Nonimaging Diagnostic Tests for Pneumonia

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KEYWORDS

• Pneumonia • Diagnosis • Laboratory tests • Bacterial • Fungal • Viral • Culture • Antigen

KEY POINTS

- Interpreting radiologists can narrow the differential diagnosis for suspected pneumonia by combining imaging findings with knowledge of nonimaging diagnostic tests for lung pathogens.
- Results from the recently developed urine pneumococcal antigen (for *Streptococcus pneumoniae*) and urine *Legionella* antigen tests, both of which demonstrate sensitivities of at least 70%, return rapidly and are often available at the time of image interpretation.
- The use of molecular testing and multiplex diagnostic platforms for viral detection in respiratory secretions allow clinicians to identify pathogens with extraordinary high speed and accuracy; however, these results should be correlated with the imaging presentation.
- Bronchoalveolar lavage galactomannan and serum 1 to 3 beta-D-glucan have high specificity and may facilitate a rapid diagnosis of invasive aspergillus in the appropriate clinical setting.

INTRODUCTION

Lower respiratory tract infections that progress to pneumonia are extremely common and account for greater morbidity and mortality than any other type of infection.[1] Of the greater than 5 million cases of community-acquired pneumonias (CAPs) that are diagnosed per year in the United States, approximately 20% require hospitalization with mortality ranging from 12% to 40%.[2]

Broad categories of infection (such as bacterial, fungal, and viral) can occasionally be suggested by characteristic imaging features, but determination of a specific organism by imaging alone is nearly impossible. Although, clinicians usually rely on the radiologist to detect thoracic infections and occasionally to hypothesize the category of the pathogen, further diagnostic testing such as sputum, blood, pleural fluid, and so forth, is usually used. These nonimaging diagnostic tests are often obtained quickly and available to the radiologist when images are interpreted. Understanding these test results can help the radiologist add value by narrowing the differential diagnosis and offering suggestions for further workup.

This article reviews the methodology of available nonimaging diagnostic tests, as well as the commonly used diagnostic tests for the major categories of organisms (bacterial, fungal, viral, and parasitic/protozoan).

METHODS FOR DIAGNOSTIC TESTING—TRADITIONAL

The role of sputum evaluation as a diagnostic tool in directing antimicrobial treatment in CAP is limited. Current guidelines only recommend acquiring pretreatment expectorated sputum Gram stain and culture in adult patients with severe CAP or when risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* are present.[3] Blood cultures should not be routinely collected from patients with CAP in the outpatient setting but are recommended before initiation of

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Radiol Clin N Am 60 (2022) 521–534

https://doi.org/10.1016/j.rcl.2022.01.009

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antibiotics in adults with severe CAP or risk factors for MRSA or *P aeruginosa*.[4,5]

Bronchoscopy with bronchoalveolar lavage (BAL) may be required to obtain more definitive samples in immunocompromised patients and can detect a pathogen causing pneumonia in up to 70% to 80% of these patients.[6] Bronchoscopy may also be performed in patients with persistent symptoms and radiologic findings despite antibiotic treatment. Data are scarce on optimal timing of bronchoscopy, but retrospective studies suggest the yield is best if performed within 4 days of initial presentation and before 7 days of completion of antimicrobial therapy.[5]

In the setting of suspected pneumonia diagnostic thoracentesis is often performed when the effusion is greater than 10 or 20 mm in depth on a decubitus radiograph.[5,7] Percutaneous computed tomography (CT)-guided transthoracic needle lung biopsy and surgical lung biopsy are occasionally considered in patients with suspected nonresolving pulmonary infections when less invasive methods are nondiagnostic. Studies have shown that CT-guided lung biopsies revealed the causative organism and changed antibiotic therapy in up to 30% to 40% of cases in which they were performed.[8]

METHODS FOR DIAGNOSTIC TESTING—NEWER METHODS

Respiratory viruses may be detected by viral culture; however, this approach can be too slow to effectively guide acute patient management. Rapid antigen detection kits have turnaround in minutes and are widely available but with low sensitivity.[9] Molecular diagnostic approaches and antigen detection in respiratory secretions through the use of nucleic acid amplification testing (NAAT) have emerged as modern technologies in identifying viruses.[10] NAAT using polymerase chain reaction (PCR), reverse-transcriptase PCR (RT-PCR), and quantitative real-time PCR provide rapid results with sensitivity and specificity approaching 100% and are considered the diagnostic standard for detection of viruses.[9] Samples are most commonly collected from a nasopharyngeal swab.[4]

Urine antigen testing can be used to diagnose significant etiologies of respiratory infections such as *Legionella pneumophilia*, *Streptococcus pneumoniae*, and *Histoplasma capsulatum,* particularly in patients with severe CAP, relevant clinical history, or immunocompromised patients.[5,11]

BACTERIAL PNEUMONIA

Bacterial pneumonias can be classified by mechanism of development (CAP, healthcare-associated [HCAP], hospital-acquired [HAP], or ventilator-associated [VAP]) or by organism ("typical" vs "atypical"). Typical organisms can be Gram stained and cultured on a standard medium and include *S pneumoniae, methicillin-sensitive Staphylococcus aureus,* and *Haemophilus influenzae,* Group A streptococci, gram-negative rods, and anaerobes, among others. Typical organisms often cause CAP but can also cause HCAP and HAP (such as MRSA and *P aeruginosa*), as well as VAP (such as *Acinetobacter* spp*, P aeruginosa,* and multidrug-resistant organisms). Atypical organisms require special media to be cultured and include organisms such as *Legionella* spp*, Mycoplasma pneumoniae,* and *Chlamydia* spp).

