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# Diagnosis and Management of Lung Infections

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## KEYWORDS

- Pulmonary infection • Hemoptysis • Antibiotic therapy for pneumonia • Fungal pneumonia
- Community-acquired pneumonia • Hospital acquired pneumonia • Ventilator associated pneumonia

## KEY POINTS

- Thoracic surgeons are often called on to assist in the diagnosis and sometimes treatment of complicated pulmonary and thoracic infections.
- Modern diagnostic techniques used to obtain microbiological and pathologic specimens include bronchoscopy, ultrasound- and electromagnetic-guided endoscopy, transthoracic biopsy, and thoracoscopy.
- Appropriate empiric treatment of bacterial pulmonary infection requires categorization according to risk factors for drug-resistant pathogens; categories include community-acquired, health care-associated, hospital-acquired, and ventilator-associated pneumonia.
- Treatment of fungal and mycobacterial disease is heavily dependent on correct diagnosis; fungal pathogens include endemic fungi, yeast, and invasive molds, whereas mycobacterial infection may be caused *Mycobacterium tuberculosis* complex or nontuberculous mycobacterium.
- Recent advances in treatment, including topical antimicrobial therapy and direct endoscopic intervention, are promising in the treatment of multidrug-resistant infection and hemoptysis.

## INTRODUCTION

Thoracic surgeons occasionally must be involved in the diagnosis and treatment of respiratory tract infections. In addition to the complication of postoperative pneumonia in surgical patients, assistance may be needed for diagnosing radiographic abnormalities, community-acquired pneumonia (CAP), nosocomial pneumonia, ventilator-associated pneumonia (VAP), and pneumonia in the immunocompromised host. Although most clinically significant infections can be identified with respiratory cultures and microbiologic

analysis, a small percentage of infections require a surgical pathologist for definitive diagnosis.<sup>1</sup>

The spectrum and burden of etiologic organisms are affected by host risk factors and immune status.<sup>2-7</sup> Because organisms are found less often in the lung tissue of patients with normal immunity, diagnosis can be facilitated by cultures, serologic studies, and epidemiologic data.<sup>8</sup> In the immunocompromised host, a broader differential must be considered, including the possibility of multiple simultaneous infections.

In addition to infection, other disorders should be considered, such as pulmonary involvement by

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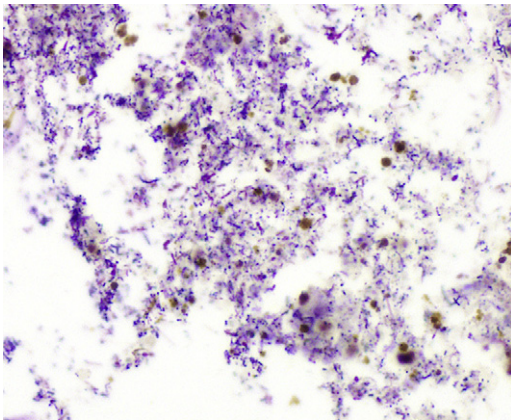
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preexisting disease, drug-induced or treatment-related injury, noninfectious interstitial pneumonias, and malignancy. Appropriate chest imaging may help narrow the differential. This information, when combined with clinical history and the timing of the disease (acute, subacute, or chronic), is critical to a successful treatment strategy. This article reviews the current diagnostic modalities and medical treatment recommendations for pulmonary infections.

## DIAGNOSIS

The successful treatment of pulmonary infections depends on accurate identification of the precipitating pathogen. In contemporary medical practice, distinction of the genus or species of an infectious organism can have important prognostic and therapeutic implications. Suspected pulmonary infections should be defined by (1) signs and symptoms consistent for diagnosing a pneumonia, (2) clinical setting consistent with acquisition of pneumonia, (3) host susceptibility predisposing to pneumonia, and (4) exposure and risk factors of specific pathogens.<sup>9</sup>

For pneumonia, sputum collection with microscopic examination and culture of expectorant is the mainstay of laboratory evaluation. Although simple, quick, and inexpensive, sputum cultures are nonetheless negative for growth 50% of the time despite proven infections. Contamination with oropharynx secretions is also a frequent issue. If sputum evaluation fails to identify causative factors and definitive identification is required for successful patient treatment, more invasive sampling techniques are available, including bronchoscopy, transthoracic needle aspiration or core



**Fig. 1.** Microscopy showing acute exudate with mixed gram-positive (blue) and gram-negative (red) bacterial organisms. Gram stain, original magnification,  $\times 400$ .

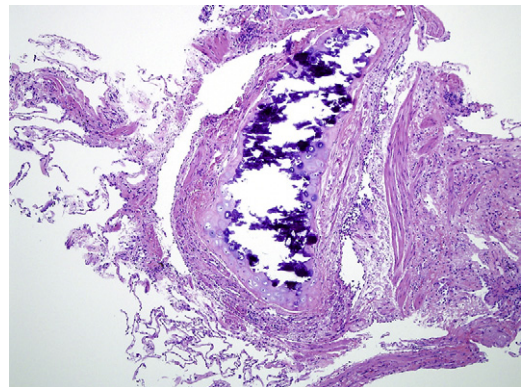


**Fig. 2.** An Olympus Endoscopic Ultrasound. (Courtesy of Olympus America, Inc, Center Valley, PA; with permission.)

biopsy, and surgical wedge biopsy of peripheral lung using a transthoracic approach.<sup>10–17</sup>

## Specimens Obtained Through the Flexible Bronchoscope

Current pulmonary endoscopy is dominated by the flexible bronchoscope. Its flexibility provides the advantage of better access to more distal airways.<sup>18,19</sup> Lavage and washings can be



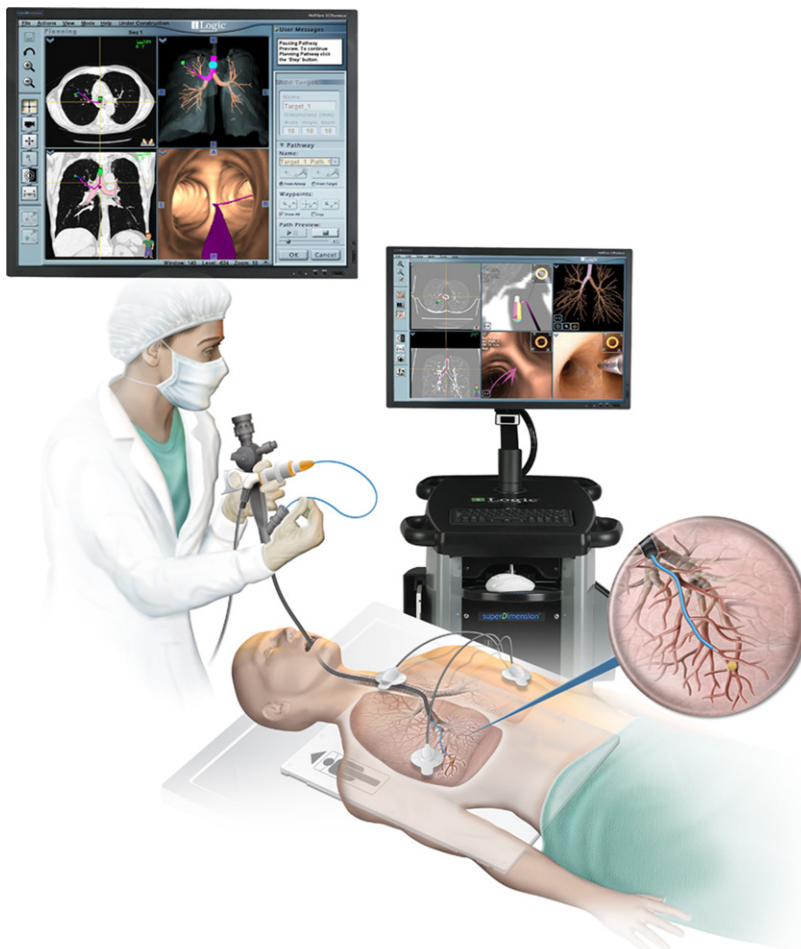
**Fig. 3.** Microscopy of transbronchial biopsies taken blindly are intended to represent alveolar lung parenchyma. Sometimes these samples are dominated by bronchial mucosa and cartilage if a branch point is directly sampled (a minor carina). This sample shows airway mucosa, lamina propria, and musculature samples with fragments of partially ossified (dark blue) cartilage. Scant alveolar parenchyma is present in the lower left of this image. Hematoxylin and eosin stain, original magnification,  $\times 100$ .

aspirated and the fluid sample of suspended cells can be sent to the laboratory for millipore filtration or cytocentrifuge-type application onto slides (Fig. 1).<sup>14,17,20–22</sup> Clinical guidelines confirm the value of a bronchoscopic approach to diagnosis, particularly in patients with VAP, in whom it has been shown to reduce 14-day mortality.<sup>23,24</sup>

