

## 2005 IDSA/ATS HOSPITAL-ACQUIRED PNEUMONIA GUIDELINES: NEW PRINCIPLES FOR IMPROVING MANAGEMENT\*

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### ABSTRACT

The recently updated guidelines on hospital-acquired pneumonia from the Infectious Diseases Society of America, in conjunction with the American Thoracic Society, have several important changes: a focus on multidrug-resistant pathogens, which includes patients with health-care-associated pneumonia; prevention focused on “modifiable risk factors”; and identification of management principles, which include early, appropriate, and adequate initial therapy, coupled with de-escalation based on clinical response and culture data and shortened duration of treatment. These evidence-based guidelines provide a scientific framework for better patient outcomes.

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### THE CURRENT CONCEPT OF PNEUMONIA

Our current conception of pneumonia classifies this disease as community-acquired pneumonia (CAP), healthcare-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP), as shown in Figure 1. Patients at risk for HCAP due to multidrug-resistant (MDR) pathogens may have been previously hospitalized, had recent treatment with antibiotics, received care in a nursing home, require dialysis, or are immunosuppressed. Note that the risk of pneumonia due to an MDR pathogen, in addition to morbidity and mortality rates, increase as one moves from CAP to HCAP and HAP/VAP.

### DIAGNOSING VENTILATOR-ASSOCIATED PNEUMONIA

The timely diagnosis of VAP and identification of the responsible pathogen are essential for optimizing patient outcomes. Most hospitals in the United States use a regular endotracheal aspirate as the pathogen source for VAP diagnosis. Conversely, some European countries use more quantitative measures for the diagnosis of VAP, such as bronchoalveolar or nonbronchoscopic (“blind”) bronchoalveolar lavage (BAL) with and without protected specimen brush (PSB). Figure 2 shows the different possible sources of microbial flora when attempting to obtain a sputum culture from intubated versus nonintubated patients with pneumonia.<sup>1</sup> In the nonintubated patient, sputum is coughed up through the trachea into the oral pharynx, which has high levels of bacteria. In the presence of an endotracheal tube, secretions with bacteria pool above the cuff and leak around the tube causing tracheal colo-

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nization, which increases the risk of VAP. Distal sputum samples from the lower airway have greater diagnostic specificity than semiquantitative sputum samples obtained by endotracheal aspiration.

Pneumonia diagnosed using quantitative samples obtained by bronchoscopy with BAL ( $10^4$  organisms/mL) or PSB ( $10^3$  organisms/mL) provide greater diagnostic sensitivity than semiquantitative endotracheal aspirates. In a large, randomized, controlled study in 33 intensive care units in France, patients with VAP diagnosed by bronchoscopy and quantitative cultures had significantly lower 14-day mortality, decreased multiple organ failure rates, and more antibiotic-free days than patients who were treated according to clinical, noninvasive management (Figure 3).<sup>2</sup> Quantitative techniques (eg, BAL and PSB) have some limitations, including use in those patients who have received antibiotic therapy within the previous 24 to 48 hours, poor BAL technique (which may produce false-negative results), and for accurate diagnosis in patients with pneumonia caused by anaerobes, *Legionella*, cytomegalovirus, *Pneumocystis carinii* (now referred to as *Pneumocystis jirovecii*), or fungi.

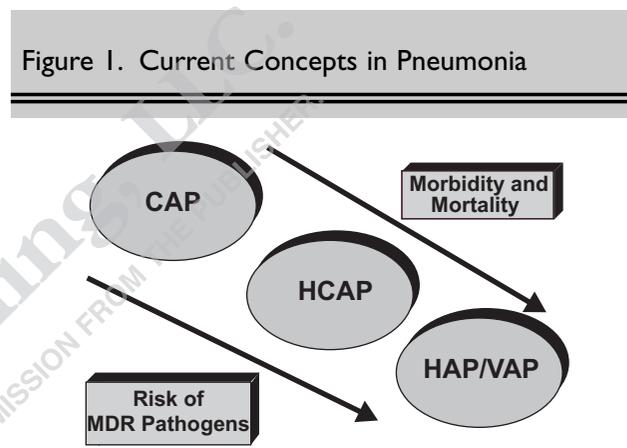
Gram stains of endotracheal aspirates or BAL cytopspins also may be important for diagnosing VAP and for helping to select an appropriate initial empiric antibiotic regimen.<sup>2,4</sup> Current guidelines recommend that the Gram stain should be used to help direct initial empiric antimicrobial therapy.<sup>3</sup> A positive Gram stain of sputum correlates with approximately  $10^5$  organisms per milliliter. The presence of inflammatory cells and macrophages on the Gram stain is also important and informative.