C-reactive protein (CRP) is a nonspecific acute-phase protein. Although not specific for pneumonia, in the setting of clinical symptoms, it can be useful in establishing the diagnosis of CAP. High plasma levels of CRP are more common with *S pneumoniae* and *Legionella pneumophila*, as well as with patients with more severe CAP.[12] A threshold of 106 mg/L in men and 110 mg/L in women (normal value <10 mg/L) has been suggested as a determinant of inpatient versus outpatient care for the treatment of CAP (sensitivity 81% and specificity 81%). Furthermore, patients with extremely high levels should be ensured to have antibiotic coverage against both *S pneumoniae* and *L pneumophila.*

For patients with suspected pneumonia, the most common nonimaging test obtained is a complete blood count with differential. In the setting of bacterial pneumonia, leukocytosis is often present (typically with a white blood cell count in the range of 15,000–30,000 cells per mm^3) accompanied by a leftward shift (increased neutrophil count). Leukopenia with a white blood cell count of less than 5000 cells per mm^3 is less common but indicates a poorer prognosis, particularly in pneumococcal pneumonia.[13]

S pneumoniae (eg, pneumococcal pneumonia) is the most commonly identified bacterial organism in CAP.[14] Sputum Gram stain and culture sensitivity have been shown to be as low as 31% and 44%, respectively,[15] and yield drops dramatically when cultures are obtained after administration of antibiotics. Urine pneumococcal antigen test, introduced in 2003, has a sensitivity of 70.4% and a specificity of 89.7%, with results available quickly (**Fig. 1**). Blood cultures are positive in up to 24.8% of patients with pneumococcal pneumonia.[16]

MRSA is an important cause of HAP, HCAP, as well as CAP and VAP, often causing a necrotic pneumonia. If MRSA is suspected, treatment with vancomycin is often instituted but can be

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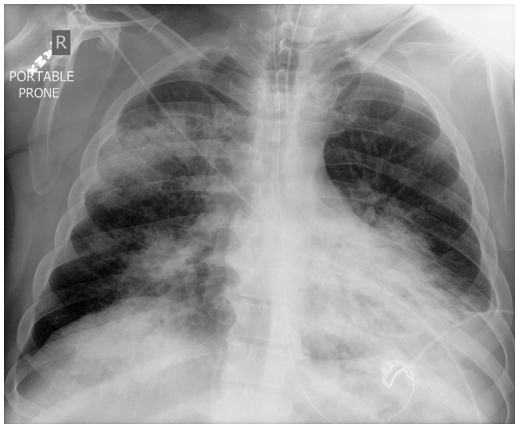

Fig. 1. Chest radiograph in a patient with multifocal consolidation and small left parapneumonic effusion secondary to pneumococcal (*Streptococcus pneumoniae*) pneumonia. Parapneumonic effusions are present in up to one-third of patients with pneumococcal pneumonia.

discontinued if MRSA infection is excluded. Therefore, use of a screening nasal swab for the detection of MRSA colonization has become routine.[17] In a recent meta-analysis, screening the nares for MRSA had a high specificity of 90.3% for ruling out MRSA pneumonia, allowing for de-escalation of antibiotics.[18] Radiologists can exclude MRSA from the differential diagnosis if the nares screening test is negative at the time of dictation.

Legionella species resulting in pneumonia are one of the organisms classified as "atypical" infections as they require a special medium to be cultured. Although there are numerous *Legionella* species, *L pneumophila* (most commonly serotype 1) is the most virulent and is responsible for greater than 95% of infections. Consideration of *Legionella* is important because antibiotic treatment for typical CAP may not cover this organism. In patients with *L pneumophila* serotype 1, antigen test on a urine sample can be performed. In a meta-analysis, the pooled sensitivity of the urine antigen was 74% and the specificity was 99%[19] (**Fig. 2**). Urine antigen tests and sputum cultures are commonly obtained for diagnosis but PCR testing on sputum or lavage fluid is considered the gold standard.[20]

Nontuberculous mycobacteria (NTM) encompass a large number (greater than 160) of acid-fast positive staining bacteria[21] but a much smaller number of these organisms are associated with pneumonia, typically causing chronic symptoms. Treatment decisions for NTM are complex and are partially based on the presence of cavitary disease, smear-positivity of sputum, as well as the species of NTM (see Faisal Jamal and Mark M Hammer's article, "Nontuberculous Mycobacterial Infections," in this issue).

Given that NTM can demonstrate cavitary lesions by imaging, differentiation of NTM from tuberculous infections is crucial (**Fig. 3**). Sputum specimens for acid-fast bacteria smear and culture are the mainstay of diagnosis, with at least 3 specimens obtained 24 hours apart in the morning. Smear results will return quickly but cultures can

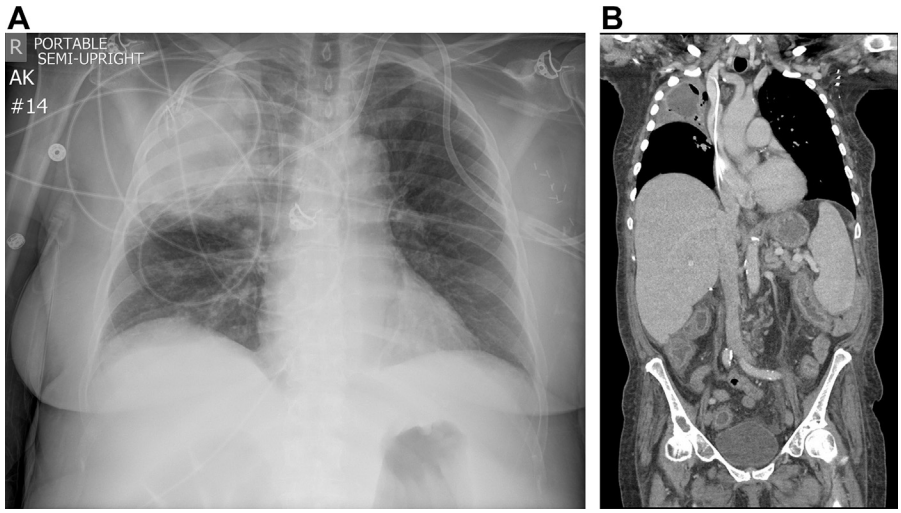

Fig. 2. Chest radiograph (*A*) and CT (*B*) in a patient with *Legionella pneumophila*. Radiograph demonstrates focal right upper lobe consolidation. Follow-up chest CT demonstrates hypoattenuating consolidation with internal gas compatible with necrosis. Urine *Legionella* antigen was positive at the time of radiographic imaging, allowing the radiologist to corroborate the imaging findings with test results.

