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MINIREVIEW

Laboratory Diagnosis of Lower Respiratory Tract Infections: Controversy and Conundrums

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Lower respiratory tract infections are among the most common infectious diseases of humans worldwide. In the United States alone, pneumonia and influenza rank as the sixth leading cause of death (18). Changes in the characteristics of the population as it ages and the swelling numbers of patients with immunocompromising conditions have increased the number of individuals at risk. An expanded variety of emerging pathogens likewise provides challenges for the microbiology laboratory. Overtreatment of acute uncomplicated bronchitis, which is largely due to viruses, has led to unparalleled levels of multidrug resistance among invasive pathogens such as *Streptococcous pneumoniae*. Practice guidelines for a rational approach to the evaluation and treatment of patients with acute bronchitis have recently been published in an effort to decrease the overuse of antibiotics and as an attempt to prevent further increases in rates of resistance (8). The laboratory's role here is very limited.

The role of the microbiology laboratory in the diagnosis of community-acquired pneumonia (CAP) remains controversial. Limitations of diagnostic tests have led to the development of guidelines for empirical treatment approaches (2, 3). Less controversial is the need to establish an etiology in the hospitalized patient and the immunocompromised host with lower respiratory tract infection. This minireview addresses the major categories of lower respiratory tract infections, the most common etiologic agents, and the laboratory tests (and their limitations) available to diagnose them.

ACUTE BRONCHITIS

Even though acute bronchitis is clearly one of the most common diagnoses made in adult clinical practice, a precise definition does not exist. A cough that lasts 1 to 3 weeks, with or without sputum production, and that is associated with upper respiratory tract and constitutional symptoms is the typical presentation. Symptoms result from inflammation and hyperresponsiveness of the bronchial tree.

Table 1 lists the most common pathogens implicated in acute bronchitis. Viruses, especially influenza virus, cause the vast majority of cases in studies that establish an etiology. Respiratory syncytial virus can also cause symptomatic lower respiratory tract disease, especially in elderly patients (1). Nonviral agents that have been implicated include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis*, and *Bordetella parapertussis.* The latter pathogens are most frequently seasonal and occur in epidemics (8). There are no data to suggest that *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are important pathogens in uncomplicated bronchitis (8).

Diagnosis is usually made clinically. Purulent sputum is not predictive of viral infections versus bacterial infections. Microscopic examination of sputum and culture are not helpful in distinguishing upper airway colonization from lower airway infection (19). Meta-analyses of numerous prospective studies have not demonstrated the value of microbiological studies in the management of patients with uncomplicated acute bronchitis (8). Rapid tests for influenza virus are limited by sensitivities equivalent to that of clinical judgment when influenza is circulating in a community (70 and 65 to 80%, respectively) (8). Perhaps the one exception to the previous statement is the patient with possible pertussis. Diagnostic tests should be performed for the patient with chronic cough in the setting of appropriate epidemiology, since pertussis is indistinguishable clinically from other causes of bronchitis and adults may be vectors of infection in nonimmunized infants or incompletely immunized children. Table 2 lists the available diagnostic tests.

Acute exacerbation of chronic bronchitis in patients with underlying lung disease is usually distinguished from the uncomplicated syndrome discussed above. Although *Streptococcus pneumoniae* and *Haemophilus influenzae* contribute more frequently to acute symptoms in patients with chronic obstructive pulmonary disease, viral pathogens are likely responsible for a significant number of episodes (30 to 40%) (19). Gram-stained smears and culture are of limited value because as many as 25% of patients with chronic obstructive pulmonary disease have upper airway colonization with bacterial pathogens in the absence of symptoms (15). Management of these patients remains controversial.

