Case Studies of Lower Respiratory Tract Infections: Community-Acquired Pneumonia

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ABSTRACT

Community-acquired pneumonia (CAP) is a common and potentially serious illness with significant human and economic costs to society. The recent collaborative statement from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) represents the most up-to-date evidence-based guidelines from North America, incorporating important advances in the management of patients with CAP. The cases presented in this review highlight many of the recent recommendations from the IDSA/ATS guidelines.

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KEYWORDS: Community-acquired infection; Fluoroquinolone; Methicillin-resistant Staphylococcus aureus; Respiratory disorders; Tuberculosis

Community-acquired pneumonia (CAP) is a common and potentially serious illness, particularly in elderly patients and those with significant comorbidities. In the United States, CAP is the most frequent cause of death due to infectious disease and is the eighth leading cause of death overall. The mortality rate of patients treated on an outpatient basis is <1%; the rate for those who require admission to the hospital averages 12%, but it approaches 40% for patients with severe CAP who require admission to the intensive care unit (ICU). The annual estimated incidence of CAP requiring hospitalization is 267 individuals per 100,000 population and 1,014 individuals ≥65 years of age. More cases occur during the winter months. The estimated economic cost in the United States exceeds $12 billion a year.

In light of the impact of CAP, numerous professional societies have developed guidelines for management of these infections. The primary purposes of these guidelines are to optimize care and, ultimately, improve outcome of patients. The most recent evidence-based guidelines from North America are the collaborative statement from the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS), which incorporates important advances in the management of patients with CAP. The cases presented in this review highlight many of the recent recommendations from the IDSA/ATS guidelines.

CASE 1

Presentation

A 66-year-old man presented to his primary care practitioner with a headache, fever, and cough for the previous 3 days, and recent bouts of confusion.

History and Physical Examination

The patient had smoked cigarettes (approximately 1 pack per day) since age 17, had had type 2 diabetes mellitus for 15 years, and had coronary artery bypass surgery 12 years ago. He was treated with a macrolide (azithromycin) for sinusitis 8 weeks before presentation. Vital signs were as follows: temperature, 100.8°F (38.2°C); pulse, 110 beats per minute, respiratory rate, 28 breaths per minute. Auscultation of his lungs revealed rhonchi in the right lower lobe. A blood test showed leukocytosis (white blood cell [WBC] count 20,000 per mm³ (20 × 10⁹/L), and his blood glucose level was 180 mg/dL (1 mg/dL = 0.0555 mmol/L).
Comment. A patient presenting to a practitioner’s office with cough (either productive or nonproductive), pleuritic chest pain, shortness of breath, temperature $>38{^\circ}C$, and crackles on auscultation shows the classic signs and symptoms of CAP. As seen with this patient, mental status changes may complement respiratory manifestations of the disease; gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) also may be present. Leukocytosis (WBC count between $15,000/mm^3$ and $30,000/mm^3$) with a leftward shift is the major blood test abnormality observed in patients with CAP. No clear constellation of symptoms and signs has been observed to universally and accurately predict the patient with pneumonia. A demonstrative infiltrate by imaging techniques and/or supporting microbiologic data also are necessary.

Diagnostic Testing
The presence of a right lower lobe infiltrate was detected on a plain chest radiograph (Figure 1). Although this patient’s clinical picture does suggest CAP, clinical symptoms and signs alone are not specific for the definitive diagnosis, especially in elderly patients. A chest imaging study is required for an accurate diagnosis. The presence of a new infiltrate on a chest radiograph is considered the “gold standard” when clinical features are supportive, as in this patient. Radiologists are unable to reliably differentiate between bacterial and nonbacterial pneumonia based on radiographic appearance.

Diagnosis
The patient was diagnosed with CAP.

Determination of Site of Care
The patient was determined to have a class III Pneumonia Severity Index (PSI) classification and a CURB-65 (confusion; urea $>7$ mmol/L; respiratory rate $\geq30$/min; low systolic [{$<90$ mm Hg}] or diastolic [{$\leq60$ mm Hg}] blood pressure; age $\geq65$ years) score of 2—a classification associated with a mortality rate of 8% to 9%. The patient was admitted to a local hospital for care.