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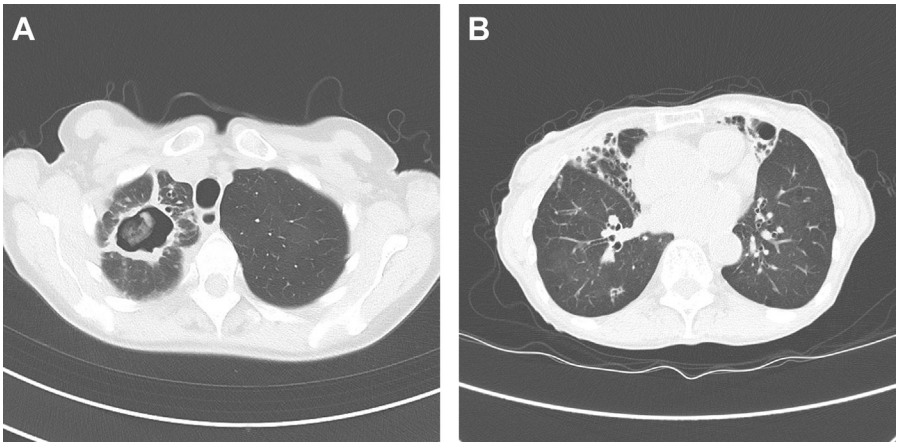

Fig. 3. (*A*) Chest CT in a man with COPD and evidence of fibrocavitary NTM involving the right upper lobe containing a mycetoma, and with surrounding bronchiectasis and tree-in-bud nodularity. (*B*) Chest CT in an elderly woman with noncavitary NTM involving the middle lobe and lingula (a common distribution).

take weeks; in one study, 20% of cultures become positive after 2 weeks and 10% of cultures after 3 weeks.[22] BAL is reserved for cases where sputum specimens cannot be obtained, or when specimens are negative but there is high clinical concern. Nucleic acid probes can be used within 1 day after recognizable culture growth and are available for several NTM species including MAC. More recently, real-time PCR tests have become available and can detect the presence of NTM directly on the sputum sample, not just the culture, with some assays reporting both excellent sensitivity and specificity of 99%.[23]

Imaging findings of mycobacterium tuberculosis (TB), can appear similar to NTM (**Fig. 4**). The same techniques used for NTM can also be used for TB sources in the chest such as pleural fluid, lymph nodes, abscesses, and so forth. Culture specimens for TB turn positive in the range of 17 to 25 days.[22] Given the long culture time and the ramifications of untreated TB, additional methods such as real-time PCR have become integral to timely diagnosis. Quantiferon TB Gold In-Tube (QFT-IT) can be ordered by clinicians, more commonly for detection of latent TB, but also for evaluation of active TB. However, its negative predictive value is only 79%, so it should not be used alone to exclude active TB.

Nocardia spp are ubiquitous gram-positive bacteria found in soil that causes disease in immunocompromised hosts in two-thirds of cases and in immunocompetent hosts in the remaining one-third.[24] In most cases, intrapulmonary infection is the predominant site of infection.[25] Timely diagnosis of *Nocardia* spp is important, given its tendency to relapse off of treatment, progress on treatment, and ability to disseminate, particularly to the brain. Unfortunately, diagnosis can be impeded by accidental destruction of *Nocardia* in the laboratory from sputum decontamination solutions. If there is a high radiological suspicion for Nocardiosis, this should be made clear to the clinician and the laboratory (**Fig. 5**). Given that *Nocardia* spp are not colonizers, a positive sputum culture for *Nocardia* should always be considered an active infection. An invasive procedure such as BAL was required 44% of the time to establish the diagnosis of Nocardiosis.[26] Given its rapidity, PCR testing is the preferred method of diagnosis, combining sensitivity and specificity of 100% with a rapid turnaround time.

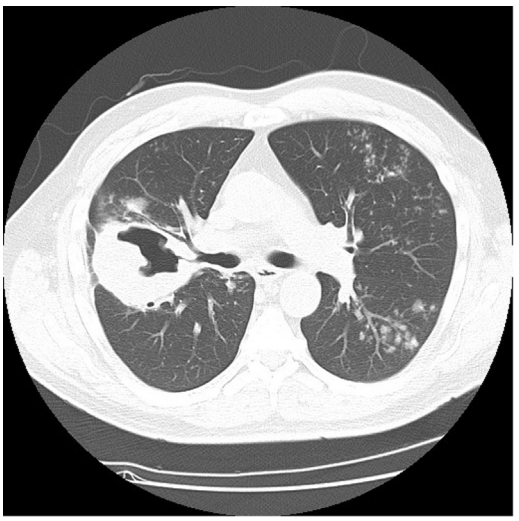

Fig. 4. Chest CT in a patient with active pulmonary tuberculosis. Appearance similar to **Fig. 3**, fibrocavitary NTM, exemplifying the importance of microbiologic evaluation.