COMMUNITY-ACQUIRED PNEUMONIA

CAP is usually characterized by fever, chills, dyspnea, cough, and pleuritic chest pain in association with physical findings suggestive of consolidation in persons who become ill outside of a hospital or chronic-care facility. Table l lists some common

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TABLE 1. Most common pathogens implicated in lower respiratory tract syndromes and their relative contributions[a]

Disease and pathogen	% of cases
Acute bronchitis	
Respiratory viruses[b]	90
Bordetella pertussis-Bordetella parapertussis	5–10[c]
Mycoplasma pneumoniae	5–10[c]
Chlamydia pneumoniae	5–10[c]
Community-acquired pneumonia	
Streptococcus pneumoniae	66
Haemophilus influenzae	1–12
Legionella species	2–15
Mycoplasma pneumoniae	2–14
Klebsiella species	3–14
Enteric gram-negative bacilli	6–9
Staphylococcus aureus	3–14
Chlamydia species	5–15
Influenza virus	5–12
Hantaviruses	<1–2
Other viruses	<1–12
Mycobacterium tuberculosis	<1–10
Moraxella catarrhalis	<1–2
Unknown	23–49
Hospital-acquired pneumonia	
Gram-negative bacilli	
Pseudomonas aeruginosa	16
Enterobacter species	11
Klebsiella pneumoniae	7
Other enteric gram-negative bacilli	9
Acinetobacter	3
Legionella species	0–2
Haemophilus influenzae	0–2
Other	0–10
Gram-positive cocci	
Staphylococcus aureus	17
Streptococcus pneumoniae	2–20
Other	2–5
Anaerobes	10–20
Fungi	0–10
Mixed	13–54

[a] The information in this table is compiled from references 3, 10, 19, 20, 23, and 25.
[b] Influenza A virus, Influenza B virus, parainfluenza virus type 3, respiratory syncytial virus, coronavirus, adenovirus, and rhinovirus.
[c] The values represent the collective contribution of all four pathogens listed.

organisms that are associated with CAP. *Streptococcus pneumoniae* is still considered the major cause of CAP. The relative contributions of agents such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* depend upon the published series, whether there was a community outbreak at the time of the study, and the diagnostic method used.

The practice guidelines of both the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) (2, 3) emphasize using the history and physical examination to aid in the selection of nonmicrobiological diagnostic tests for assessment of the severity of illness and as a guide to empirical antibiotic choices. The history may also provide certain epidemiological clues that may be important when considering a particular etiology. For example, hantavirus pulmonary syndrome should be considered in the otherwise healthy patient who presents with a prodromal illness that rapidly progresses to adult respiratory distress syndrome following activities in an area of endemicity that increase the risk of exposure to rodents.

Both ATS and IDSA (2, 3) recommend chest radiography to distinguish pneumonia, which requires antibiotics, from acute bronchitis, which is most commonly viral in etiology (2, 3). The chest radiograph lacks specificity in establishing a microbial cause of CAP, but it may provide clues to the diagnosis of perhaps unsuspected illnesses that may be mistaken for CAP such as tuberculosis and *Pneumocystis carinii* infection (24).

Detection of an etiologic agent causing infection such that directed therapy is permitted is the role of microbiological tests. Unfortunately, the ideal test for most pathogens does not yet exist. Methods include sputum Gram stain and culture, blood cultures, serologic studies, antigen detection tests, and nucleic acid amplification methods. Table 2 lists the methods available for the detection of most common pathogens associated with CAP.

Among these methods, perhaps the most controversial are the sputum Gram stain and culture. The IDSA guidelines recommend these for patients with CAP who require hospitalization, whereas the ATS guidelines do not. While often regarded as a simple test, proper collection of the sputum sample, rapid transport to the laboratory, adequate sampling of the purulent component of the sample, preparation of the stain, and interpretation are all required. The values of the sputum stain and culture results are also dependent upon the pretest probability that the patient has bacterial pneumonia and upon whether the patient has received antibiotics. Add to this a recent study which demonstrated the intralaboratory sampling variability of expectorated sputum in five centers (17) and it is clear why the value of the Gram stain has been challenged. However, proponents argue that when the caveats mentioned above are fulfilled, namely, adequate sputum collection from a patient with productive purulent sputum who has not received antibiotics, the demonstration of a predominant morphotype may be useful in guiding pathogen-oriented antimicrobial therapy (21). In a recent study by Rozon et al. (21), the sensitivity and specificity of a Gram stain from a good-quality specimen for the diagnosis of pneumococcal pneumonia and *Haemophilus influenzae* pneumonia were 57 and 82%, respectively, and 97 and 99%, respectively. Moreover, in those patient samples in whom a predominant morphotype was seen, 95% of patients received monotherapy as opposed to combination therapy (21), leading to potential cost savings and less antimicrobial agent-related adverse events.

