personnel
	• High-dose corticosteroids		• PCR on BAL or sputum: rapid turnaround/inability to distinguish colonization from infection
	• Rituximab		• β-1,3-D-glucan: typically elevated (nonspecific)

Definition of abbreviations: BAL = bronchoalveolar lavage; *C.* = *Cryptococcus*; CNS = central nervous system; CSF = cerebrospinal fluid; *P.* = *Pneumocystis*; PCR = polymerase chain reaction.

species cause disease in hosts with impaired cellular immunity, neutrophil dysfunction, or structural lung disease. Invasive pulmonary aspergillosis is the most severe manifestation and presents as fever, cough, pleuritic chest pain, hemoptysis, and nonspecific nodular or ground-glass infiltrates on chest imaging (Figures 3 and 4). Hosts with prolonged neutropenia, those receiving prolonged high-dose systemic corticosteroids, and those after solid-organ transplant or bone marrow
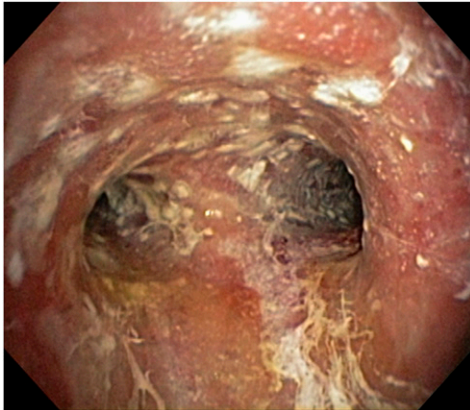
Figure 3. *Aspergillus* tracheobronchitis. A 78–year–old man receiving chemotherapy for diffuse large B-cell lymphoma was found to have diffuse mucosal plaques and ulcerations on bronchoscopy. Bronchial washings grew *A. fumigatus*.

transplant are at greatest risk (3). Diagnosis requires direct visualization of *Aspergillus* species invading tissue or blood vessels on histopathologic examination. As biopsies can be difficult to obtain because of illness severity, antigen testing (galactomannan cell-wall component) and *Aspergillus* polymerase chain reaction (PCR) measured on either serum or bronchoalveolar lavage (BAL) may be a less invasive approach to aid diagnosis (4).

*C. neoformans* causes disease in hosts with severe defects in cellular immunity. Hosts with exposure to pigeons or other bird droppings may be at higher risk. *C. neoformans* enters the host via inhalation and has a predilection for the central nervous system. Patients present with fever, cough, and headache or meningeal signs. Chest imaging may show pulmonary nodules, lymphadenopathy, and/or pleural effusions (Figure 5). Culture or direct visualization is the gold standard for diagnosis, but antigen testing of serum or cerebrospinal fluid is often used, and thus lumbar puncture is recommended during evaluation (5).

P. jirovecii pneumonia (PJP) typically occurs in patients with defects in cell-mediated immunity, but reports of PJP in patients receiving rituximab exist (6). Presentation ranges from mild nonproductive cough to severe hypoxemic respiratory failure with diffuse infiltrates on chest imaging (Figure 6). Because *P. jirovecii* cannot be cultured, direct visualization of the organism on histopathologic specimens is the gold standard for diagnosis. The diagnosis is often made using PCR testing on BAL specimens (7). Serum β-1,3-D-glucan may also be significantly elevated in PJP but is a nonspecific marker of disease.
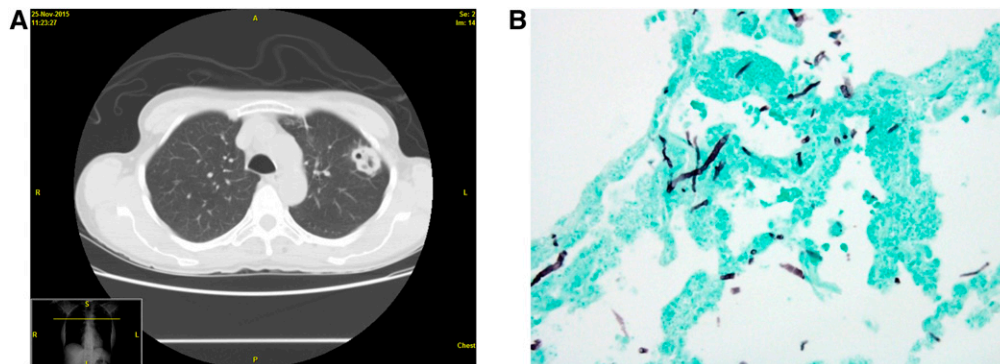
Figure 4. Invasive pulmonary aspergillosis. (*A*) A 58–year–old woman on high–dose inhaled corticosteroids presented with an incidentally discovered left upper-lobe cavitary nodule on chest computed tomography (CT). (*B*) CT-guided biopsy of the nodule revealed acute branching and septate hyphae consistent with *Aspergillus* species.
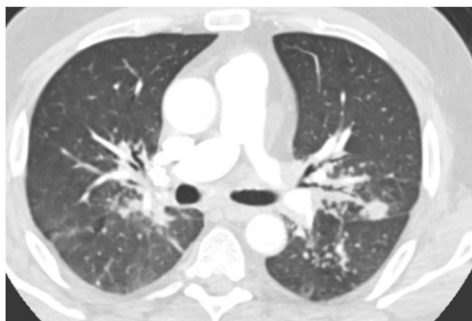
Figure 5. *Cryptococcus neoformans* pulmonary infection. A 66-year-old man with pulmonary sarcoidosis on high-dose prednisone presented with fever, altered mental status, and progressive cough. A computed tomographic scan of the chest revealed bilateral peri-hilar and nodular opacities consistent with sarcoidosis. Serum and cerebrospinal-fluid cryptococcal antigens were positive.