Endobronchial ultrasound has also added to the available diagnostic options (Fig. 2). Both transbronchial lung biopsy of peripheral pulmonary lesions and sampling of mediastinal and hilar lymph nodes may provide access to infectious pathogens that cannot be identified otherwise.<sup>25,26</sup>

The transbronchial biopsy technique allows obtaining of samples of alveolar lung parenchyma beyond the cartilaginous bronchi.<sup>17,19,20,27</sup> Endoscopic transbronchial biopsies taken blindly are intended to represent alveolar lung parenchyma. Sometimes these samples have bronchial

mucosa and cartilage if a branch point, such as a minor carina, is sampled directly (Fig. 3). Many types of pulmonary infections can be diagnosed using fine needle aspiration and cytologic evaluation.<sup>28–31</sup> Fine needle aspiration is an especially useful technique, because respiratory secretions (eg, sputum, bronchial washings, brushings, bronchoalveolar lavage) are often limited by the need to differentiate true pathogens from contaminant organisms. Nevertheless, these diagnostic tools are complementary and both remain excellent options in the diagnosis of localized or diffuse pulmonary infection. Electromagnetic navigation bronchoscopy has proven effective in assessing pulmonary nodules accurately with low complication rates. Electromagnetic navigation bronchoscopy uses computer guidance to enable bronchoscopic access to pulmonary lesions (Fig. 4).<sup>32,33</sup>



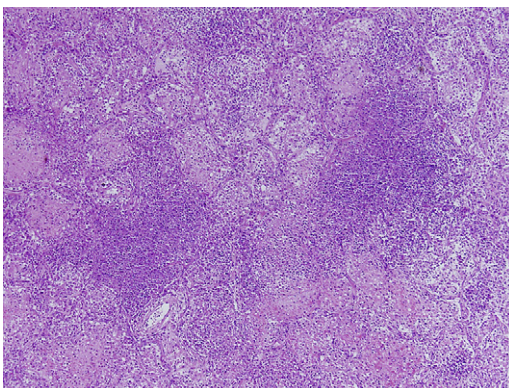
**Fig. 4.** The iLogic Electromagnetic Navigation Bronchoscopy allows virtual planning and biopsy of pulmonary lesions. (Courtesy of SuperDimension, Inc, Minneapolis, MN; with permission.)

### ***Specimens Obtained With Transthoracic Needle Biopsy, Aspiration, and Cores***

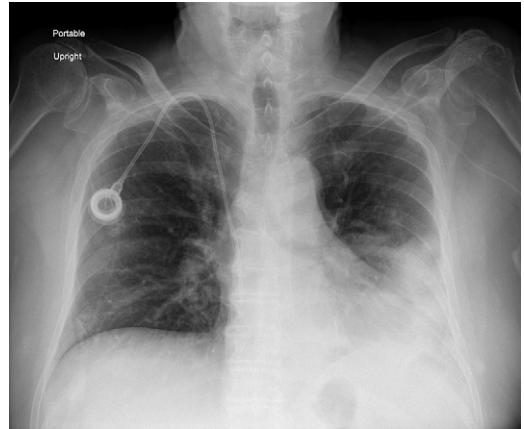
Contamination can be minimized when the upper respiratory tract can be bypassed. With either transtracheal or transthoracic needle aspiration, the presence of bacteria becomes much more significant, especially when sheets of neutrophils and/or necroinflammatory debris are present (**Fig. 5**), as would be the case with a typical lobar or lobular consolidation, lung abscess, or other complex pneumonia (**Fig. 6**).<sup>34–37</sup> In this context, transthoracic needle aspiration can establish the etiologic diagnosis of CAP and nosocomial pneumonia when coupled with contemporary microbiologic methods.<sup>38–41</sup> In current practice, the use of transthoracic needle aspiration biopsy has become commonplace,<sup>16,42–47</sup> and it is often used to target well-circumscribed nodules when an infectious process must be ruled out (**Fig. 7**). Besides the morphologic features of the microorganism, important cytologic clues to the diagnosis include the accompanying cellular response and the presence and character of any necrotic debris. Anaerobic pulmonary infections, typically in the form of a lung abscess, can also be approached in this way or with transthoracic needle aspiration (**Fig. 8**).<sup>48</sup>

In some cases, core biopsy is preferable to an aspirate. Needle core biopsies may provide better and more abundant diagnostic tissue, whereas aspirate is preferred when evaluating suspected bacterial abscess. Based on the microscopic features of the organism obtained, this technique may yield rapid diagnostic results.<sup>39</sup>

In addition to respiratory samples, pleural fluid can be tapped when effusions are present. Positive cultures of these normally sterile fluids circumvent the interpretive problems associated with bacterial growth in sputum samples. Persistent



**Fig. 5.** Microscopy showing sheets of neutrophils and necrotic inflammation.

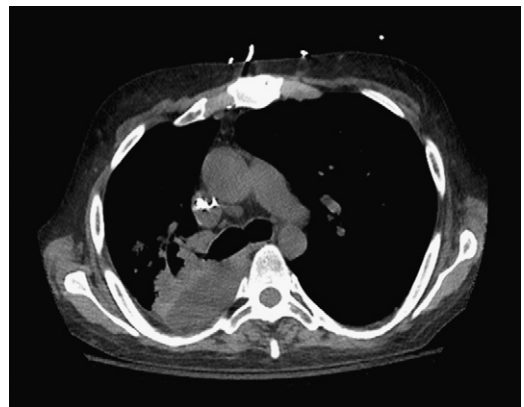


**Fig. 6.** Chest radiograph showing a lobar pneumonia with consolidation pneumonia in the left lower lobe.

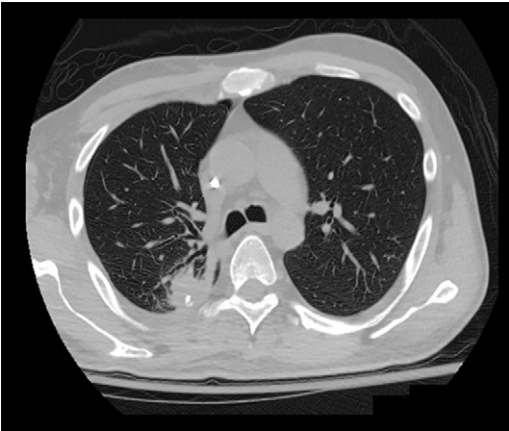
effusions and suspected empyema can be easily analyzed with thoracentesis (**Fig. 9**).<sup>49–51</sup>

### ***Specimens Obtained Through Thoracoscopy***

Surgical biopsy of lung parenchyma is indicated to distinguish infection from interstitial and inflammatory lung disease. The introduction of high-resolution video equipment has changed elective thoracic surgery. With small incisions and a thoroscopic video camera (**Fig. 10**), surgeons can directly biopsy affected lung tissue, with large quantities of parenchyma available for both microbiologic and pathologic evaluation (**Fig. 11**). Video-assisted thoracic surgery has become the standard approach for most surgical biopsies. Mortality is low and length of hospital stay and recovery are improved over those with the standard thoracotomy.<sup>52</sup> When the same thoracic access ports are used,



**Fig. 7.** CT scan showing consolidation secondary to severe lobar pneumonia and consolidation in the right lower lobe.



**Fig. 8.** CT scan showing a nodular abscess in the right lower lobe.

ipsilateral lymph nodes that may contain disease or abnormalities can be biopsied simultaneously. Before a wedge lung biopsy is performed, consultation among the radiologist, chest physician, and thoracic surgeon is essential to identify ideal locations for biopsy.

### CAUSES AND TREATMENT OF PULMONARY INFECTION

Pneumonia may be classified according to several parameters, including pathogenesis, epidemiology, anatomic pattern (see **Fig. 4**), clinical course, and organism.<sup>53</sup> In this article, pulmonary bacterial infection is divided into CAP, health care–associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), and VAP. Mycobacterial, fungal, and viral infections are also addressed because these entities require special diagnostic and treatment considerations. The pathologic patterns and



**Fig. 9.** CT scan showing a large pleural empyema on the left.

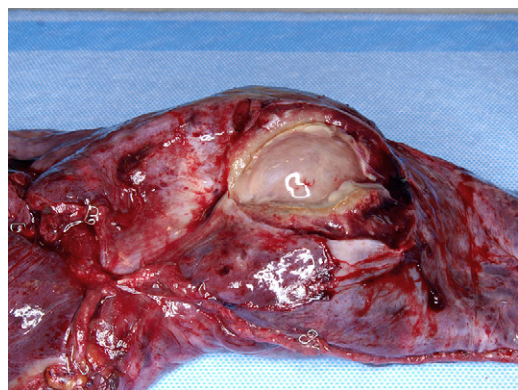


**Fig. 10.** Minimally invasive surgery with video images allows biopsy of parenchyma and lymph nodes for evaluation.

agents of the most common pulmonary infections are listed in **Table 1**.