Comment. After establishment of the diagnosis, the next management decision is to determine the site of care. This determination has an impact on the intensity of diagnostic testing and options for empirical antimicrobial therapy. Advantages of outpatient therapy include preference by most patients (if considered safe), association with faster convalescence of illness, avoidance of potential nosocomial complications, and decreased cost. The general consensus in the medical care community is that the majority of patients with CAP can indeed be treated safely as outpatients. However, selected patients (like the patient in this case study) should...
be hospitalized based on their risk for poor outcome, which may be mitigated by close observation, respiratory support, intravenous antibiotics, and management of comorbid illness. Deciding on whether to hospitalize a patient is based on such tools as the Pneumonia Prediction Rule and the CURB-65 Rule. The Pneumonia Prediction Rule utilizes a combination of demographic variables, comorbidities, physical observations, and laboratory and radiographic variables to assign patients to 1 of 5 classes. The classes are demarcated by distinct risks of mortality and consequent recommendations regarding site of care as shown in Table 1; scoring to determine class is shown in Table 2.

Our current patient merits a class III status (PSI score 86 points [age 66 years + confusion 20]) with a risk of mortality of <5%, and is suggested for brief hospital observation. Although the Pneumonia Prediction Rule is effective in determining mortality risk, it is not “user-friendly” in the clinical setting, because it includes laboratory results that may not be available when a disposition decision must be made. The CURB-65 Rule is more useful at the bedside, because it uses a much less rigorous process in its clinical determination—measurements include confusion, urea concentration, respiratory rate, blood pressure, and age. The patient with CAP in this case study scored a 2 (age ≥65 years + confusion), which also merits hospitalization. Despite its simplicity, however, the CURB-65 may be considered impractical because both a blood sample and laboratory analysis of blood urea are often required. As a result, the CRB-65 was devised; it eliminates the blood urea determination but is otherwise identical to the CURB-65 and, therefore, is optimally designed for the office setting (see Figure 2 and Figure 3). The performance of CRB-65 was shown to be comparable to CURB-65 and PSI in a study by Capelastegui and colleagues. Thus, once the diagnosis is established, the PSI or CURB-65 (or CRB-65) scores can support an initial site-of-care decision (i.e., hospital versus outpatient).

### Diagnostic Testing for Etiology

A blood culture, sputum Gram stain, and urinary antigen test were performed. In recent guidelines most tests are considered optional, but I advocate performing blood cultures, sputum Gram stain and culture, and urinary antigen tests for Streptococcus pneumoniae and Legionella species for patients requiring admission to the hospital. However, obtaining these tests should never delay administration of antimicrobial therapy because timely administration is critical for good outcome. Positive blood cultures are observed in approximately 11% of high-risk patients with CAP, although false-positive blood cultures can lead to prolonged hospital stays with significantly greater use of vancomycin.

It may be difficult to obtain a good sputum sample, and validity of the Gram stain may be influenced by such factors as specimen collection, transport time to the microbiology laboratory, rapidity of sample processing, satisfactory use of cytologic criteria, absence of prior antibiotic therapy, and experience of the interpreter; however, when stringent criteria are applied, specificity for pneumococcal pneumonia can approach 90%. Epidemiologic trends should be considered in deciding to perform additional diagnostic tests for less usual CAP pathogens, such as fungus or Mycobacteria species.

The urinary antigen test for S pneumoniae is 50% to 80% sensitive and ≥90% specific in adults. In a prospective study of 269 patients with CAP and no identifiable pathogen, S pneumoniae urinary antigen was detected in 69 (27.5%) of those patients. The additional information on etiology may help narrow down choices of antibiotic therapy.

### Table 1 Pneumonia prediction rule

<table>
<thead>
<tr>
<th>Total Points</th>
<th>Class</th>
<th>Mortality (%)</th>
<th>How to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤70</td>
<td>I</td>
<td>0.1</td>
<td>Outpatient</td>
</tr>
<tr>
<td>71-90</td>
<td>II</td>
<td>0.6</td>
<td>Outpatient</td>
</tr>
<tr>
<td>91-130</td>
<td>III</td>
<td>0.9-2.8</td>
<td>Brief hospital observation</td>
</tr>
<tr>
<td>&gt;130</td>
<td>IV</td>
<td>8.2-9.3</td>
<td>Inpatient</td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>27.0-29.2</td>
<td>Inpatient ICU</td>
</tr>
</tbody>
</table>

ICU = intensive care unit. Adapted from N Engl J Med.