Figure 6. *Pneumocystis jirovecii* pneumonia. A 41-year-old man with a history of kidney and pancreas transplant 3 years prior presented with progressive hypoxemic respiratory failure and diffuse bilateral ground-glass opacities on chest computed tomographic images. Serum β-1,3-D-glucan was greater than 10 times the upper limit of normal. Sputum *P. jirovecii* pneumonia polymerase chain reaction was positive.

Limitations of Common Diagnostic Tests

The gold standard for diagnosing most opportunistic infections is direct visualization and/or culture, but this is usually not feasible secondary to illness severity, bleeding risk, and time to culture positivity. Limitations exist with antigen and PCR testing modalities. For example, galactomannan may be falsely positive in patients with mucositis (4, 8) and falsely negative in patients on antifungal prophylaxis (3). Serum β-1,3-D-glucan is nonspecific and can be falsely positive in patients receiving hemodialysis, intravenous immunoglobulin, cardiopulmonary bypass, or blood transfusion (9). PCR testing is limited by contamination and inability to distinguish colonization from infection. Serum *Aspergillus* PCR has high sensitivity and low specificity with single-sample testing, but sensitivity decreases and specificity increases with repeated samples (3).

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COVID–19

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On December 31, 2019, an outbreak of pneumonia of unknown cause was first announced by the Chinese Center for Disease Control and Prevention (1). Less than 3 months later, the World Health Organization declared the global outbreak of this infection a pandemic (2). The genomic sequence of the virus was identified as a severe acute respiratory syndrome (SARS)-like coronavirus and named SARS coronavirus 2 (SARS-CoV-2), with the associated disease termed coronavirus disease (COVID-19) (3).

SARS-CoV-2, a novel, enveloped, single-stranded RNA β-coronavirus, is believed to have a zoonotic source, with bats as a possible reservoir. Person-to-person transmission via respiratory droplets and direct contact are believed to be the primary mechanisms of spread, although other routes of transmission are under investigation (4, 5).

The clinical manifestations of COVID-19 range from asymptomatic to fulminant respiratory failure. A median incubation period of 4 days (interquartile range, 2–7) has been reported (5). Commonly reported symptoms include fevers, cough, dyspnea, fatigue, myalgias, and headache, with gastrointestinal symptoms being less common (5–7).

SARS-CoV-2 PCR is the primary method used to diagnose COVID-19. Test characteristics are unclear because of the lack of a reference standard; however, specificity is likely high. Sensitivity depends in part on adequate sample collection (8). Nasopharyngeal swab samples are the preferred specimen source because of higher yields than oropharyngeal samples. Methods that result in aerosol generation, such as induced sputum, are relatively contraindicated because of concern for nosocomial spread. Bronchoscopy should only be considered if upper respiratory samples are negative and other diagnoses under consideration would significantly change clinical management (9). Serologic tests are commercially available, but they have variable sensitivity, particularly early in the course of disease. Antibody production is reported to start 1 week after the onset of infection (8).

Characteristic imaging findings at chest radiography include consolidation or ground-glass opacities that are usually bilateral, peripheral, and lower-lobe predominant (10). Chest CT images often show peripheral, bilateral ground-glass opacities in early or mild disease, whereas cases with severe disease demonstrate more diffuse ground-glass opacities and consolidation; often with
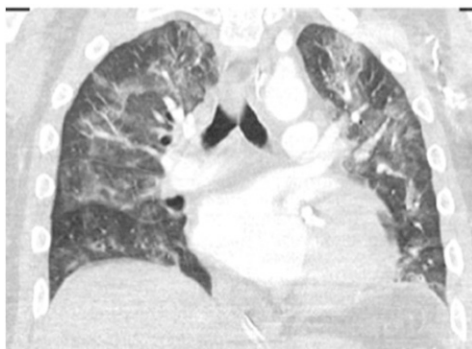
Figure 7. Chest computed tomographic image showing pattern of bilateral patchy peripheral infiltrates in patient with coronavirus disease (COVID-19) infection.

reticular abnormality and traction bronchiectasis reflecting more severe lung injury (11) (Figures 7 and 8). Lung ultrasound shows thickening and irregularity of the pleural line, B-lines, and consolidation, with pleural effusions being uncommon (12).