If it is decided to send a sample to the laboratory, patients should be given proper instructions. Food should not have been ingested for 1 to 2 h prior to expectoration. The mouth should be rinsed with saline or water, and the patient should be encouraged to breathe and cough deeply and expectorate immediately into a sterile container. Ideally, the sample is then transported immediately to the laboratory, where it is stained and plated as soon as possible upon receipt. At the University of Utah, attempts to standardize collection as part of an institutionwide focus on appropriate management of respiratory tract infections failed because the burden fell to already over-

TABLE 2. Diagnostic studies for specific agents of lower respiratory tract infections[a]

Pathogens	Available assays	Comments
Bacteria		
Streptococcus pneumoniae, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, gram-negative bacilli, other	Gram stain and culture of expectorated sputum, BAL, or other deep respiratory secretions; Gram stain and culture of pleural fluid; blood cultures	NOW *S. pneumoniae* (Binax, Inc.) urinary antigen test is available; high specificity; sensitivity, 52 to 80%
Atypical agents		
Legionella species	Culture of respiratory secretions and tissues on BCYE, selective BCYE	Considered the "gold standard"
	Urine antigen detection	Several kits available; reliably detects only *Legionella pneumophila* serogroup 1
	Serology	Serology with acute- and convalescent-phase specimens; 1–3 months may be required for seroconversion
	PCR[b] with respiratory secretions	Most promising
Mycoplasma pneumoniae	Serology	Method of choice
	Culture	Rarely performed; requires specialized media, prolonged incubation
	PCR[b]	Available through reference laboratories
Chlamydia pneumoniae	Serology	MIF is best assay
	Culture	Not widely available; sensitivity, 50 to 70%
	PCR[b]	
Chlamydia psittaci	Serology	Culture not recommended in routine clinical labs due to safety risks
Bordetella species	Culture	NP swabs, aspirates, and washings are specimens of choice; requires specialized media for transport and culture
	DFA	Sensitivity of 65% and specificity of 99.6% with monoclonal antibody reagents
	Serology	IgA and IgG antibodies to PT and FHA
	PCR[b]	Rapid, sensitive; calcium alginate swabs are inhibitory to PCR
Coxiella burnetii	Serology	Titer of antibody to phase II IgG, ≥200 by IFA
Nocardia species	Gram stain and modified acid fast stain; culture of respiratory specimens and tissues	
Mycobacterium species	Acid-fast stain; culture with combination of broth and solid media	
	Direct amplification techniques available	Two amplification assays have been cleared by FDA: Gen-Probe AMTDT and Roche Amplicor and COBAS assays (Roche Molecular)
Viruses		
Influenza virus, respiratory syncytial virus, and parainfluenza viruses 1 to 4	NP aspirates, washings, and swabs are preferred specimens; virus isolation is test of choice with exception of detection of respiratory syncytial virus (for which antigen detection is test of choice)	
Adenovirus	Antigen detection methods have variable sensitivities and specificities	Point-of-care rapid tests are least sensitive
	PCR	Commercial multiplex PCR assay available as RUO for RNA viruses
Herpes simplex virus	Virus isolation	
	PCR[b]	Available through reference laboratories
Cytomegalovirus	Shell vial culture in combination with early antigen detection by DFA	Detection of antigen on peripheral blood leukocytes and amplification techniques with plasma and serum used to monitor at-risk patients
Varicella-zoster virus	Virus isolation	
	DFA	
Hantavirus	Serology: EIA for IgM and IgG	Serology is available through most state health laboratories
Fungi		
Pathogenic	Fungal stains—GMS, calcofluor white, PAS	
Blastomyces, *Histoplasma*, *Coccidioides immitis*, *Sporothrix schenckii*	Recovery in culture from tissue, respiratory secretions, etc.	Probes available for rapid confirmation of culture isolates for *Blastomyces, Histoplasma*, and *Coccidioides; Histoplasma* antigen (blood, urine, respiratory secretions) available for acute disseminated infections
	Serology	May be unreliable in immunocompromised host