### INITIAL ANTIBIOTIC THERAPY

Current recommendations for initial antibiotic treatment of pneumonia differ from previous versions of the guidelines. As shown in Figure 4, suspicion of HAP, VAP, or HCAP should prompt blood and sputum cultures for microbiology and patient assessment for MDR risk factors (ie, prior antibiotic use or hospitalization in the previous 90 days, chronic or nursing home care, dialysis, presence of immunosuppressive disease or therapy, and late-onset HAP).<sup>3</sup> Patients without MDR risk factors should receive limited-spectrum antibiotics, similar to those used for CAP. However, most patients will require broad-spectrum therapies (eg, third- or fourth-generation

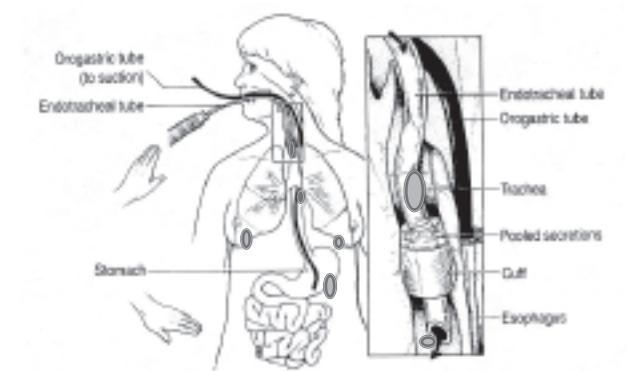
cephalosporin, a carbapenem, and a beta-lactam/beta-lactamase inhibitor, in addition to a quinolone or an aminoglycoside). If methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected, initial coverage with vancomycin or linezolid is recommended.<sup>3</sup>

The guidelines also discuss several studies that measure the effect of appropriate initial antibiotic therapy on mortality in patients with pneumonia. As shown in Figure 5, all of these studies showed improved mortality rates with appropriate versus inap-



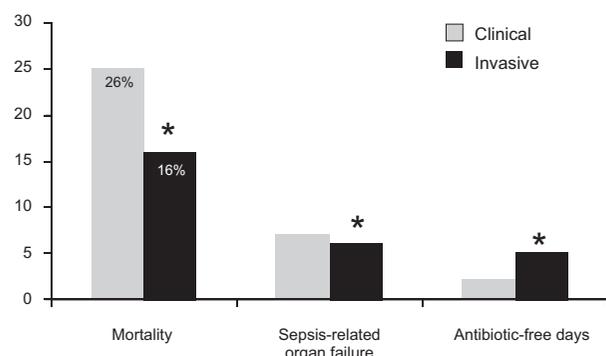
CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; MDR = multidrug-resistant; VAP = ventilator-associated pneumonia.

Figure 2. Diagnosis of VAP: Effect of the Endotracheal Tube on Culture Source



VAP = ventilator-associated pneumonia. Reprinted with permission from Craven and Steger. *Semin Respir Infect*. 1996;11:32-53.

**Figure 3. Improved Outcomes with Invasive Diagnosis of VAP**



This was a multicenter, randomized, uncontrolled trial of 413 patients suspected of having ventilator-associated pneumonia. The invasive management strategy was based on direct examination of bronchoscopic protected specimen brush samples or bronchoalveolar lavage samples and their quantitative cultures. The noninvasive (“clinical”) management strategy was based on clinical criteria, isolation of micro-organisms by nonquantitative analysis of endotracheal aspirates, and clinical practice guidelines. \**P* < .05.

VAP = ventilator-associated pneumonia.