### CAP

CAP is defined as pneumonia acquired in an outpatient setting by patients in whom common lower respiratory pathogens are suspected. Although viruses (**Fig. 12**) and endemic fungi may cause CAP, the definition and treatment regimens presuppose a bacterial origin. The most common origins are listed in **Table 2** (**Figs. 13** and **14A, B**). Coverage of these agents forms the basis for initial empiric treatment of CAP. However, clinicians must be aware of factors that predispose patients to pneumonia caused by drug-resistant bacteria, such as methicillin-resistant *Staphylococcus*



**Fig. 11.** A wedge biopsy from minimally invasive thoracic surgery shows a large cavitory fungal infection.

**Table 1**  
**Pathologic patterns and agents of pulmonary infection**

Pattern	Most Common Agents
<b>Airway disease</b>	
Bronchitis/bronchiolitis	Virus; bacteria; mycoplasma
Bronchiectasis	Bacteria; mycobacteria
<b>Acute exudative pneumonia</b>	
Purulent (neutrophilic)	Bacteria
Lobular (bronchopneumonia)	Bacteria
Confluent (lobar pneumonia)	Bacteria
With granules	Botryomycosis; actinomycosis
Eosinophilic	Parasites
Foamy alveolar cast	Pneumocystis
Acute diffuse/localized alveolar damage	Virus; polymicrobial
<b>Chronic pneumonia</b>	
Fibroinflammatory	Bacteria
Organizing diffuse/Localized alveolar damage	Virus
Eosinophilic	Parasite
Histiocytic	Mycobacteria
<b>Interstitial pneumonia</b>	
Perivascular lymphoid	Virus; atypical agents
Eosinophilic	Parasite
Granulomatous	Mycobacteria
<b>Nodules</b>	
<b>Large</b>	
Necrotizing	Fungi; mycobacteria
Granulomatous	Fungi; mycobacteria
Fibrocaceous	Fungi; mycobacteria
Calcified	Fungi; mycobacteria
<b>Miliary</b>	
Necrotizing	Viral; mycobacteria; fungi
Granulomatous	Fungi
Cavities and cysts	Fungi; mycobacteria
Intravascular/Infarct	Fungi
Spindle cell pseudotumor	Mycobacteria
Minimal "Id" type reaction	Polymicrobial

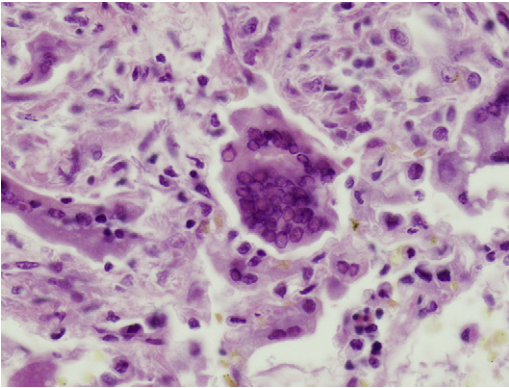
From Jaroszewski DE, Viggiano RW, Leslie KO. Optimal processing of diagnostic lung specimens. In: Leslie KO, Wick MR, editors. Practical pulmonary pathology: a diagnostic approach, 2nd edition. Philadelphia: Elsevier/Saunders; 2011. (Pattern Recognition Series). p. 15–25; with permission.

*aureus* (MRSA) or *Pseudomonas aeruginosa*; antibiotic selection for these patients should take into consideration additional breadth of spectrum (**Box 1**).<sup>23</sup>

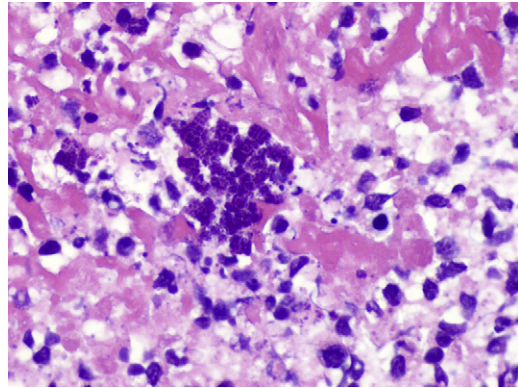
### **Treatment of CAP**

The American Thoracic Society and the Infectious Disease Society of America have published joint guidelines on the diagnosis and management of

CAP. **Box 2**<sup>55</sup> summarizes the recommended empiric antibiotics for CAP. Recommended treatment regimens vary based on severity of illness and setting (eg, outpatient, inpatient, intensive care). For empiric inpatient therapy, strong evidence supports use of either a respiratory fluoroquinolone or a combination of a  $\beta$ -lactam plus a macrolide.<sup>56</sup> In patients requiring intensive care, guidelines recommend a  $\beta$ -lactam plus a fluoroquinolone.<sup>55</sup> However, in this critically ill population, in whom



**Fig. 12.** Multinucleated cell with glassy viral nuclear inclusions consistent with a measles virus are identified in a patient with measles pneumonia. (hematoxylin-eosin, original magnification,  $\times 400$ ).



**Fig. 13.** Staphylococcal organisms (center) in a necrotizing pneumonia. Aggregated bacteria tend to be dark blue in routine stains. Hematoxylin and eosin stain, original magnification,  $\times 400$ .

the margin for error is low, many clinicians favor an initial broad-spectrum regimen that includes anti-MRSA and antipseudomonal coverage.

If an etiologic agent is identified, antimicrobial therapy should be narrowed to target that pathogen (**Table 3**). Guidelines recommend that before

discontinuation of therapy, a minimum of 5 days of treatment should occur, and patients should have achieved clinical stability as evidenced by the absence of fever for greater than 48 hours, hypoxia, tachypnea, tachycardia, and hypotension. Patients can be safely switched from intravenous to oral therapy when they are hemodynamically stable and able to absorb oral medication.<sup>58,59</sup> A longer duration of therapy may be necessary if the patient does not experience improvement, the identified pathogen was not sensitive to initial empiric therapy, or an extrapulmonary infection is present.

**Table 2**  
Most common causes of community-acquired pneumonia

Patient Type	Cause
Outpatient	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Haemophilus influenzae</i> <i>Chlamydia pneumoniae</i> Respiratory viruses <sup>a</sup>
Inpatient (non-ICU)	<i>S pneumoniae</i> <i>M pneumoniae</i> <i>C pneumoniae</i> <i>H influenzae</i> <i>Legionella</i> spp Aspiration Respiratory viruses <sup>a</sup>
Inpatient (ICU)	<i>S pneumoniae</i> <i>Staphylococcus aureus</i> <i>Legionella</i> spp Gram-negative bacilli <i>H influenzae</i>

Based on collective data from recent studies.<sup>54</sup>

Abbreviation: ICU, intensive care unit.

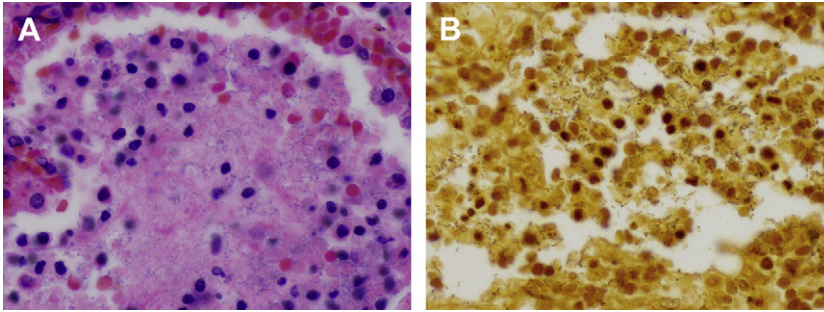
<sup>a</sup> Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

From Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:S27–72; with permission.

### HCAP

A subset of patients presenting with pneumonia acquired in the community will have risk factors for disease caused by drug-resistant pathogens (DRP). In the 2005 guidelines from the American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) for HAP and VAP, an additional category, HCAP, was proposed to the existing paradigm.<sup>23</sup> These patients share risk factors for DRP with those susceptible to HAP and VAP, including exposure to *P aeruginosa*, extended spectrum  $\beta$ -lactamase producing *Escherichia coli* and *Klebsiella*, *Acinetobacter*, *Burkholderia*, drug-resistant *Enterobacteriaceae*, and MRSA. Included in the new classification are patients hospitalized within the past 90 days; those receiving chemotherapy, wound care, or intravenous antibiotics; residents of nursing homes or long-term facilities; and patients undergoing hemodialysis. For these patients, the guidelines recommend a more aggressive empiric antibiotic regimen, including an antipseudomonal  $\beta$ -lactam plus either an aminoglycoside or an





**Fig. 14.** Streptococcus pneumoniae infection. (A). On routine hematoxylin and eosin staining, the organisms present a fine granular blue appearance in a background of more eosinophilic fibrinous exudate. The round blue structure are the nuclei of degenerated inflammatory cells. (B) Silver impregnation methods highlight many bacterial forms, making their morphology more discernible in black (Dieterle silver stain). Both images original magnification,  $\times 400$ .

antipseudomonal fluoroquinolone, plus an agent active against MRSA if risk factors for MRSA are present (**Table 4**).