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TABLE 2—*Continued*

Pathogens	Available assays	Comments
Cryptococcus species	Stains as listed above Recovery in culture	Serum cryptococcal antigen by LA or EIA
Opportunistic		
Candida species	Gram stain or fungal stain	Recovery from culture alone is insufficient to make a diagnosis; histology is required
Aspergillus	GMS or calcofluor stain Recovery in culture	Recommended, as other hyaline molds may have similar histopathologic appearance
Zygomycetes	GMS or calcofluor stain Recovery in culture Histopathology of tissue section	Nonseptate broad hyphae are suggestive of a zygomycete
Pneumocystis	Giemsa stain, GMS, other; DFA stain	Induced sputum; bronchoscopy gives higher yield

[a] The information in this table is compiled from references 3, 10, 11, 12, 16, 19, 25, and 26. Abbreviations: BCYE, buffered charcoal yeast extract; MIF, microimmunofluorescence; NP, nasopharyngeal; IgA, immunoglobulin A, DFA, direct fluorescent-antibody test; PT, pertussis toxin; FHA, filamentous hemagglutinin; IFA, immunofluorescent antibody; AMTDT, amplified *Mycobacterium tuberculosis* direct test; EIA, enzyme immunoassay; GMS, Gomori's methenanine silver; PAS, periodic acid-Schiff; LA, latex agglutination; FDA, U.S. Food and Drug Administration; RUO, research use only.

[b] Not standardized; not cleared by the U.S. Food and Drug Administration.

worked nurses or respiratory therapists who simply could not perform these time-consuming steps (personal communication).

Once the specimen reaches the microbiology laboratory, it has been established that a microscopic screen to exclude those samples that represent upper airway contamination is beneficial and cost-effective. The specimen is viewed under low power (×10 objective), and the numbers of epithelial cells and/or polymorphonuclear leukocytes (PMNs) present establish the degree of contamination. The presence of many epithelial cells and few to no PMNs is suggestive of a poorly collected sample and the sample should not be planted. Multiple specific criteria incorporating PMNs, epithelial cells, mucus stranding, and the presence of bronchial epithelial cells have been published; but the superiority of one method over the others has not been established (19). If the sample is inadequate, a new one can be requested. In good-quality screened samples, the presence of a predominant bacterial morphotype should also be reported. Screening should not be applied to samples obtained from patients with possible *Legionella* or *Mycobacterium tuberculosis* infection (19, 25).

Routine sputum specimens are typically planted on blood agar, chocolate agar, and MacConkey agar. Although patients with *Legionella* pneumonia rarely produce purulent sputum (25), a Gram stain that demonstrates abundant PMNs with scant respiratory flora (in a patient not on antibiotics) is cause for suspicion for this pathogen, and the use of a medium selective for *Legionella* should be considered after consultation with the physician (25).

While the diagnostic yield from blood samples from patients with CAP is low (5 to 16%) (23), both ATS and IDSA recommend obtaining them from hospitalized patients before antibiotic therapy is administered (2, 3). The benefits include definitive identification of the etiologic agent and an estimate of a prognosis, which is helpful for patient management.

Up to 40% of patients admitted with CAP will have an accompanying pleural effusion (24). The decision to perform a thoracentesis is a clinical one, but a Gram stain and culture of the fluid with the media discussed above should be performed. Infected fluids are managed aggressively with chest tube drainage, whereas small parapneumonic effusions typically resolve on their own.

Antigen detection tests have a role in the establishment of viral etiologies such as respiratory syncytial virus and influenza virus. Direct fluorescent-antibody tests are more sensitive than point-of-care rapid tests (11). The specimen of choice is a nasal aspirate or wash or a nasopharyngeal swab. Throat swab specimens are less useful. Urinary antigen tests should be performed for patients suspected of having *Legionella pneumophila* infection, particularly in geographic settings where serogroup 1 predominates. The sensitivity ranges from 70 to 90%, and the specificity is >99% (10, 23, 25). Recently, a new method for detection of *Streptococcus pneumoniae* antigen in urine, an immunochromatographic assay (NOW *S. pneumoniae* urinary antigen test; Binax, Inc., Portland, Maine), has become available. A large study of 420 adults with CAP and 169 control patients demonstrated that the test has a high degree of specificity and a sensitivity of 80% when positivity by blood culture was used for comparison (16).