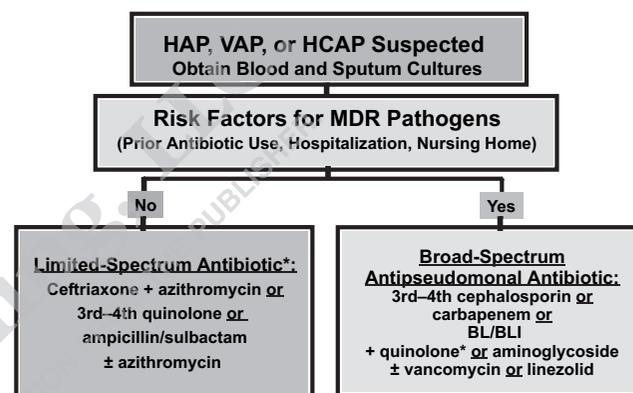
Reprinted with permission from Fagon et al. *Ann Intern Med.* 2000;132:621-630.<sup>2</sup>

appropriate therapy, although only 2 were statistically significant.<sup>3,5-11</sup> One of these studies examined the role of delayed, initial antibiotic therapy. Of 107 VAP patients, 31% had appropriate therapy delayed more than 24 hours, either due to delay in administering the antibiotic or the intrinsic resistance of the pathogen to the antibiotic that was administered. The odds ratio for mortality due to delayed appropriate therapy was greater (odds ratio [OR], 7.68; 95% confidence interval [CI], 4.50–13.09; *P* < .001) than for increasing APACHE II scores (OR, 1.13; 95% CI, 1.09–1.18; *P* < .001) or the presence of malignancy (OR, 3.20; 95% CI, 1.79–5.71; *P* = .044).<sup>12</sup>

Appropriate therapy is defined in part as that therapy to which the targeted disease-causing organism is sensitive; adequate therapy refers to an appropriate dose of antibiotic. The criteria for determining appropriate therapy will depend on the pathogens in each institution. Pathogens may also differ between the medical and surgical intensive care units within an institution. Thus, clinicians should be aware of the MDR pathogens in their community. Specific antibiotic initial recommendations are outlined in Table 1, and new increased doses of antibiotics are summarized

in Table 2.<sup>3</sup> For example, as shown in Table 1, if pneumonia due to a gram-negative bacillus (eg, *Pseudomonas aeruginosa*) was suspected, initial therapy would include a third- or fourth-generation cephalosporin (eg, cefepime) plus an aminoglycoside (eg, gentamicin) or a fluoroquinolone (eg, lev-

**Figure 4. Empiric Antibiotic Therapy: IDSA/ATS Guidelines**

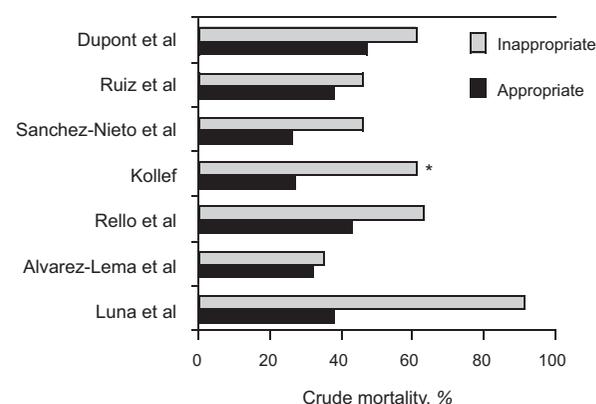


\*3rd or 4th generation only.

ATS = American Thoracic Society; BL = beta-lactam; BLI = beta-lactamase inhibitor; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; IDSA = Infectious Diseases Society of America; MDR = multidrug-resistant; VAP = ventilator-associated pneumonia.

Adapted with permission from American Thoracic Society, Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2005;171:388-416.<sup>3</sup>

**Figure 5. Appropriate Antibiotic Therapy Improves Mortality Rate**



\**P* < .05.