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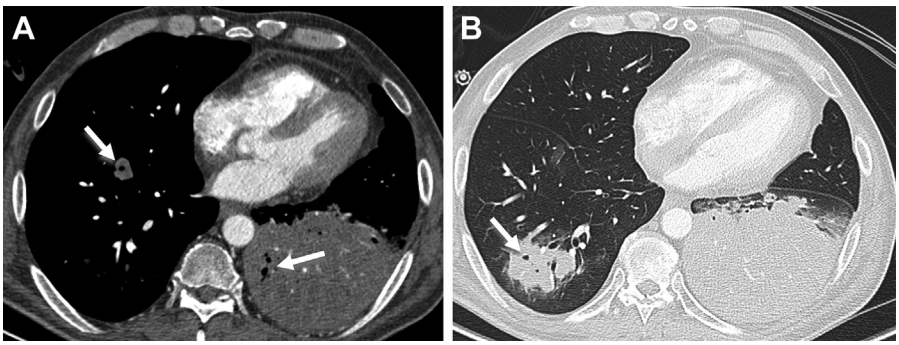

Fig. 5. Chest CT of pulmonary nocardia infection in a 55-year-old man receiving systemic chemotherapy. (*A*) Low attenuation consolidation in the left lower lobe and middle lobe nodule both containing bubbles of air at sites of necrosis (*arrows*). (*B*) More inferior CT section shows a consolidative mass in the right lower lobe which also contains a focus of necrosis.

FUNGAL PNEUMONIA

Fungal pneumonias are divided into endemic and opportunistic infections. Endemic fungal infections include organisms such as *Coccidioides immitis*, *Cryptococcus gattii*, *H capsulatum*, and *Blastomyces dermatitidis* and affect immunocompetent individuals in geographic regions where the fungi are present in the environment (see Jeffrey P. Kanne's article, "North American Endemic Fungal Infections," in this issue). Opportunistic fungal infections include pathogens such as *Aspergillus fumigatus*, *Candida albicans*, and *Mucor* spp, which are ubiquitous environmental fungi that typically do not cause disease unless the host is immunocompromised.

Coccidioidomycosis is caused by the endemic fungi *C immitis* and *Coccidioides posadasii*. It is found in the desert regions of the southwestern United States and northwestern Mexico, accounting for 29% of cases of CAP in these areas[27,28] (**Fig. 6**).

Diagnosis of coccidioidomycosis relies on serologic testing including immunoglobulin (Ig) antibodies subtype M (indicating acute infection) via enzyme-linked immunoassays (EIAs) and immunodiffusion and IgG antibodies (indicating prior infection) by complement fixation.[29] The sensitivity of EIAs for detection of acute infection ranges from 21% to 100% depending on immune status and symptom burden.[29,30] Up to 20% of patients seroconvert after an initial negative test, therefore, an initial negative test should not deter the radiologist from this diagnosis if the imaging findings are suspicious.[31]

Sensitivity of cytology and histology is low (33%) and these tests are rarely used alone.[32,33] In contrast, urine coccidioidomycosis antigen is positive in approximately 70% of patients.[34,35] Specimen culture remains the gold standard, but is insensitive with one study demonstrating a 54% rate of positivity. Owing to the overall low sensitivity of testing for *Coccidioides*, the American

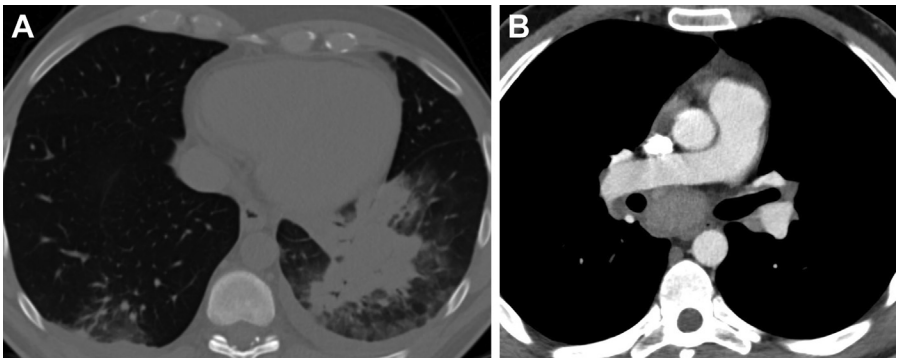

Fig. 6. Two CT images of the chest from a patient residing in Arizona demonstrate (*A*) dense left lower lobe consolidation with surrounding ground glass and septal thickening, as well as (*B*) presence of multifocal mediastinal lymphadenopathy on soft tissue images. Coccidioidomycosis was diagnosed via positive serologies.

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Thoracic Society (ATS) recommends using more than one test for diagnosis.[36] Specificity for both antigen testing and IgM is high in symptomatic patients (>96%), so a positive result should be regarded as indicative of active disease.[29,30,35,37]

Cryptococcus spp are unique in that they can be considered both opportunistic and endemic fungi, affecting both immunocompromised and immunocompetent hosts.[38,39] *Cryptococcus neoformans* is the most common pathogen but *C gattii* is endemic to several parts of the world, recently recognized in the Pacific Northwest. In addition to pneumonia, Cryptococcal organisms can also exist in a latent stage as a granuloma presenting as a chronic pulmonary nodule[40] (**Fig. 7**).