Laboratory findings are nonspecific and often show an elevation in inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, ferritin), leukopenia, and elevated D-dimer, lactate dehydrogenase, and interleukin-6 levels (13).

Risk factors for severe COVID-19 infection include advanced age; chronic medical conditions such as advanced cardiopulmonary disease, hypertension,

Figure 8. Chest computed tomographic image showing pattern of bilateral ground-glass opacities in patient with coronavirus disease (COVID-19) infection.

diabetes, and obesity; cancer; and immunosuppression (14). African American, Native American, and Hispanic persons are much more likely to be hospitalized than non-Hispanic white persons (14).

Mortality rates have varied (1.4–3.2%), with a larger series of 44,672 confirmed cases reporting a case fatality rate of 2.3% (1, 5). Reports of mortality among critically ill patients have ranged from 16.7% to >40% (15–17). Renal failure requiring renal replacement therapy and mechanical ventilation are risk factors associated with a higher mortality (16, 17). Scarcity of resources to provide advanced respiratory and renal support may have contributed to increased mortality rates in locations where the caseload has exceeded capacity.

Treatment focuses on supportive care, with close monitoring for rapidly increasing oxygen demands and impending respiratory failure. Intubated patients should receive best practices for acute respiratory distress syndrome, including lung-protective ventilation strategies, prone positioning, and conservative fluid management (18–20). There are currently no FDA-approved therapies for COVID-19, but multiple agents are under investigation. Initial enthusiasm for hydroxychloroquine based on *in vitro* benefit has waned, as trials have failed to demonstrate a clear benefit for hospitalized patients while highlighting potential, harms including QT interval prolongation and arrhythmias (18, 21, 22). The antiviral drug remdesivir was shown in a preliminary report to reduce time to recovery in patients who need supplemental oxygen or mechanical ventilation (23). Treatment with convalescent plasma appears safe, but rigorous studies have not yet demonstrated a benefit (24, 25). These studies evaluated the clinical response as well as the anti–SARS-CoV-2 antibody levels.

A number of antiinflammatory approaches are under investigation, including the interleukin-6 inhibitors tocilizumab and sarilumab. A retrospective study suggested a reduction in the need for mechanical ventilation or death with tocilizumab use (26). Prospective studies are underway. Preliminary data from the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial (a large multicenter, randomized, open-label study) suggest a 17% reduction in 28-day mortality for hospitalized patients with low-dose dexamethasone (29.0% vs. 40.7%) (27). The benefit appeared to be greatest in patients with severe disease, whereas no benefit was observed in patients not requiring supplemental oxygen. These data have not yet been published in a peer-reviewed journal; however, the observed benefit led the National Institutes of Health COVID-19 Treatment Guidelines Panel to recommend dexamethasone 6 mg daily for up to 10 days for patients receiving mechanical ventilation (18).

Patients with COVID-19 appear to have an increased incidence of thromboembolic events (28). Although hospitalized patients frequently have coagulation parameters measured, it is unclear how results should influence therapy (18). Hospitalized patients should receive DVT prophylaxis on the basis of risk stratification independent of COVID-19 status. Those with confirmed or suspected thromboembolic events should receive full-dose anticoagulation (18). Multiple trials evaluating anticoagulation regimens and thrombolytic use are underway. Multiple COVID-19 vaccines are in development.

It is important to recall that data before the pandemic demonstrate that viruses result in 25–44% of all cases of CAP and that 16–49% of pneumonias lead to severe respiratory illness (29, 30). Coinfections with COVID-19 and other respiratory viruses appear relatively uncommon; however, a case series demonstrated that 20% of samples from patients with COVID-19 infection had other respiratory pathogens identified (6, 31). A case series describes four patients who presented with COVID-19 and influenza (32). Diagnostic testing should assess for influenza depending on community activity, as antiviral therapy is indicated for hospitalized patients with influenza (33). A positive test result for other respiratory viruses does not exclude a diagnosis of COVID-19.

Public health efforts aimed at controlling the spread of COVID-19 include social distancing with an emphasis on hand washing and wearing masks in public where social distancing is not possible (particularly indoors). Testing programs and contact tracing are additional public health measures employed to control the spread of disease. Although these results are preliminary, the global race continues as we seek to curb the effects of this highly contagious and virulent organism.

<u>Author disclosures</u> are available with the text of this article at www.atsjournals.org.

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