Data from American Thoracic Society, Infectious Diseases Society of America<sup>3</sup>; Dupont et al<sup>5</sup>; Ruiz et al<sup>6</sup>; Sanchez-Nieto et al<sup>7</sup>; Kollef<sup>8</sup>; Rello et al<sup>9</sup>; Alvarez-Lerma et al<sup>10</sup>; Luna et al.<sup>11</sup>

ofloxacin).<sup>3</sup> If there was evidence or suspicion of MRSA, additional coverage would be needed until culture results were available (eg, vancomycin or linezolid). In intensive care units with extended-spectrum beta-lactamase plus *Klebsiella pneumoniae* or *Acinetobacter*, imipenem or meropenem should be used for initial therapy, until the identification and sensitivity of the pathogen is known. If there is suspicion of *Legionella pneumophila*, a macrolide (eg, azithromycin) or a fluoroquinolone (eg, ciprofloxacin) should be included in the initial regimen. Thus, the initial therapy should be broad enough to provide coverage against the offending pathogen until more information is known.<sup>3</sup>

**HOSPITAL-ACQUIRED PNEUMONIA THERAPY CONTROVERSIES**

One of the remaining questions with HAP therapy is whether a second drug should be used to treat HAP or VAP due to *P aeruginosa*. The guidelines do not recommend combination therapy, based on a study comparing imipenem monotherapy to combination therapy with imipenem and netilmicin for nosocomial pneumonia, nosocomial sepsis, and severe diffuse peritonitis (*n* = 280).<sup>3,13</sup> Rather, the current recommendation is for a maximum of 5 days of aminoglycoside therapy; if the organism's sensitivity is unknown, combination therapy can be used until the sensitivity is determined.

A second common question is whether linezolid or vancomycin is preferred for VAP due to MRSA. Data from Wunderink et al suggest that mortality rates with vancomycin treatment are higher (Figure 6); however, the study has several limitations, including small numbers of patients and suboptimal dosing (although linezolid concentrations in the epithelial lining fluid are higher than with vancomycin).<sup>14</sup> A randomized trial currently under way is comparing higher doses of vancomycin to linezolid, which should help clarify this issue. (Please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov), identifier NCT00084266, for more information.) If vancomycin is used for MRSA-VAP, one should monitor the patients for nonresponse. If the sputum remains positive for MRSA, the initial vancomycin therapy may be inadequate. Other antibiotics to consider would be trimethoprim-sulfamethoxazole or rifampin, or switching the patient to linezolid. Daptomycin is contraindicated for treating HAP or VAP because it binds to lung surfactant.

**Table 1. Initial Empiric Therapy for HAP,VAP, and HCAP in Patients with Late-Onset Disease or Risk Factors for MDR Pathogens and All Disease Severity**

Potential Pathogens	Combination Antibiotic Therapy
<i>Pseudomonas aeruginosa</i>	Antipseudomonal third- or fourth-generation cephalosporin
	OR
	Carbapenem
<i>Acinetobacter</i>	OR
	Piperacillin-tazobactam ± aminoglycoside or antipseudomonal quinolone
ESBL + <i>Klebsiella</i>	Carbapenem ± aminoglycoside
MRSA	Linezolid or vancomycin

ESBL = extended-spectrum beta-lactamase; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; MDR = multidrug-resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia. Adapted with permission from American Thoracic Society, Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2005;171:388-416.<sup>3</sup>

**Table 2. Initial Intravenous, Adult Doses of Antibiotics for Empiric Therapy of HAP, Including VAP and HCAP in Patients with Late-Onset Disease or Risk Factors for MDR Pathogens**

Pathogen	New Antibiotic Dosage*
Antipseudomonal cephalosporin	
Cefepime	2 g every 12 hours
Ceftazidime	2 g every 8 hours
Carbapenems	
Imipenem	500 mg every 6 hours or 1 g every 8 hours
Meropenem	1 g every 8 hours
β-lactam/β-lactamase inhibitor	
Piperacillin-tazobactam	4.5 g every 6 hours
Aminoglycosides	
Gentamicin	7 mg/kg per day†
Tobramycin	7 mg/kg per day†
Amikacin	20 mg/kg per day‡
Antipseudomonal quinolones	
Levofloxacin	750 mg every day
Ciprofloxacin	400 mg every 8 hours
Vancomycin	15 mg/kg every 12 hours‡
Linezolid	600 mg every 12 hours