Options for laboratory detection of *Cryptococcus* spp are similar to *Coccidioides* spp and include antigen detection tests, molecular PCR tests, direct microscopic examination of a cytologic or histopathologic specimen, and specimen culture. The classic method of serum cryptococcal antigen detection using EIA has a sensitivity of 83% to 100% with higher sensitivities in immunocompromised patients.[41,42] A newer method of antigen testing using lateral flow assay allows detection of antigen in as soon as 5 minutes[43] and may often be available at the time of radiologic interpretation. Sensitivity of urine antigen testing is also high at 94%.[44]

Histoplasmosis fumigatus is a fungus endemic to the Ohio and Mississippi river valleys and is found in soil containing bird and bat droppings. It most commonly occurs in immunocompetent hosts and can result in either subclinical/minimal symptoms, or disseminated disease.

Testing for histoplasmosis is similar to the endemic fungi above. Although fungal culture is the gold standard, testing begins with urine antigen (sensitivity 79.5% and specificity 99%) and serum antigen (sensitivity 83.9% and specificity 97%) detection.[45] Combining antigen and serologic testing increases the diagnostic yield to 93.3% for pulmonary histoplasmosis.[46] Unfortunately, serologies may be of low utility in patients with solid organ transplants.[47] Sensitivities and specificities for laboratory tests tend to be higher in patients with disseminated histoplasmosis in which antigen levels may correlate with severity of illness.[47,48]

Blastomycosis is an endemic fungal infection caused by *B dermatitidis*, found primarily in the central and southeastern United States. The most common site of infection is the lungs although it can disseminate to skin, bones, and the central nervous system[36] (**Fig. 8**). No one test has sufficient sensitivity to be used alone for the diagnosis of Blastomycosis.[36] Use of multiple simultaneous tests to increase diagnostic yield and improve accuracy is recommended by the ATS. Antigen testing is the usual first step and can be detected in urine (sensitivity 55%–93%), serum (sensitivity 55.6%), or BAL (sensitivity 62.5%) specimens.[49,50] Combining antigen and serology testing increases the diagnostic yield to 97.6%.[51] Although fungal culture or direct visualization remain the gold standards, diagnostic yield

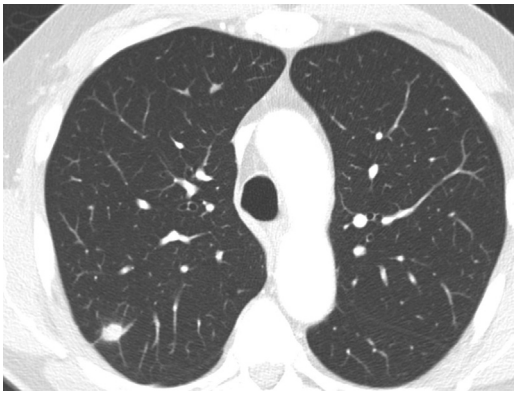

Fig. 7. Axial chest CT demonstrates presence of a rounded soft tissue density solitary pulmonary nodule in the posterior aspect of the right upper lobe. A serum cryptococcal antigen was positive in a 1:20 dilution. Diagnosis of *Cryptococcus* spp was confirmed with surgical wedge resection.

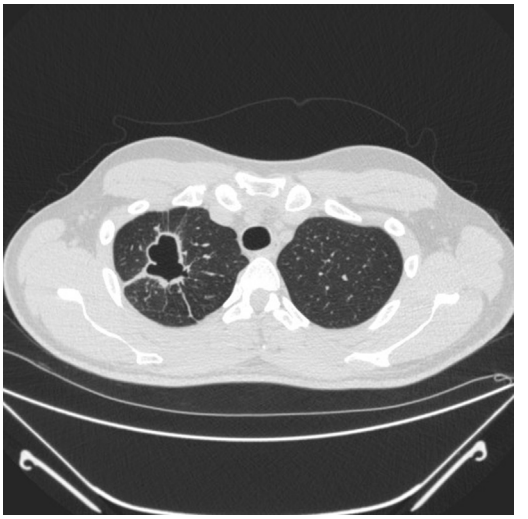

Fig. 8. Axial chest CT demonstrates a thick-walled right upper lobe cavitary lesion in a 38-year-old man residing in Nashville, Tennessee. The patient underwent bronchoscopy with transbronchial biopsies with tissue cultures confirming the diagnosis of Blastomycosis.

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is low, requires an experienced microbiologist, and cultures may take 5 weeks to grow.[52]

Pneumocystis pneumonia is caused by *Pneumocystis jirovecii*, formerly *Pneumocystis carinii*. It occurs in immunocompromised patients, particularly those with defects in cell-mediated immunity such as AIDS and glucocorticoid use.[53] The most common radiographic finding is centrally predominant ground-glass opacities without pleural effusions and with occasional presence of cysts or pneumothorax[54] (**Fig. 9**). Laboratory findings that suggest pneumocystis infection include elevated lactate dehydrogenase and elevated serum beta-D-glucan levels but these are not specific to pneumocystis pneumonia.[55,56] Other diagnostic options include PCR testing or direct visualization on a respiratory specimen.[57,58]

The diagnostic yield of sputum for direct visualization of PJP ranges from 4% to 58%,[59–61] is higher in patients with human immunodeficiency virus (HIV) compared with non-HIV patients.[60,61] Diagnostic yield of BAL fluid is also higher in patients with HIV.[59] As sensitivity for direct visualization can be low, serum beta-D-glucan may be useful. The sensitivity and specificity of serum beta-D-glucan depend on the threshold used to define positivity.[62] High levels of beta-D-glucan (>200 pg/mL) increase specificity to 100%. Nucleic acid amplification of a respiratory specimen has a higher sensitivity of 82%. Although not widely available,[58] it does have a negative predictive value at 98.7%.