### HAP

Nosocomial pneumonia is generally subdivided into HAP, including postoperative pneumonia, and VAP. HAP is defined as pneumonia occurring in patients hospitalized for longer than 48 hours

before onset and is associated with high mortality rates.<sup>23</sup> The treatment algorithm for HAP is based on individual risk for DRP (see **Box 1**) and time of onset. Patients with no preexisting risk factors for DRP in whom early HAP develops (within the first four hospital days) may be treated with a  $\beta$ -lactam such as a third-generation cephalosporin, ampicillin-sulbactam, or ertapenem, or with a respiratory fluoroquinolone such as levofloxacin. Patients with late-onset HAP (five or more inpatient days) or with risk factors for DRP should be treated with a broad-spectrum regimen (see **Table 4**).<sup>23</sup>

#### Box 1

##### Risk factors for multidrug-resistant pathogens causing HAP, HCAP, and VAP

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of 5 days or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP
  - Hospitalization for 2 days or more in the preceding 90 days
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 days
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

*Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and health-care-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416. Official journal of the American Thoracic Society.*

### VAP

VAP is defined as pneumonia occurring more than 48 hours after initiation of endotracheal intubation and mechanical ventilation.<sup>60</sup> Prior hospitalization within the past 90 days or prior antibiotic therapy predisposes to colonization and infection with antibiotic-resistant pathogens.<sup>61</sup> Suspected cases of VAP should be reviewed for risk factors and signs of antibiotic multidrug resistance (MDR) (**Fig. 15**).

VAP is the most frequently acquired infection in intensive care units (ICUs), with an incidence of 6% to 52%.<sup>60</sup> Generally, VAP is more prevalent in surgical ICUs than in medical ICUs.<sup>60</sup> Risk factors for VAP include both host and intervention factors (**Table 5**). The microbes commonly associated with VAP are similar to those that cause HAP (**Table 6**). VAP caused by more than one pathogen was identified in 30% to 70% of cases.<sup>60,61</sup> Treatment with initial empiric therapy should be guided by the risk for MDR pathogens as described earlier for HCAP and HAP (**Table 7**). A strategy for de-escalation from an empiric broad-spectrum, multi-drug regimen to a targeted therapy with a narrower

## Box 2 Recommended empiric antibiotics for CAP

### Outpatient treatment

1. Previously healthy and no use of antimicrobials within the previous 3 months

A macrolide (strong recommendation; level I evidence)

Doxycycline (weak recommendation; level III evidence)

2. Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions; or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)

A respiratory fluoroquinolone: moxifloxacin, gemifloxacin, or levofloxacin (750 mg) (strong recommendation; level I evidence)

A  $\beta$ -lactam plus a macrolide (strong recommendation; level I evidence)

3. In regions with a high rate (>25%) of infection with high-level (minimum inhibitory concentration  $\geq 16$   $\mu\text{g/mL}$ ) macrolide-resistant *Streptococcus pneumoniae*, consider use of alternative agents listed in #2 for patients without comorbidities (moderate recommendation; level III evidence)

### Inpatients, non-intensive care unit treatment

A respiratory fluoroquinolone (strong recommendation; level I evidence)

A  $\beta$ -lactam plus a macrolide (strong recommendation; level I evidence)

### Inpatients, intensive care unit treatment

A  $\beta$ -lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin (moderate recommendation; level II evidence) or a respiratory fluoroquinolone (strong recommendation; level I evidence)

For patients allergic to penicillin, a respiratory fluoroquinolone and aztreonam are recommended

### Special concerns

If *Pseudomonas* is a consideration

An antipneumococcal or antipseudomonal  $\beta$ -lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg)

or

The above  $\beta$ -lactam plus an aminoglycoside and azithromycin

or

The above  $\beta$ -lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for patients allergic to penicillin, substitute aztreonam for above  $\beta$ -lactam) (moderate recommendation; level III evidence)

If community-acquired MRSA is a consideration, add vancomycin or linezolid (moderate recommendation; level III evidence)

*Modified from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:527-72; with permission.*

spectrum is recommended to reduce antibiotic use and the selective pressure for MDR bacteria.<sup>62,63</sup>

### Aerosolized Antibiotic Therapy in the ICU

A growing body of data suggests that aerosolized antibiotics may have a role in the treatment of

pulmonary infections in mechanically ventilated patients.<sup>64,65</sup> Several aerosolized antibiotics have been described in the literature for off-label use (**Box 3**). Several small randomized controlled trials comparing systemic antibiotics plus aerosolized agents versus systemic treatment alone have recently shown a reduction in clinical pulmonary

**Table 3**  
**Recommended antimicrobial therapy for specific pathogens**

Organism	Preferred Antimicrobial(s)	Alternative Antimicrobial(s)
<i>Streptococcus pneumoniae</i>		
Penicillin-nonresistant; MIC < 2 µg/mL	Penicillin G, amoxicillin	Macrolide, cephalosporins (oral [cefepodoxime, cefprozil, cefuroxime, cefdinir, cefditoren] or parenteral [cefuroxime, ceftriaxone, cefotaxime]), clindamycin, doxycycline, respiratory fluoroquinolone <sup>a</sup>
Penicillin-resistant; MIC ≥ 2 µg/mL	Agents chosen based on susceptibility, including cefotaxime, ceftriaxone, fluoroquinolone	Vancomycin, linezolid, high-dose amoxicillin (3 g/d with penicillin MIC ≤ 4 µg/mL)
<i>Haemophilus influenzae</i>		
Non-β-lactamase-producing	Amoxicillin	Fluoroquinolone, doxycycline, azithromycin, clarithromycin <sup>b</sup>
β-Lactamase-producing	Second- or third-generation cephalosporin, amoxicillin-clavulanate	Fluoroquinolone, doxycycline, azithromycin, clarithromycin <sup>b</sup>
<i>Mycoplasma pneumoniae</i> / <i>Chlamydophila pneumoniae</i>	Macrolide, a tetracycline	Fluoroquinolone
<i>Legionella</i> spp	Fluoroquinolone, azithromycin	Doxycycline
<i>Chlamydophila psittaci</i>	A tetracycline	Macrolide
<i>Coxiella burnetii</i>	A tetracycline	Macrolide
<i>Francisella tularensis</i>	Doxycycline	Gentamicin, streptomycin
<i>Yersinia pestis</i>	Streptomycin, gentamicin	Doxycycline, fluoroquinolone
<i>Bacillus anthracis</i> (inhalation)	Ciprofloxacin, levofloxacin, doxycycline (usually with second agent)	Other fluoroquinolones; β-lactam, if susceptible; rifampin; clindamycin; chloramphenicol
Enterobacteriaceae	Third-generation cephalosporin, carbapenem <sup>c</sup> (preferred drug if extended-spectrum β-lactamase producer)	β-lactam/β-lactamase inhibitor, <sup>d</sup> fluoroquinolone
<i>Pseudomonas aeruginosa</i>	Antipseudomonal β-lactam <sup>e</sup> plus (ciprofloxacin or levofloxacin <sup>f</sup> or aminoglycoside)	Aminoglycoside plus (ciprofloxacin or levofloxacin <sup>f</sup> )
<i>Burkholderia pseudomallei</i>	Carbapenem, ceftazidime	Fluoroquinolone, TMP-SMX
<i>Acinetobacter</i> spp	Carbapenem	Cephalosporin-aminoglycoside, ampicillin-sulbactam, colistin

(continued on next page)

**Table 3**  
(continued)

Organism	Preferred Antimicrobial(s)	Alternative Antimicrobial(s)
<i>Staphylococcus aureus</i>		
Methicillin-susceptible	Antistaphylococcal penicillin <sup>g</sup>	Cefazolin, clindamycin
Methicillin-resistant	Vancomycin or linezolid	TMP-SMX
<i>Bordetella pertussis</i>		
Anaerobe (aspiration)	β-Lactam/β-lactamase inhibitor, <sup>d</sup> clindamycin	Carbapenem
Influenza virus		
<i>Mycobacterium tuberculosis</i>	Isoniazid plus rifampin plus ethambutol plus pyrazinamide	Refer to Ref. <sup>57</sup> for specific recommendations
<i>Coccidioides</i> spp	For uncomplicated infection in a normal host, no therapy generally recommended; for therapy, itraconazole, fluconazole	Amphotericin B
Histoplasmosis	Itraconazole	Amphotericin B
Blastomycosis	Itraconazole	Amphotericin B

Choices should be modified based on susceptibility test results and advice from local specialists. Refer to local references for appropriate doses.