\*Dosages are based on normal renal and hepatic function.  
 †Trough levels for gentamicin and tobramycin should be less than 1 µg/mL, and for amikacin they should be less than 4 to 5 µg/mL.  
 ‡Trough levels for vancomycin should be 15 to 20 µg/mL.  
 HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; MDR = multidrug-resistant; VAP = ventilator-associated pneumonia. Reprinted with permission from American Thoracic Society, Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2005;171:388-416.<sup>3</sup>

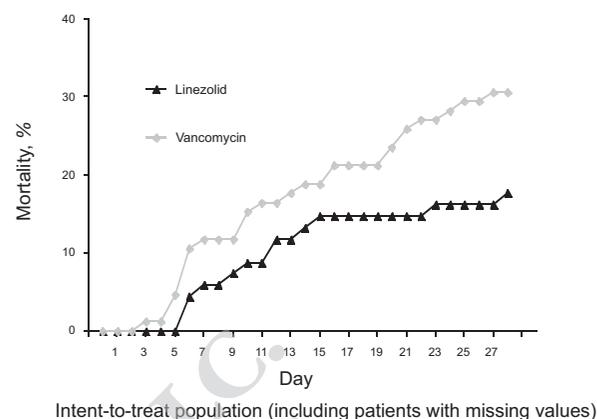
### DE-ESCALATION OF THERAPY

Although initial empiric antibiotic therapy is stage 1 of the treatment protocol, de-escalation is stage 2 (Figure 7).<sup>3</sup> Once treatment is initiated, the clinician needs to monitor cultures and the patient's clinical response, white blood cell count, and chest X-ray changes. If clinical improvement occurs in the setting of positive cultures, initial antibiotic therapy can be de-escalated to target the organism(s) isolated, and total treatment duration should be limited to 7 to 8 days (in responders). Once antibiotics are discontinued, the patient should be carefully followed for relapse, especially if the HAP or VAP was caused by *P aeruginosa*.<sup>3</sup> For example, if a patient starts treatment with cefepime, gentamicin, and vancomycin for suspected VAP, and improves and is extubated within 48 hours, with cultures that have only *K pneumoniae*, pan-sensitive to multiple antibiotics, the initial cefepime, gentamicin, and vancomycin coverage can be discontinued. Ceftriaxone (once daily, intravenously [IV]) or levofloxacin (orally or IV) can then be prescribed for 5 additional days.

The recommendation for limiting therapy to 7 to 8 days is based on several studies showing that shorter treatment courses are as effective as longer courses. For example, Chastre et al compared 8-day and 15-day antibiotic regimens in 401 patients with VAP in 51 intensive care units.<sup>15</sup> Both regimens were clinically effective against VAP among patients who had received appropriate initial empirical therapy (Figure 8). However, the 8-day treatment group had fewer MDR pathogens and a lower recurrence with these organisms, but higher rates of *P aeruginosa*, which was not statistically significant.<sup>15</sup> Therefore, the guidelines recommend increased monitoring (and perhaps longer treatment duration) for patients with *P aeruginosa* VAP.<sup>3</sup>

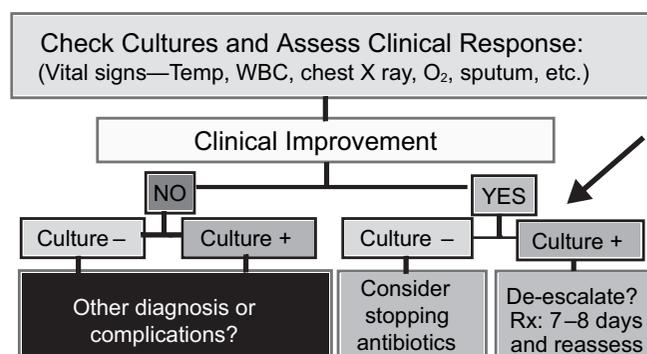
Overall, the guidelines recommend liberal initial therapy with more conservative approaches over the long term. Early, appropriate, and adequate therapy, including combination therapy based on MDR risk factors and local epidemiology, is associated with better outcomes. De-escalation should begin after 48 hours of treatment, at which time clinicians should consider streamlining the antibiotic regimen, switching to oral treatments, and limiting the duration of therapy, all while continually reassessing all patients with pneumonia.<sup>3</sup> Table 3 summarizes the HAP recommendations, and the Sidebar presents a brief example of how to implement de-escalation.<sup>3</sup>