Serologic studies are usually reserved for the atypical pathogens including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*, among others. The relative contributions of these pathogens to cases of CAP vary depending upon the population studied and the diagnostic methods used. Diagnosis of infections caused by these pathogens is particularly problematic because the clinical presentations may be confused with a variety of other infectious agents, and culture, while possible, is either insensitive or slow and requires specialized culture techniques. Unfortunately, the most reliable serologic evidence implicating infection with one of the organisms mentioned above requires a fourfold increase in immunoglobulin G antibody titers between acute- and convalescent-phase serum samples, which confirms but which does not establish the diagnosis early enough to be useful in routine patient management. Given the lack of rapid or reliable methods for the detection of these agents, the practice guidelines of

both ATS and IDSA have incorporated empirical therapeutic regimens that are routinely used for the treatment of infections caused by these organisms (2, 3).

Nucleic acid amplification tests have been developed by many laboratories to more rapidly and accurately detect those pathogens that are difficult to culture. A commercial multiplex PCR assay for the detection of respiratory virus infections is available as a test for research use only (application for approval has been submitted to the U.S. Food and Drug Administration). It has excellent sensitivity and specificity but is costly and time-consuming (12). Likewise, PCR detection of *Bordetella pertussis* and *Bordetella parapertussis* has been shown to be more rapid and at least equivalent to culture, provided that calcium alginate swabs are not used for specimen collection (26). Two U.S. Food and Drug Administration-approved commercial nucleic acid amplification tests for direct detection of *Mycobacterium tuberculosis* from respiratory samples are available, the AMTDT (Gen-Probe Inc., San Diego, Calif.) and the Amplicor and COBAS (Roche Molecular, Branchburg, N.J.) tests. Optimal protocols for detection of other pathogens have yet to be established. The following parameters should be established before a nucleic acid test is incorporated into routine clinical use for a particular pathogen: optimum specimen type, internal inhibition control, analytical and clinical sensitivity and specificity, and reproducibility (CAP guidelines) (6)

NOSOCOMIAL PNEUMONIA

Pneumonia is the most frequent nosocomial infection (30 to 33% of cases) among combined medical-surgical intensive care units participating in the National Nosocomial Infections Surveillance System (20). In the intensive care unit setting, 83% of cases of pneumonia are associated with mechanical ventilation (20). *Staphylococcus aureus* is the most frequently reported isolate at 17% (20). Fifty-nine percent of reported isolates are aerobic gram-negative species, the most common of which is *Pseudomonas aeruginosa* (15.6%), followed by *Enterobacter* species (10.9%) and *Klebsiella pneumoniae* (7.0%) (20). Frequently, infection is polymicrobial (19).

The diagnosis of pneumonia in the hospitalized patient is even more challenging than the diagnosis of CAP. When fever, leukocytosis, and purulent tracheal secretions develop in association with an abnormal chest radiograph, the likelihood of pneumonia is high (20). However, symptoms suggesting pneumonia may be muted in debilitated or elderly patients, and a variety of other noninfectious conditions may mimic pneumonia (9, 19, 22). Clinical findings alone, then, are not sufficient for a definitive diagnosis.

A variety of noninvasive and invasive tests have been proposed as guides for diagnosis and treatment of hospital-acquired pneumonia. The American College of Chest Physicians convened a panel of experts to establish diagnostic recommendations for ventilator-associated pneumonia based upon an evidence-based assessment of the medical literature (9). The executive summary prepared by that committee concluded that the lack of specificity of clinical findings and the poor reproducibility of chest radiography warrant the performance of additional procedures, such as cultures of specimens from the lower respiratory tract (9). Although qualitative culture and Gram stain of endotracheal sputum samples are the least invasive tests, they have the same pitfalls for hospitalized patients as for patients in the community, that is, poor predictive values. Both pathogens and nonpathogens alike may be recovered.