### Table 2 Point scoring system for assignment to risk classes II, III, IV, and V

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points Assigned</th>
</tr>
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<tbody>
<tr>
<td>Demographic Factor</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Nursing home resident</td>
<td></td>
</tr>
<tr>
<td>+10</td>
<td></td>
</tr>
<tr>
<td>Coexisting illnesses</td>
<td></td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>+30</td>
</tr>
<tr>
<td>Liver disease</td>
<td>+20</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>+10</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>+10</td>
</tr>
<tr>
<td>Renal disease</td>
<td>+10</td>
</tr>
<tr>
<td>Physical examination findings</td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+20</td>
</tr>
<tr>
<td>Respiratory rate ≥30/min</td>
<td>+20</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mm Hg</td>
<td>+20</td>
</tr>
<tr>
<td>Temperature &lt;35°C or ≥40°C</td>
<td>+15</td>
</tr>
<tr>
<td>Pulse ≥125 beats/min</td>
<td>+10</td>
</tr>
<tr>
<td>Laboratory and radiographic findings</td>
<td></td>
</tr>
<tr>
<td>Arterial pH &lt;7.35</td>
<td>+30</td>
</tr>
<tr>
<td>Blood urea nitrogen ≥30 mg/dL (11 mmol/L)</td>
<td>+20</td>
</tr>
<tr>
<td>Sodium &lt;130 mmol/L</td>
<td>+20</td>
</tr>
<tr>
<td>Glucose ≥250 mg/dL (14 mmol/L)</td>
<td>+10</td>
</tr>
<tr>
<td>Hematocrit &lt;30%</td>
<td>+10</td>
</tr>
<tr>
<td>Partial pressure of arterial oxygen &lt;60 mm Hg</td>
<td>+10</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>+10</td>
</tr>
</tbody>
</table>

Adapted from N Engl J Med.
Treatment

The patient was administered levofloxacin 750 mg once daily for 5 days. The patient was stabilized by the second day of therapy and was switched from intravenous to oral therapy.

For the majority of patients, an etiologic pathogenic agent will not be identified owing to the lack of rapid diagnostic methods. Consequently, an empirical approach to initial therapy is typically based on the likelihood that a key pathogen is responsible. For this patient (hospitalized, non-ICU) the most common pathogens include *S pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Haemophilus influenzae*, or *Legionella* species.

Empirical treatment of CAP is nearly universal because pathogen identification, when possible, is generally not available when a treatment decision needs to be made, and the presenting clinical features are not specific enough to reliably predict the etiology of CAP. The recommended treatment option for an inpatient on the general ward is either combination therapy with a β-lactam, such as cefotaxime, ceftriaxone, ertapenem, or ampicillin-sulbactam, plus azithromycin, or monotherapy with a respiratory fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin). Because the patient previously had been treated with a macrolide, levofloxacin 750 mg once daily was administered. A switch from intravenous to oral treatment is recommended once the patient is stable, typically by the second or third day of treatment in most cases even if *S pneumoniae* bacteremia is present. A treatment duration of 5 days is often adequate for either an outpatient or general ward patient with CAP, assuming the patient is doing well at 48 to 72 hours and in the absence of an unusual pathogen.

When deciding on initial therapy, the clinician should always ask the patient whether she or he has received antimicrobials within the last 3 months, because this is an important risk factor for antimicrobial resistance. In such cases, empirical therapy with a different antibiotic class is preferred.

Outcome

The patient’s fever was reduced within 3 days of therapy. His cough and fatigue remained for several weeks. Despite an initial good response from antimicrobial therapy with resolution of fever and acute morbidity, it is very common for patients to experience prolonged cough and malaise. To increase their understanding of their illness and expected clinical course, patients should be informed that symptoms can last for a prolonged period.

Although this patient was treated successfully, up to 15% of patients may not respond appropriately to initial antibiotic treatment. The most common causes of treatment failure are lack of or delayed response by the host despite appropriate antibiotics or infection with an organism that is not covered by the initial antibiotic regimen. Other causes of treatment failure include a resistant pathogen, an unusual pathogen, a suppurative complication (e.g., empyema), or obstruction. It should be noted that a chest radiograph can...
remain abnormal for weeks (even in the presence of successful treatment).