Figure 6. Mortality Rates in Patients with MRSA-VAP



In this retrospective study, 1019 patients with suspected gram-positive nosocomial pneumonia, including 339 patients with documented *Staphylococcus aureus* pneumonia (*S aureus* subset) and 160 patients with documented MRSA pneumonia (MRSA subset), received linezolid 600 mg or vancomycin 1 g every 12 hours for 7 to 21 days, each with aztreonam. The results showed that initial therapy with linezolid was associated with significantly better survival and clinical cure rates than was vancomycin in patients with nosocomial pneumonia due to MRSA. MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia. Reprinted with permission from Wunderink et al. *Chest*. 2003;124:1789-1797.<sup>14</sup>

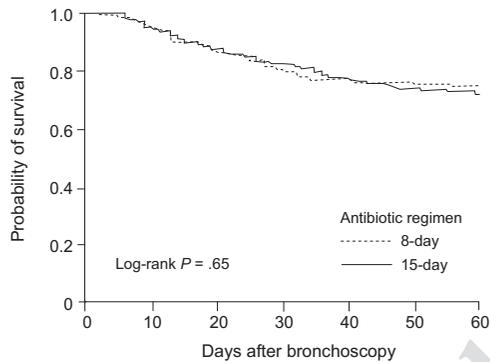
Figure 7. Stage 2: De-Escalation



Temp = temperature; WBC = white blood cells. Adapted with permission from American Thoracic Society, Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2005;171:388-416.<sup>3</sup>

If the patient is not responding to the initial antibiotic regimen, the guidelines recommend stopping the antibiotic (Figure 7).<sup>3</sup> Lack of response indicates an incorrect diagnosis of organism, an incorrect antibiotic choice, an incorrect clinical diagnosis (eg, missing tuberculosis), or a complication (eg, empyema and lung abscess).<sup>3</sup>

**Figure 8. Outcomes Based on Duration of VAP Therapy**



	No. at risk						
8-day antibiotic regimen	197	187	172	158	151	148	147
15-day antibiotic regimen	204	194	179	167	157	151	147

A total of 197 patients were randomly assigned to receive 8 days and 204 to receive 15 days of therapy with an antibiotic regimen selected by the treating physician. The results showed comparable clinical effectiveness against VAP was obtained with the 8- and 15-day treatment regimens among patients who had received appropriate initial empirical therapy (with the possible exception of those developing nonfermenting gram-negative bacillus infections). VAP = ventilator-associated pneumonia. Reprinted with permission from Chastre et al. *JAMA* 2003;290:2588-2598.<sup>15</sup>

**Table 3. Summary of HAP Recommendations**

Liberal Initial Therapy	Conservative Long-term Therapy
<ul style="list-style-type: none"> <li>• Early, appropriate, and adequate antibiotic therapy</li> <li>• Combinations: MDR risk factors, local antibiotic resistance</li> </ul>	<ul style="list-style-type: none"> <li>• De-escalate at 48 hours</li> <li>• Streamline and switch to orally administered antibiotic</li> <li>• Limit duration to 7–8 days</li> <li>• Reassess patient</li> </ul>

Prevention is preferable to cure. HAP = hospital-acquired pneumonia; MDR = multidrug-resistant. Data from American Thoracic Society, Infectious Diseases Society of America.<sup>3</sup>

**CONCLUSIONS**

The cardinal management principles in the recently updated guidelines are to: use early, appropriate, and adequate initial antibiotic therapy based on an assessment of the patient’s MDR risk factors and local resistance patterns; assess the response to initial therapy and de-escalate initial antibiotic therapy when appropriate;

**Sidebar. Case Study: Implementing De-Escalation**

A patient with ventilator-associated pneumonia (VAP) due to methicillin-resistant *Staphylococcus aureus* (MRSA) was treated for 7 days with vancomycin and is clinically stable. The endotracheal aspirate taken on day 6 was positive for MRSA. Should you:

- A) Continue therapy for 5 to 7 more days
- B) Stop therapy and follow
- C) Switch and add an additional antibiotic?