Invasive aspergillosis (IA) is caused by *A fumigatus*, *Aspergillus flavus*, and *Aspergillus terreus,* which are ubiquitous and are frequent colonizers of the respiratory tract. Therefore, it is not uncommon to culture aspergillus in a sputum or BAL specimen. However, tissue invasion is rare and primarily occurs in immunocompromised patients.[63] Radiologic findings are discussed in detail elsewhere in this issue (see Godoy and colleagues' article, "Invasive Fungal Pneumonia in Immunocompromised Patients"). Presence of a halo sign manifest by a solid lesion with surrounding ground glass can suggest the diagnosis in an immunocompromised patient (**Fig. 10**). As aspergillus is a frequent colonizer, diagnosis of IA requires clinical evidence of active infection in addition to fungal invasion into tissue, elevation of serum or BAL galactomannan (GM), or beta-D-glucan or culture of aspergillus within a sterile site.[36]

Galactomannan is a component of the fungal cell wall and can be detected by EIA. Using positivity as an optical index greater than 0.5, sensitivity and specificity for serum galactomannan are 79% and 88%, respectively.[64] BAL galactomannan greater than 1.0 has a much higher sensitivity and specificity of 90% and 94%, respectively.[64] As galactomannan is also present on fungi other than *Aspergillus* such as *Candida*, *Histoplasma*, *Blastomyces*, and *Penicillium*, serum galactomannan can yield false positives.[65]

Beta-D-glucan is also a component of the fungal cell wall and aside from aspergillus is also present on *Candida* spp. and *P jirovecii*. Its utility is similar to serum galactomannan. In a meta-analysis of 1771 patients, sensitivity was low at 50% but specificity was outstanding at 99% for detection of invasive aspergillus.[66] False-positive results may occur with infection with *P aeruginosa*.[67] Newer methods to diagnose pulmonary aspergillosis and IA include serum and BAL PCR (sensitivity 79.2%, specificity 79.6%, and sensitivity

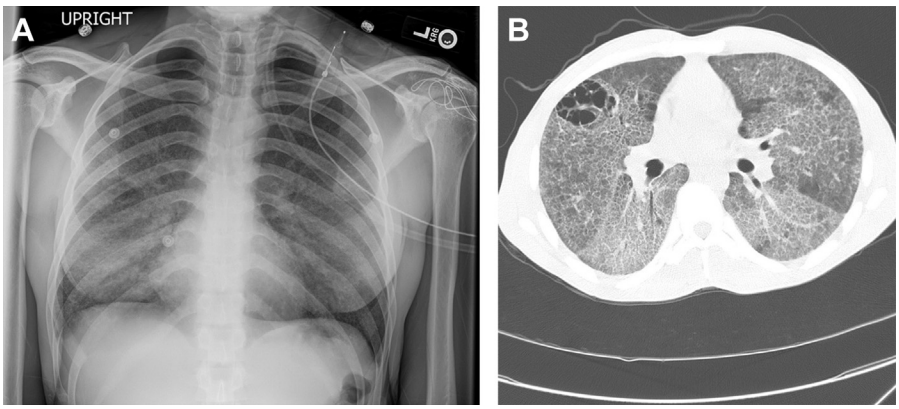

Fig. 9. (*A*) Front radiograph demonstrates the presence of bilateral perihilar ground-glass opacities without pleural effusions. (*B*) Axial high-resolution CT demonstrates a middle lobe cyst in conjunction with "crazy paving," septal thickening on a background of ground-glass opacities. Pneumocystis stain demonstrating organisms on induced sputum sample.

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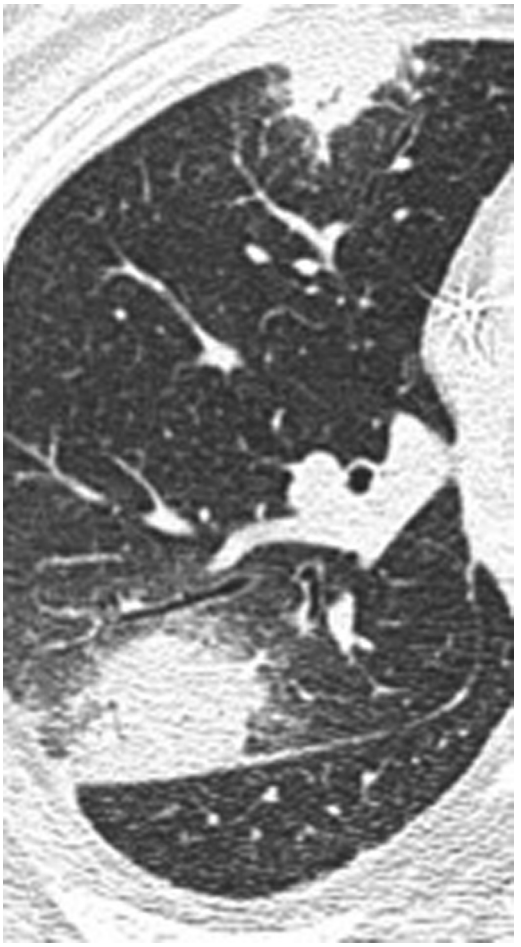

Fig. 10. Axial CT of the right lung of an immunocompromised patient demonstrates 2 solid pulmonary masses with surrounding ground glass, a halo sign. The patient was diagnosed with angioinvasive aspergillus by bronchoscopy.