Abbreviations: MIC, minimum inhibitory concentration; TMP-SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup> Levofloxacin, moxifloxacin, gemifloxacin (not a first-line choice for penicillin susceptible strains); ciprofloxacin is appropriate for *Legionella* and most gram-negative bacilli (including *H influenza*).

<sup>b</sup> Azithromycin is more active in vitro than clarithromycin for *H influenza*.

<sup>c</sup> Imipenem-cilastatin, meropenem, ertapenem.

<sup>d</sup> Piperacillin-tazobactam for gram-negative bacilli; ticarcillin-clavulanate, ampicillin-sulbactam, or amoxicillin-clavulanate.

<sup>e</sup> Ticarcillin, piperacillin, ceftazidime, cefepime, aztreonam, imipenem, meropenem.

<sup>f</sup> 750 mg/d.

<sup>g</sup> Nafcillin, oxacillin flucloxacillin.

From Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44:527–72; with permission.

infection score, facilitation of weaning, and use of systemic antibiotics.<sup>64,66,67</sup> A summary of microbiologic response to aerosolized antibiotics in recent studies is provided in **Table 8**.

With proper delivery, antimicrobial therapy may be targeted directly at the site of infection, increasing concentrations in the lung while minimizing systemic toxicity (**Table 9**).<sup>64</sup> Delivery mechanisms range from atomizers to jet and ultrasonic nebulizers, and vibrating mesh technology. Given the rise in incidence of DRPs in the ICU, large multicenter trials are needed to validate these novel treatment options. The current guidelines from the American Thoracic Society do not recommend routine use of aerosolized antibiotic therapy but do state that aerosolized antibiotics may be considered for treatment of microorganisms with a high minimum inhibitory concentration to parenteral antibiotics.<sup>23</sup>

## MYCOBACTERIAL INFECTION

Mycobacterial infection may manifest clinically with vast variation. Pulmonary infection is common and may be diagnostically challenging because of significant overlap in presenting symptoms with other pulmonary infections. Therefore, diagnosis is often delayed until confirmation with an invasive procedure, such as transbronchial biopsy, trans-thoracic needle biopsy, or surgical lung biopsy.<sup>69,70</sup> Direct acid-fast bacillus smears of respiratory specimens are negative in approximately 50% of cases,<sup>71</sup> and a biopsy may be the first suggestion of a mycobacterial infection (**Fig. 16**).<sup>72</sup> Mycobacterial species can be categorized into two clinically relevant groups: *Mycobacterium tuberculosis* complex and nontuberculous mycobacteria (NTM).

*M tuberculosis* is the most virulent mycobacterial species and is the etiologic agent of

**Table 4**

**Initial empiric therapy for HAP, VAP, and HCAP in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity**

Potential Pathogens	Combination Antibiotic Therapy <sup>a</sup>
Pathogens listed in <b>Table 2</b> and MDR pathogens <i>Pseudomonas aeruginosa</i> <i>Klebsiella pneumoniae</i> (ESBL+) <sup>b</sup> <i>Acinetobacter</i> spp <sup>b</sup>	Antipseudomonal cephalosporin (cefepime, ceftazidime) or Antipseudomonal carbapenem (imipenem or meropenem) or β-Lactam/β-lactamase inhibitor (piperacillin-tazobactam) plus Antipseudomonal fluoroquinolone <sup>b</sup> (ciprofloxacin or levofloxacin) or Aminoglycoside (amikacin, gentamicin, or tobramycin) plus Linezolid or vancomycin <sup>c</sup>
MRSA <i>Legionella pneumophila</i> <sup>b</sup>	

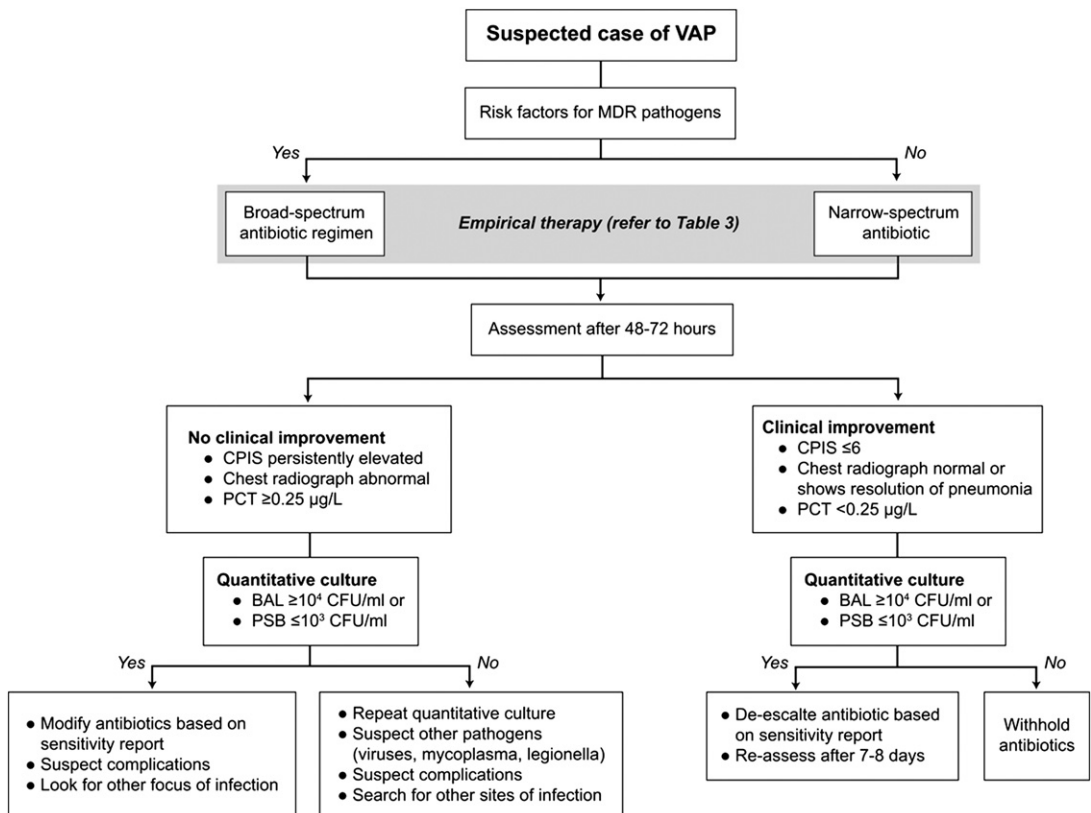
Abbreviation: ESBL, extended-spectrum β-lactamase.

<sup>a</sup> Initial antibiotic therapy should be adjusted or streamlined based on microbiologic data and clinical response to therapy.

<sup>b</sup> If an ESBL<sup>+</sup> strain, such as *K pneumoniae* or an *Acinetobacter* sp is suspected, a carbapenem is a reliable choice. If *L pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (eg, azithromycin) or a fluoroquinolone (eg, ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

<sup>c</sup> If MRSA risk factors are present or there is a high incidence locally.

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**Fig. 15.** Algorithm for treatment of VAP. BAL, bronchoalveolar lavage; CPIS, clinical pulmonary infection score; MDR, multi-drug resistant; PCT, procalcitonin; PSB, protected specimen brush. (From Joseph NM, Sistla S, Dutta TK, et al. Ventilator-associated pneumonia: a review. Eur J Inter Med 2010;21:360; with permission.)

**Table 5**  
Risk factors for VAP

Host Factors	Intervention Factors
Oropharyngeal colonization	Emergency intubation
Gastric colonization	Reintubation
Thermal injury (burns)	Tracheostomy
Posttraumatic	Bronchoscopy
Postsurgical	Nasogastric tube
Impaired consciousness	Duration of hospital stay/ICU stay
Immunosuppression	Multiple central venous line insertions
Organ failure	Sedatives
Sinusitis	Stress ulcer prophylaxis
Severity of underlying illness	Prior antibiotics/no antibiotic prophylaxis
Old age ( $\geq 60$ y)	Immunosuppressives (corticosteroids)
Presence of comorbidities	Supine head position

From Joseph NM, Sista S, Dutta TK, et al. Ventilator-associated pneumonia: a review. *Eur J Intern Med* 2010;21:360–8; with permission.

tuberculosis worldwide in its various forms. This organism is responsible for more deaths worldwide than any other single microbe. Postprimary tuberculosis, the most common form in adults, typically involves the apices of the upper lobes, producing granulomatous lesions with cavities and variable degrees of fibrosis and retraction of the parenchyma.<sup>73–75</sup> In a minority of patients, the lesions enlarge and progress secondary to increased necrosis and/or liquefaction.<sup>76</sup>