Bronchoscopy has been advocated by many. Samples that can be obtained by bronchoscopy include bronchial brushings, bronchial washings, bronchoalveolar lavage (BAL) fluid, and transbronchial biopsy specimens (4, 9, 22). It is important that a standardized approach be followed. Baselski and Wunderink (4) describe in detail appropriate collection and handling techniques. Two diagnostic approaches are described: the serial dilution method, in which two 100-fold dilutions are made, followed by plating of a measured 0.1-ml amount of material on an agar medium, with direct colony counts reported as the number of CFU per milliliter, and the calibrated loop method, which is similar to the method used for the plating of urine samples (4). Established quantities for contamination versus infection are $>10^3$ CFU of a single organism per ml for protected specimen brushes (PSBs) and $>10^4$ CFU of a single organism per ml for BAL fluid (4).

The PSB technique involves advancing a double-catheter brush that contains a distal occluding plug through a fiberoptic bronchoscope. After the bronchoscope is wedged, the plug is ejected and distal secretions are sampled via the brush. The brush is then retracted through the inner lumen of the catheter, which in turn is retracted into the outer cannula (4, 22). A limitation of this procedure is the small volume obtained ($\sim$0.001 ml), which is diluted in 1 ml of transport medium (22). A criticism of the literature advocating the PSB technique is that the quality of the samples is usually not reported (9). Mertens et al. (14) suggest that samples obtained by the PSB technique be screened by using cytospin Gram stains. Specimens containing <10 cells per high-power field may reflect poor sampling, indicating unreliable results (14).

Many intensive care specialists prefer BAL fluid because a large number of alveoli ($\sim 10^6$) are sampled. Reported sensitivities of quantitative BAL fluid cultures range from 42 to 93% (9, 19), with a mean of 73%, and specificities range from 45 to 100%, with a mean of 82% (9, 19). The specificity is higher (89 to 100%) when intracellular organisms are detected (13). Results vary due to differences in the population studied, the prior administration of antibiotics, and the reference test compared (9).

Finally, blinded invasive procedures have been advocated by some because of the expense and potential risk of invasive procedures. Some of these methods include mini-BAL, blinded bronchial sampling, and blinded sampling by the PSB technique (9). The reported sensitivities and specificities are similar to those for invasive techniques (20). Since the involved portion of the lung may be missed, this technique should probably be reserved for patients too unstable to undergo bronchoscopy (5).

Regardless of the quantitative method used, the American College of Chest Physicians' position is that there are insufficient outcomes data to show that treatment based on the results of quantitative testing ensures a better clinical outcome (9). In contrast, a large randomized trial among 31 intensive care units in France showed that a management strategy involving invasive procedures was significantly associated with reduced rates of mortality and morbidity and resulted in less

antibiotic use (7). Perhaps the greatest utility of quantitative cultures of specimens obtained by invasive procedures at present may be in reducing antibiotic use for clinically insignificant organisms and for distinguishing between pneumonia and adult respiratory distress syndrome or other noninfectious causes. Also, there is general agreement at this time that the usefulness of repeated quantitative cultures to assess the response to therapy needs to be better studied.

PNEUMONIA IN IMMUNOCOMPROMISED HOSTS

Pneumonia is one of the most life-threatening infections in the immunocompromised host. A broad range of pathogens needs to be excluded; and the infectious agents to be considered vary depending upon the type and duration of immunosuppression, past exposures, geographic location, and the nature of the treatments administered.

Less controversial than the diagnostic utility of ventilator-associated pneumonia is perhaps the diagnostic utility of fiberoptic bronchoscpy in this setting. BAL protocols which process samples for both viral and bacterial pathogens, *Pneumocystis*, *Legionella*, fungi, and mycobacteria as well as cytologic analysis for noninfectious causes may be appropriate. Such protocols require communication between the clinical microbiology laboratory, infectious diseases specialists, pulmonologists, and transplant teams.

In summary, lower respiratory tract infections are among the most commonly encountered infectious diseases causing significant morbidity and mortality. The role of the microbiology laboratory in diagnosis remains controversial until better standardization of methods and outcomes data are generated. Empirical treatment approaches are recommended for bronchitis and CAP not requiring hospitalization. In the hospitalized patient, although diagnostic tests are imperfect, they are suggested. This is particularly true for the immunocompromised host, for whom invasive procedures guided by clinical and epidemiological data may reveal unsuspected opportunistic pathogens.

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