90.2%, specificity 96.4%, respectively), which are recommended by the ATS.[36,68,69]

Mucormycosis accounts for 8% of invasive fungal infections in immunocompromised patients[70] usually from the genera *Rhizopus*, *Mucor*, and *Rhizomucor*.[71] These organisms are ubiquitous and are frequent colonizers of the respiratory tract, but can result in disease in immunocompromised hosts (**Fig. 11**). The diagnosis of mucormycosis requires demonstration of tissue invasion and clinical symptoms of pneumonia. On microscopic examination, the hyphae have an irregular branching pattern, unlike aspergillus which tends to branch at 90°.[72,73] PCR testing has also been used although is not widely available.[74,75] In one study of 27 patients with confirmed mucormycosis, 22 patients had a positive PCR.[75] Equally important, PCR positivity occurred in 12 of 15

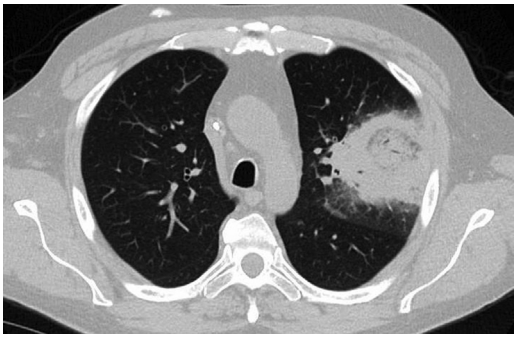

Fig. 11. CT from a febrile neutropenic patient demonstrates focal subpleural consolidation with central ground glass (reversed halo sign) shown to be caused by Mucormycosis by BAL PCR. A single subpleural lesion is a common imaging appearance for this disease.

cases that were negative by culture, indicating the utility of PCR.

VIRAL PNEUMONIA

Respiratory viruses are a major cause of pneumonia in immunocompetent and immunocompromised populations (see Febbo and colleagues' article, "Viral Pneumonias,"in this issue). Over the last several decades, NAAT PCR-based testing has emerged as a technique that can simultaneously detect multiple respiratory virus nucleic acids. These assays can detect multiple previously unrecognized respiratory viruses on a single sample[76] with a quick turnaround time while maintaining high sensitivity and specificity of greater than 90%.[10]

Influenza virus (**Fig. 12**) is the most significant cause of viral pneumonia. Rapid antigen testing can be specific (up to 94.5%) at detecting the virus from respiratory secretions, although sensitivity is low (40.5%) so cannot be used to exclude infection. Rapid influenza molecular assays based on PCR detection are recommended to identify different subtypes of influenza viruses with a reported sensitivity and specificity of up to 100%.[10,76]

CAP caused by the currently pandemic (SARS-CoV-2) (**Fig. 13**) can be detected by rapid antigen tests but has low sensitivity due to variable viral loads, which has limited their use. NAAT (RT-PCR) remains the currently recommended test[77] (see Sing and colleagues' article, "Review of Thoracic Imaging Manifestations of COVID-19 & Other Pathologic Coronaviruses,"in this issue). Diagnostic testing is recommended on an upper respiratory specimen, preferably a nasopharyngeal sample, with acceptable alternative

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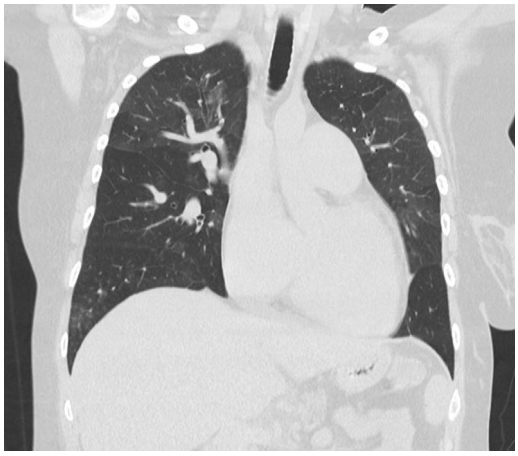

Fig. 12. Coronal CT image in a patient with fever and cough demonstrates bilateral upper lobe ground-glass opacities, which was later confirmed to be influenza A positive by PCR nasopharyngeal swab.

specimens obtained from the anterior nares, nasal midturbinate, oropharyngeal tract, or BAL fluid. Viral load is greatest in throat swabs at the time of viral onset and rapid specimen collection is recommended as soon as the decision to evaluate for the virus is made.[78]

VZV infection—which is associated with chickenpox and shingles—can lead to severe pneumonia in the elderly, pregnant, and immunocompromised patients although the incidence has decreased due to efficacy of the varicella vaccine.[76] Acute VZV infection can be diagnosed by PCR testing or isolating the virus/growth on cell culture, such as from vesicle fluid.[79]

Patients who have undergone a solid organ/hematopoietic stem cell transplant or have active hematologic malignancies are at risk for CMV pneumonia. Diagnosis can be made by PCR assay, CMV viral load quantification, or cytologic examination of the BAL fluid or lung biopsy samples.[76] PCR testing is the most sensitive method of detecting CMV. Quantitative real-time PCR can be helpful in monitoring viral loads in the blood although has a low specificity and positive predictive value in BAL fluid.[80]

Herpes simplex virus (HSV)—more commonly HSV-1 rather than HSV-2—can be a rare cause of pneumonia in immunocompromised patients and those who are critically ill or mechanically ventilated (**Fig. 14**). It has been reported in approximately 3% of patients with hematologic malignancies and 1% of hematopoietic stem cell transplant recipients.[81] When detected in BAL samples of ventilated patients, it is unclear whether it represents viral shedding or a true pathogen.[76] The virus can be detected through rapid antigen testing detection (sensitivity of 80% and specificity of 100%) or shell-vial culture (sensitivity of 57% and specificity of 100%) from respiratory secretions, BAL fluid, or lung tissue.[81] Although PCR testing is more rapid and sensitive, it is unable to distinguish between active disease and contamination from the oral cavity. Finally, histopathologic inspection of BAL fluid or lung tissue can demonstrate characteristic findings of multinucleated giant cells "owl-eyes."[81]