NTM include more than 125 species<sup>77,78</sup>; however, relatively few cause pulmonary disease.<sup>72,79–81</sup> NTM species are subdivided according to growth rates. Of the rapid growers, *M abscessus* is the most frequently recovered pulmonary pathogen, whereas *M fortuitum* and *M chelonae* are more often associated with wound infection and soft tissue disease.<sup>68</sup> Among the slow growers, *M avium-intracellulare* complex is the most common NTM respiratory pathogen, followed by *M kansasii* in the United States and *M xenopi* in Europe. NTM may cause a wide spectrum of pulmonary and extrapulmonary disease, but most frequently cause fibronodular bronchiectasis or cavitation.<sup>68</sup>

**Table 6**  
Microbial agents causing VAP

Common Causes	Rare/Unusual Causes
Gram-positive cocci	Gram-positive bacilli
<i>Staphylococcus aureus</i>	<i>Corynebacterium</i> spp (diphtheroids)
<i>Streptococcus pneumoniae</i>	<i>Listeria monocytogenes</i>
Other streptococci	<i>Nocardia</i> spp
Coagulase-negative staphylococci	Aerobic gram-negative bacilli
Enterococci	<i>Serratia</i> spp
Aerobic gram-negative bacilli	<i>Hafnia alvei</i>
Enteric gram-negative bacilli	<i>Stenotrophomonas maltophilia</i>
<i>Escherichia coli</i>	<i>Burkholderia cepacia</i>
<i>Klebsiella</i> spp	Gram-negative cocci
<i>Enterobacter</i> spp	<i>Neisseria</i> spp
<i>Proteus</i> spp	<i>Moraxella</i> spp
<i>Citrobacter</i> spp	Anaerobic bacteria
Nonfermentative	Bacilli
Gram-negative bacilli	<i>Bacteroides</i> spp
<i>Pseudomonas</i> spp	<i>Fusobacterium</i> spp
<i>Acinetobacter</i> spp	<i>Prevotella</i> spp
<i>Haemophilus influenzae</i>	<i>Actinomyces</i> spp
Fungi	Cocci
<i>Candida</i> spp	<i>Veillonella</i> spp
	Peptostreptococci
	Atypical bacteria
	<i>Legionella</i> spp
	<i>Mycoplasma pneumoniae</i>
	<i>Chlamydia pneumoniae</i>
	Fungi
	<i>Aspergillus</i> spp and other molds
	<i>Pneumocystis jiroveci</i>
	Viruses
	Influenza and other respiratory viruses
	Herpes simplex virus
	Cytomegalovirus
	Miscellaneous causes
	<i>Mycobacterium tuberculosis</i>

From Joseph NM, Sista S, Dutta TK, et al. Ventilator-associated pneumonia: a review. *Eur J Intern Med* 2010;21:360–8; with permission.

**Table 7**  
Initial empiric therapy for VAP

VAP With No Risk Factors for MDR Pathogens	VAP With Risk Factors for MDR Pathogens
Ceftriaxone or Levofloxacin, moxifloxacin, or ciprofloxacin or Ampicillin/sulbactam or Ertapenem	Antipseudomonal cephalosporin (cefepime, ceftazidime) or Antipseudomonal carbapenem (imipenem or meropenem) or $\beta$ -Lactam/ $\beta$ -lactamase inhibitor (piperacillin-tazobactam) plus Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or Aminoglycoside (amikacin, gentamicin, or tobramycin) plus Linezolid or vancomycin (if risk factors for MRSA are present)

From Joseph NM, Sistla S, Dutta TK, et al. Ventilator-associated pneumonia: a review. *Eur J Intern Med* 2010;21:360–8; with permission.

### Treatment of Mycobacterial Pulmonary Infection

Treatment of mycobacterial disease is generally more complicated than that for other bacteria because of the slow growth of the organisms, mechanisms of drug resistance (eg, the unique cell wall characteristics of the genus), and poor drug tolerability. Multidrug regimens are required for extended duration. Once the diagnosis of active pulmonary tuberculosis is confirmed, initial recommended treatment comprises a four-drug regimen of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin, according to local patterns of susceptibility.<sup>82</sup> Duration of therapy depends on the drug susceptibility of the isolate, presence of extrapulmonary involvement, and immune status of the patient. Although acquired resistance does occur, the more common cause of treatment failure is medication

### Box 3

#### Aerosolized antibiotics described in the literature: off-label use and U.S. Food and Drug Administration–approved drugs

#### Cystic fibrosis

Gentamicin  
Amikacin  
Tobramycin<sup>a</sup>  
Aztreonam lysine<sup>b</sup>  
Liposomal amikacin<sup>c</sup>

#### Mechanically ventilated patients

Sisomicin  
Gentamicin  
Amikacin  
Cefuroxime/ceftazidime  
Colistin-polymyxin B  
Vancomycin  
Amikacin proprietary preparation<sup>d</sup>

<sup>a</sup> U.S. Food and Drug Administration (FDA)–approved medication for maintenance therapy for patients with cystic fibrosis who are known to be colonized with *P aeruginosa*; tobramycin (Tobi, PARI Pharma GmbH, Weilheim, Germany) delivered with PARI LC Plus nebulizer or Pulmo-Aide compressor.

<sup>b</sup> FDA-approved medication for patients with cystic fibrosis for more than 7 years with chronic *Pseudomonas* infection; aztreonam (Cayston inhalation, PARI Pharma GmbH, Weilheim, Germany) delivery with Altera Nebulizer System using eFlow.

<sup>c</sup> Phase 2 completed. For patients with cystic fibrosis with *Pseudomonas* infections; liposomal amikacin (Arikace, PARI Pharma GmbH, Weilheim, Germany).

<sup>d</sup> Phase 2 trial completed. Aerosol amikacin, Bayer Healthcare. Delivered with Nektar Therapeutics LPT.

From Palmer LB. Aerosolized antibiotics in the intensive care unit. *Clin Chest Med* 2011;32:559–74; with permission.

nonadherence. For this reason, evidence strongly supports direct observational therapy. Confirmation of clearance of sputum acid-fast bacilli is recommended at 3 months.

Given the increase in MDR and extensively drug-resistant *M tuberculosis* strains, repeat susceptibility testing is warranted with documented treatment failure. If drug-resistant strains are identified, expert consultation is recommended, and a regimen composed of at least four agents should be selected in a stepwise approach from the following classes: (1) all first-line agents to which the strain is sensitive: isoniazid, rifampin, pyrazinamide, and ethambutol; (2) one fluoroquinolone, if susceptible; (3) one injectable aminoglycoside, such as streptomycin or kanamycin;

**Table 8**  
**Microbiological response to aerosolized antibiotics**

Authors	Year	Setting	Design	Indication	Method of Aerosolization; Drug	No of Patients	No of Patients on Systemic Antibiotic Use	No of Organisms in Patients	No of Patients with Eradication of Causative Organism	No of Patients with Resistant Organisms
Michalopoulos et al <sup>117</sup>	2005	ICU, Greece	Retrospective chart review	VAP for 6 patients, HAP for 2 patients	Aerosolized via Siemens Servo Ventilator; colistin	8	7/8	<i>Acinetobacter</i> , 7; <i>Pseudomonas</i> , 1	4/5	None
Kwa et al <sup>118</sup>	2005	ICU, Singapore	Retrospective chart review	VAP	Aerosolized colistin; no data on method	21	Yes, but not active against causative organism	<i>Acinetobacter</i> , 17; <i>Pseudomonas</i> , 4	11/11 available cultures	Not described
Berlana et al <sup>119</sup>	2005	ICU, Spain	Retrospective chart review	Pulmonary infection	Aerosolized with various compressors; colistin	71	78% of patients	<i>Acinetobacter</i> , 60; <i>Pseudomonas</i> , 11	<i>Acinetobacter</i> , 33/33; <i>Pseudomonas</i> , 4/7	Not described
Michalopoulos et al <sup>120</sup>	2008	ICU, Greece	Prospective	VAP	Aerosolized via Siemens Servo Ventilator; colistin	60	57	<i>Acinetobacter</i> , 37; <i>Pseudomonas</i> , 12; <i>Klebsiella</i> , 11	50/60	Not described
Palmer et al <sup>65</sup>	2008	ICU, United States	Randomized, double-blind, placebo-controlled	VAT $\geq$ 2 mL sputum produced over 4 h and organisms on Gram stain	AeroTech jet nebulizer; vancomycin and/or gentamicin	24, placebo; 19, AA	32/43	Multiple species of gram-negative and gram-positive organisms	Placebo, 19; aerosolized, 17	Placebo (8/24), AA (0/19)
Kofteridis et al <sup>121</sup>	2010	ICU, Greece	Retrospective review, matched case control	VAP	Aerosolized colistin; no details on method	43 IV and aerosolized colistin; 43 IV colistin	All patients	<i>Acinetobacter</i> , 66; <i>Klebsiella</i> , 12; <i>Pseudomonas</i> , 8	Placebo, 17 (50%); aerosolized, 19 (45%)	Not described
Korbila et al <sup>122</sup>	2010	ICU, Greece	Retrospective review, matched case control	VAP	Aerosolized via Siemens Servo Ventilator; colistin	43 IV colistin; 78 aerosolized and IV colistin	All patients	MDR gram-negative organisms	Placebo, 26 (60.5%); aerosolized, 62 (79.5%)	Not described

Abbreviations: AA, aerosolized antibiotic; IV, intravenous; VAT, ventilator-associated tracheobronchitis.