**Discussion**

If a patient is clinically stable and has a positive sputum culture for MRSA, the physician should stop therapy and follow the patient. The patient is stable and has no signs or symptoms of VAP. Therefore, the MRSA cultures represent colonization and not VAP. The principle is to treat diseases and not colonization.

**CASE STUDY**

**A 77-YEAR-OLD NURSING HOME RESIDENT**

**CASE HISTORY**

*PART I*

Mr. L is a 77-year-old nursing home resident who presents to the emergency department for evaluation of a fever and persistent, nonproductive cough.

His medical history includes diabetes mellitus, hypertension, and stroke. He also has had urinary tract infections, which were treated with levofloxacin.

His vital signs are:

Blood pressure	115/60 mm Hg
Resting heart rate	120 beats per minute
Respiratory rate	26 breaths per minute
Temperature	100°F
Weight	80 kg (176 lb)

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The patient's oxygen saturation is 90% on room air, and his white blood cell count is 20 000 cells/mm<sup>3</sup>, with 85% polymorphonuclear monocytes.

Mr. L was treated with 500 mg of levofloxacin in the emergency department. He was admitted with the diagnosis of community-acquired pneumonia (CAP), which was thought to be most likely due to *Pneumococcus*.

#### Discussion

Mr. L had all the signs and symptoms of pneumonia, but the diagnosis of CAP was not correct. Coming from a nursing home, he would be better categorized as having healthcare-associated pneumonia (HCAP). He certainly had multiple risk factors for infection with a multidrug-resistant (MDR) pathogen, and he had received prior levofloxacin treatment. For these reasons, levofloxacin would not be the best choice for initial therapy of HCAP. Instead, initial antibiotic therapy should have included gram-negative coverage for *Pseudomonas aeruginosa* (eg, cefepime + gentamicin) and possibly coverage with vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA).

#### PART II

Mr. L did poorly with the levofloxacin treatment on the medical floor and ultimately progressed. He was admitted to the intensive care unit (ICU) and intubated (ie, he was a nonresponder). He was started on broader antibiotic coverage with imipenem and gentamicin due to lack of response to the levofloxacin. Sputum was obtained during intubation and the Gram stain demonstrated polymorphonuclear leukocytes, many gram-negative rods, and gram-positive cocci. The

sputum culture subsequently grew MRSA and *P aeruginosa* resistant to gentamicin and levofloxacin. Blood cultures were also positive for *P aeruginosa*. Although vancomycin (600 mg intravenously twice daily) was started later, when cultures were available, the initial broad-spectrum antibiotic therapy did not include vancomycin initially (ie, inappropriate therapy for MRSA), and when it was started, the vancomycin dose was not calculated by the patient's weight (ie, inadequate therapy). The patient died and a clinical postmortem was performed.

#### Discussion

Mr. L had diabetes and hypertension (and thus increased risk of infections or poor response to infection) and history of stroke (which increases the risk of aspiration). All of his vital signs and laboratory changes were consistent with pneumonia. However, the CAP diagnosis was most likely incorrect. This case should prompt the consideration of HCAP, possibly due to *Pneumococcus*, but other pathogens need to be considered. Also, nursing home patients, especially those who have been treated with prior antibiotics, are more likely to be colonized with MDR pathogens, which may require broader-spectrum initial therapy. Mr. L did not respond to the levofloxacin and subsequently needed additional coverage in the ICU with imipenem and gentamicin, which was appropriate for the *P aeruginosa* that was isolated. However, gram-positive cocci in clusters suggestive of MRSA were also present on the Gram stain, which were not covered by imipenem and gentamicin (ie, inappropriate therapy). When vancomycin was started, the dose was inadequate; linezolid could have been prescribed. All of these factors may have contributed to his poor outcome.

and limit the duration of antibiotic treatment in responders to 7 to 8 days and reassess. Although the guidelines provide a scientific framework for infectious diseases specialists, the clinician must ultimately rely on clinical skill to make appropriate treatment decisions.

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