PNEUMONIA SECONDARY TO PARASITES/PROTOZOA

Parasitic infections are increasingly encountered in western countries in both immunocompromised and immunocompetent individuals. In the United States, most cases occur with travel to endemic regions.[82,83] (See Restrepo and colleagues' article, "Endemic Thoracic Infections in Latin America and the Caribbean," in this issue; Ching Ching and Lynette LS Teo's article, "Endemic Thoracic Infections in Southeast Asia," in this issue; Rydzak and colleagues' article, "Endemic Thoracic Infections in sub-Saharan Africa," in this issue)

Pulmonary amebiasis is rare but is the second most common site of this infection outside the abdomen[83] and often extends from the liver

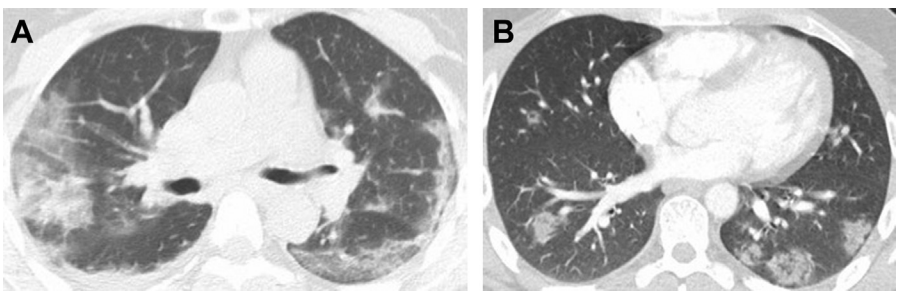

Fig. 13. Two axial CT images of the chest demonstrate basilar and peripheral predominant mixed ground glass and consolidative opacities in a distribution typical for SARS-CoV-2 viral pneumonia.

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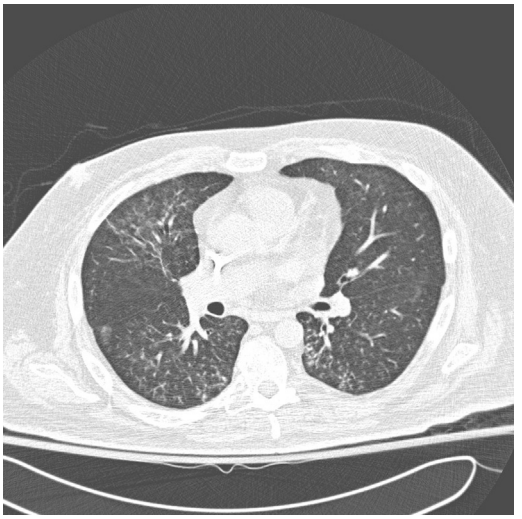

Fig. 14. Axial chest CT demonstrates extensive bilateral ground-glass opacities and centrilobular nodules in an immunocompromised patient diagnosed with HSV pneumonia by BAL culture.

(Fig. 15). Diagnostic options include serology, antigen detection, and trophozoite visualization on aspirated fluid. Antibody detection is positive in greater than 90% of patients and is the most widely available test.[83,84] Often, patients in endemic areas have antibodies from remote prior exposure[83] so clinical history is important.

Acute pulmonary schistosomiasis (Katayama syndrome) is caused by *Schistosoma mansoni* (Africa and South America) and *Schistosoma haematobium* (Africa and the Middle East). Peripheral eosinophilia can occur but is nonspecific. Diagnostic tools include microscopic visualization of eggs in stool or urine (the gold standard), antigen detection in serum, serum and urine PCR testing, serologic testing. Uncommonly, biopsy can be performed if testing is negative and clinical suspicion remains high. Antibodies develop 6 to 12 weeks after exposure, so PCR testing may be more useful in[85] the acute setting.[86] Pulmonary manifestations of schistosomiasis often occur in chronic infection where diagnosis relies on serologic testing.[87]

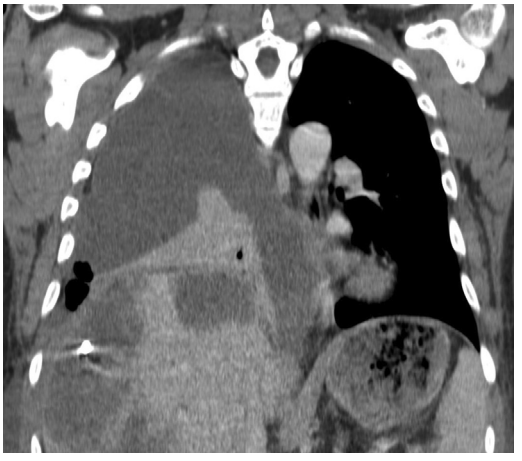

Fig. 15. Coronal CT image of a patient diagnosed with *Entamoeba histolytica* by elevated *E histolytica* serum antibodies demonstrates multiple intrahepatic abscesses and a large loculated right pleural effusion with intrapleural gas secondary to empyema.

Pulmonary strongyloidiasis usually causes symptoms of cough, throat irritation, dyspnea, and wheezing but severe disease from "hyperinfection" can be seen in immunosuppressed patients (see articles by Ryzdak, Teo, and Restreppo).[88] Serology is the main diagnostic tool. Most serologic tests measure IgG response and a specificity of 81% has been reported in patients with proven disease.[89] Limitations of serologic testing include reduced sensitivity in immunocompromised patients and inability to distinguish current from prior infection.[89] Other options include direct microscopic visualization of a stool specimen, but sensitivity is low at 21% due to intermittent larval excretion.[90]

SUMMARY

The differential diagnosis of organisms causing pneumonia can often be narrowed by a combination of imaging patterns and nonimaging diagnostic tests. The breadth and speed with which these nonimaging tests can be obtained has markedly increased in this century. Knowledge of the accuracy of diagnostic tests that have been performed as well familiarity with the utility of additional diagnostic tests can allow the radiologists to assist clinicians in suggesting the optimal course of action.

DISCLOSURE

The authors have nothing to disclose.

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