From Palmer LB. Aerosolized antibiotics in the intensive care unit. Clin Chest Med 2011;32:559–74; with permission.



**Table 9**  
**Toxicity related to aerosolized antibiotics**

Drug	Adverse Effects
Aminoglycosides	Bronchial constriction, renal toxicity, <sup>a</sup> tinnitus, vestibular toxicity, hoarseness
Colistin	Nephrotoxicity, <sup>b</sup> bronchospasm, <sup>b</sup> neurologic toxicity
Aztreonam lysine	Cough, bronchoconstriction
Vancomycin	Not well described
Cefotaxime/ceftazidime	Not well described

<sup>a</sup> Renal toxicity rarely seen with tobramycin (Tobi, RARI Pharma GmbH, Weilheim, Germany).

<sup>b</sup> Nephrotoxicity and bronchospasm more severe than with aminoglycosides.

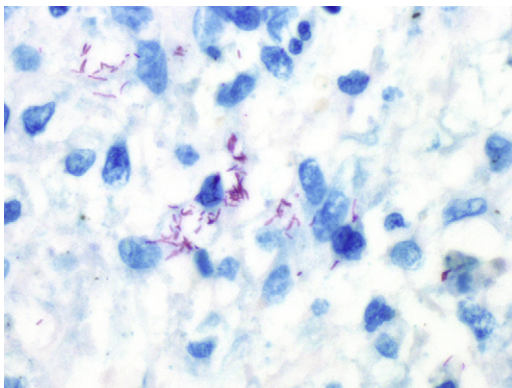
From Palmer LB. Aerosolized antibiotics in the intensive care unit. Clin Chest Med 2011;32:559–74; with permission.

(4) less effective second-line antituberculous drugs, such as ethionamide or cycloserine; and (5) second-line agents for which few data are available: linezolid, clarithromycin, amoxicillin-clavulanate, or clofazamine.<sup>83</sup>

Treatment of pulmonary NTM is less well defined. Although the principles of management are similar to those for *M tuberculosis*, antibiotic regimens vary by species.<sup>68</sup> For *M avium* complex, ATS/IDSA guidelines recommend a combination of clarithromycin, rifampicin, and ethambutol, whereas for *M kansasii*, the initial regimen comprises isoniazid, rifampicin, and ethambutol.<sup>72</sup> For localized pulmonary *M abscessus* infection, medical management alone is not effective and surgical resection is required.

### Hemoptysis

Tuberculosis remains the most common cause of hemoptysis worldwide; however, in the United States, invasive fungal infections, chronic



**Fig. 16.** Histiocytic exudate with many mycobacteria (red) in this mycobacterial pneumonia. The relatively large number of organisms seen here and the loose appearance of the histiocytes together suggests an immunocompromised host. Fite mycobacterial stain, original magnification,  $\times 600$ .

granulomatous disease, bronchiectasis, and bronchitis account for most cases.<sup>84,85</sup> Conservative management can often control bleeding. The current recommended strategy for hemoptysis is initial nonoperative management and stabilization, with surgery reserved for isolated cases.<sup>86–88</sup> For a patient presenting with massive hemoptysis, the immediate goals of the surgeon are to preserve life through protecting the healthy lung from aspiration, to stabilize the patient hemodynamically, and to correct any coagulopathy.<sup>85</sup> Bronchoscopy can often be effective if bleeding is mild.<sup>89</sup>

More than 80% of patients can be treated successfully with bronchoscopic localization.<sup>84,89</sup> The bleeding site can be controlled with balloon tamponade, laser ablation, and local vasopressor therapy. The decision to intervene angiographically should be made based on the clinical examination, imaging results, bronchoscopic findings, and physician expertise. Transcatheter arterial embolization is successful in most patients.<sup>84,85,90–94</sup> Although bronchial embolization is the mainstay of treatment, emergency surgery can be considered if initial attempts to control bleeding and stabilize the patient prove unsuccessful. The decision to take the patient to the operating room requires at a minimum known laterality of the lesion and, optimally, lobar location (**Fig. 17**).<sup>85</sup>

### INVASIVE FUNGAL PULMONARY INFECTION

With the rapid increase in bone marrow and solid organ transplantation, invasive fungal infection has become a significant cause of morbidity and mortality. Although nearly 100 fungi have been recovered from respiratory infections,<sup>95</sup> only a small number are consistently implicated as pathogenic (**Box 4**). Broadly, fungal pathogens that infect the lung include yeasts such as *Candida* spp and *Cryptococcus*; endemic dimorphic fungi such as *Histoplasma* and *Coccidioides*; filamentous molds, of which *Aspergillus* is most

## Management of Hemoptysis

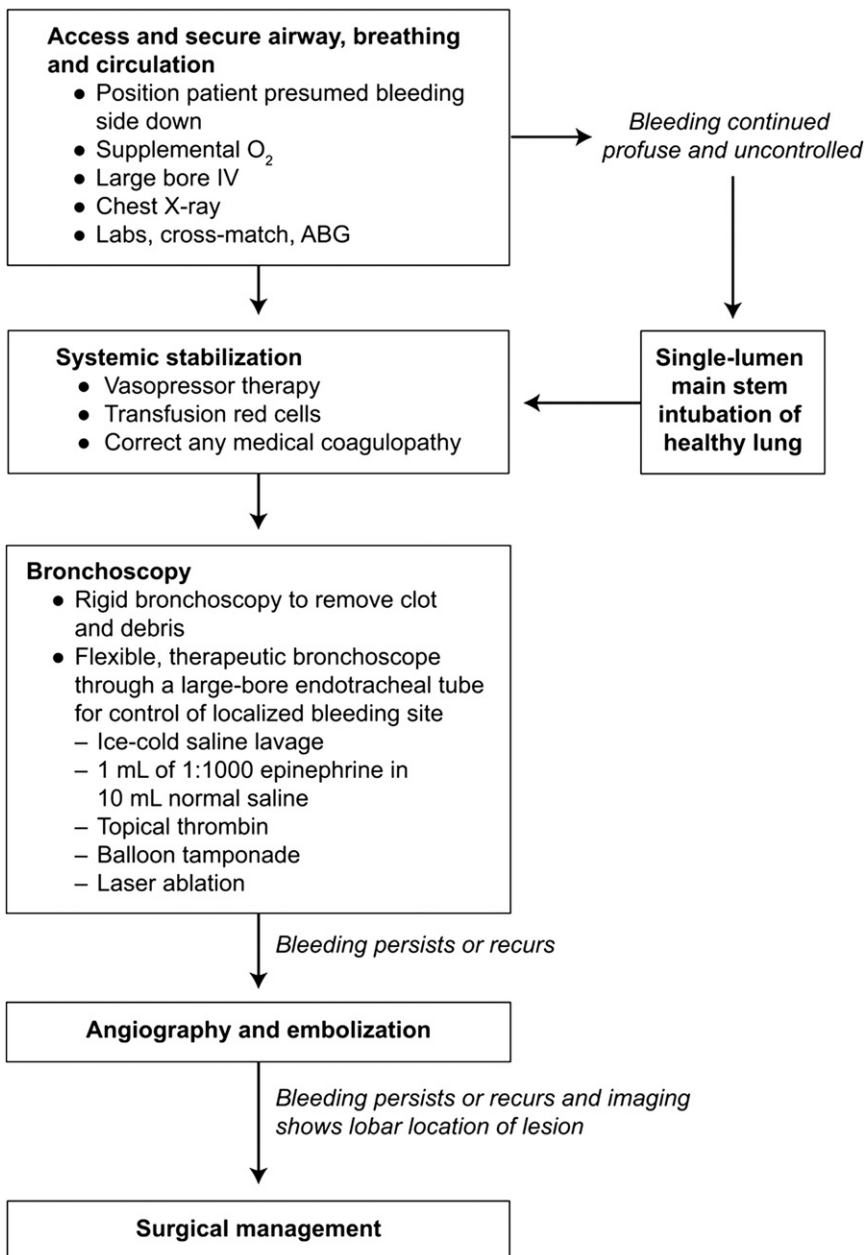


Fig. 17. Algorithm for management of hemoptysis. BG, arterial blood gas.

common; and members of the family Mucorales. The most effective method of diagnosis is often identification of fungi in tissue sections or cytologic samples (Fig. 18).<sup>31,96,97</sup>

The patient may present with a wide spectrum of radiographic pulmonary disease. In the healthy host, fungal pathogens typically produce one or more nodular lesions (Fig. 19), which, in turn,

may become cavitory as the lesions evolve (Fig. 20). However, clinical presentation may vary widely and may include solitary or multiple and bilateral nodular lesions; segmental or lobar consolidation; cavitory lesions, fistulas, infarcts; direct extension into mediastinal, thoracic soft tissue, chest wall, and diaphragm; chronic tracheal and endobronchial infection; and fungus

**Box 4****Common fungal pathogens in the lung**

Dimorphic fungi (mycelia at 25°C–30°C; yeast at 37°C)

*Blastomyces dermatitidis*

*Coccidioides immitis*

*Histoplasma capsulatum*

*Paracoccidioides braziliensis*

*Sporothrix schenckii*

*Penicillium marneffeii*

## Yeasts

*Cryptococcus neoformans*

*Candida* spp

## Hyaline (nonpigmented) molds

*Aspergillus* spp

Zygomycetes organisms

## Phaeoid (pigmented; dematiaceous) molds

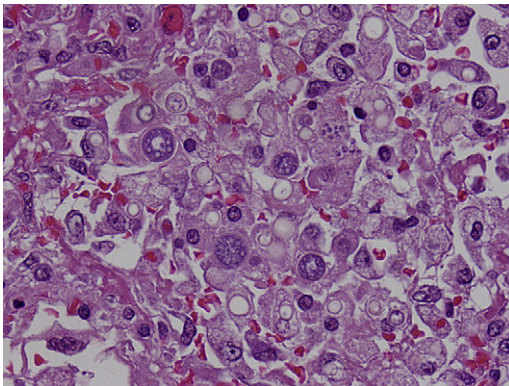
*Bipolaris* spp, *Alternaria*, *Curvularia*

*Pseudoallescheria boydii*/*Scedosporium apiospermum*

## Miscellaneous pathogens

*Pneumocystis jirovecii*

Data from Rosati LA, Leslie KO. Lung infections. In: Leslie KO, Wick MR, editors. Practical pulmonary pathology: a diagnostic approach. Philadelphia: Elsevier/Saunders; 2011.



**Fig. 18.** Disseminated coccidioidomycosis with confluent spherules of *Coccidioides immitis*. Each spherule has a thick refractile wall and contains numerous tiny endospores. Spherules enlarge and eventually burst, so many sizes are present typically, some of which may be ruptured and empty. Hematoxylin and eosin stain, original magnification,  $\times 200$ .



**Fig. 19.** CT scan shows multiple nodules in patient's lung subsequently shown to be infection with *Coccidioidomycosis*.

ball such as aspergilloma.<sup>98</sup> Proximal endobronchial disease mimicking a neoplasm has also been described for various fungal species.<sup>99</sup>

### **Treatment of Fungal Infection**

Until recently, effective treatment options for invasive fungal infection were largely limited to amphotericin B deoxycholate, which is well known for its potential for systemic toxicity. However, the development of lipid, liposomal, and aerosolized formulations of amphotericin B, and newer triazole and echinocandin antifungal agents, has greatly expanded treatment options for these diseases. Because of differences in antifungal susceptibility and prognosis between dimorphic endemic fungi, filamentous fungi, and other molds (eg, *Mucor*), a definitive microbiologic or pathologic diagnosis is strongly preferred before treatment.

For invasive *Aspergillus* infection, a large randomized controlled trial showed the superiority of voriconazole over amphotericin B,<sup>100</sup> and now voriconazole is recommended as the primary



**Fig. 20.** CT scan shows invasive *Aspergilloma* fungal ball in the left lower lobe.

treatment of invasive pulmonary aspergillosis in most patients.<sup>101</sup> Limited data suggest that in certain populations, such as heart transplant recipients, voriconazole in combination therapy with caspofungin may contribute to improved outcomes; additional data are anticipated.<sup>102,103</sup> In lung transplant recipients, aerosolized amphotericin B has been used for antifungal prophylaxis and as adjunct therapy in invasive fungal disease.<sup>104</sup>

In pulmonary mucormycosis, however, voriconazole is ineffective. The preferred treatment remains amphotericin B, although some data suggest that liposomal amphotericin B may be more efficacious than the deoxycholate formulation.<sup>105</sup> A novel triazole, posaconazole, has also been approved for salvage therapy, but it is limited by its availability in oral formulation only and its inconsistent bioavailability.<sup>105</sup> Limited evidence also suggests improved outcomes with a combination therapy of amphotericin B and posaconazole or an echinocandin.<sup>105</sup> When empiric therapy is required in critically ill patients in whom hemodynamic instability or cytopenia may prevent invasive diagnostic procedures, the logical approach is combination therapy with voriconazole and amphotericin B.

## VIRAL PNEUMONIA

Viruses cause more infections in the respiratory tract than all other types of microorganisms combined.<sup>106</sup> The viruses that commonly infect the lung are presented in **Box 5**. The common

### Box 5

#### Viruses linked to CAP in children and adults

- Respiratory syncytial virus
- Rhinovirus
- Influenza A, B, and C viruses
- Human metapneumovirus
- Parainfluenza viruses types 1, 2, 3, and 4
- Human bocavirus<sup>a</sup>
- Coronavirus types 229E, OC43, NL63, HKU1, SARS
- Adenovirus
- Enteroviruses
- Varicella-zoster virus
- Hantavirus
- Parechoviruses
- Epstein-Barr virus
- Human herpesvirus 6 and 7
- Herpes simplex virus
- Mimivirus
- Cytomegalovirus<sup>b</sup>
- Measles<sup>b</sup>

<sup>a</sup> Mostly in children.

<sup>b</sup> Mostly in developing countries.

Data from Ruuskanen O, Lahti E, Jennings LC, et al. Viral pneumonia. *Lancet* 2011;377:1264–75.

**Table 10**

#### Possibilities for antiviral treatment and prevention of severe viral pneumonia

	Treatment	Prevention
Influenza A and B viruses	Oseltamivir (oral); zanamivir (inhalation, intravenous); peramivir (intravenous)	Vaccines (inactivated, live); oseltamivir; zanamivir
Influenza A virus	Amantadine (oral); rimantadine (oral)	Vaccines (inactivated, live); oseltamivir; zanamivir
Respiratory syncytial virus	Ribavirin (inhalation, intravenous)	Palivizumab (intramuscular)
Adenovirus	Cidofovir (intravenous)	Vaccine for types 4 and 7 <sup>a</sup>
Rhinovirus	Pleconaril <sup>b</sup>	Alfa interferon (intranasal)
Enteroviruses	Pleconaril <sup>b</sup>	Alfa interferon (intranasal)
Human metapneumovirus	Ribavirin (intravenous)	Alfa interferon (intranasal)
Hantavirus	Ribavirin (intravenous)	Alfa interferon (intranasal)
Varicella-zoster virus	Acyclovir (intravenous)	Vaccine

<sup>a</sup> Long successful use in U.S. military conscripts, no production now.

<sup>b</sup> Has been used for compassionate cases.

Data from Ruuskanen O, Lahti E, Jennings LC, et al. Viral pneumonia. *Lancet* 2011;377:1264–75.

respiratory viruses (eg, influenza, parainfluenza, respiratory syncytial virus, adenovirus) cause outbreaks of respiratory illness in the general population each year. Fortunately, most viral respiratory infections are mild and self-limited. However, viruses are also capable of producing serious or life-threatening infections, such as in the case of primary varicella-zoster pneumonia<sup>107</sup> or respiratory disease caused by highly pathogenic strains of influenza.<sup>108,109</sup> In addition, viral-mediated bronchial epithelial damage predisposes susceptible patients to secondary bacterial infection, which is associated with significant morbidity and mortality.<sup>110</sup> Recent outbreaks of the H1N1 strain of influenza A have served to highlight the increased risk of mortality associated with influenza complicated by secondary bacterial infection, especially with *S aureus*.<sup>111,112</sup>

In immunocompromised hosts, less common viral agents may cause severe clinical disease. In these patients, diagnosis may be made through respiratory cytologic specimens, from which herpes simplex, *Cytomegalovirus*, and adenovirus are the most commonly identified viral pathogens.<sup>113</sup> The cytologic features of viral infections in the respiratory tract are most likely to be found in exfoliative specimens, such as bronchial washings and bronchoalveolar lavage.<sup>114,115</sup>

### **Treatment of Viral Pulmonary Infection**

In most respiratory infection caused by viruses, no treatment is necessary. No consensus exists on prophylactic antibiotic treatment of influenza-like illness. However, when secondary bacterial pneumonia is suspected, antibacterial agents targeting the most common causative pathogens (*S pneumoniae* and *S aureus*, including MRSA) should be initiated. Treatment options for primary viral respiratory tract infections are limited. For influenza A, early treatment with oseltamivir or zanamivir within 48 hours of the onset of symptoms has been shown to decrease complications, especially in the very young, elderly individuals, and patients with impaired immune status or comorbid conditions. **Table 10<sup>116</sup>** summarizes the possible for antiviral treatments for prevention of severe viral pneumonia.

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