CASE 2

Presentation
A 79-year-old woman presented to her primary care practitioner with progressive weight loss, malaise, and a nonproductive cough that had developed over the past 3 weeks.

History
The patient had several comorbid conditions, including obesity, type 2 diabetes, and hypertension. The last time she recalled having a persistent cough (although less severe than what she was now experiencing) was 10 years prior, when she had been administered an angiotensin-converting enzyme (ACE) inhibitor to control her hypertension; the ACE inhibitor was discontinued and she remained on a daily regimen of an angiotensin receptor blocker with a diuretic. Her greatest complaint in recent visits had been deteriorating vision related to macular degeneration. She had a stilted gait secondary to a hip fracture repair experienced 5 years ago. Her history also included a nonmalignant breast mass that had been biopsied approximately 10 years ago. She had a remote smoking history of approximately 2 packs of cigarettes per day, but she had quit in her late 40s.

Physical Examination
Physical examination revealed a fever (100.5°F [38.1°C]), elevated blood pressure 140/90 mm Hg, and a loss of 3 lb (1.35 kg) since her last visit 4 months prior. The patient had shortness of breath and, upon auscultation of her lungs, rales were heard bilaterally. Blood analysis showed hemoglobin of 11.4 g/dL, WBC of 9.48 × 10^9/L, and a platelet count of 349 × 10^9/L. A chest radiograph performed in the office was interpreted as showing chronic fibrotic changes and probable small patchy infiltrates.

Treatment
The patient was treated with an oral fluoroquinolone for 5 days and was scheduled for a return to the office at the end of therapy. In such cases as this patient with several comorbidities, empirical antibiotic therapy for an outpatient with CAP includes a respiratory fluoroquinolone. These agents
are widely chosen as empirical therapy for CAP owing to their broad-spectrum activity, high bioavailability, and convenient dosing schedules.

Posttreatment Assessment
The patient felt improved at the conclusion of therapy and canceled her follow-up appointment. The office receptionist placed her call through to the physician assistant, to whom the patient reported that her cough had dissipated somewhat and that she no longer had a fever.

Return Visit
The patient returned to the office 2 months later concerned that she had been “coughing up blood” over the previous 2 days. In addition to hemoptysis, the patient revealed that since her previous visit she had continued to feel malaise, was continuing to lose weight, and had been experiencing night sweats. The primary care physician suspected tuberculosis (TB) (the patient now recalled that a family member had once been diagnosed with TB) and had the patient transferred immediately for isolation in a local hospital.

A repeat chest radiograph revealed progressive bilateral fibronodular diseases with a “miliary” pattern (see Figure 4). The hospitalist ordered a sputum culture and the culture was subsequently positive for *Mycobacterium tuberculosis*.

Diagnosis
The patient was diagnosed with TB. Although TB is frequently overlooked as a cause of CAP, it is responsible for approximately 0.3% of cases in the United States. This is far removed from the prevalence seen in the epicenter of the human immunodeficiency virus (HIV) pandemic in sub-Saharan Africa. An indication of TB as a common cause of CAP is illustrated by a prospective study of 266 patients admitted with a diagnosis of CAP in a hospital in Durban, South Africa, between May 2000 and July 2001—a high-prevalence HIV setting. A microbiologic diagnosis of 169 patients (64%) showed 44 with TB, 31 with *Pneumocystis jirovecii* pneumonia, and 35 with bacterial pneumonia.

A retrospective review of patients with active TB shows how pulmonary TB was unsuspected in a 515-bed, university-affiliated, community teaching hospital located in Akron, Ohio. In patients with cultures for *M tuberculosis* (1983 to 1987), of 31 cases with active disease (admitted to 9 different services), TB was not suspected in 13 (42%). The patients with unsuspected TB were older, had a delay in isolation (1 vs. 6 days; *P* = 0.002), had a longer hospitalization (16 vs. 11 days; *P* = 0.02), and showed a higher mortality rate (46% vs. 11%; *P* = 0.07). Interestingly, most were admitted with a diagnosis of CAP as well as carcinoma of the lung and congestive heart failure, among the admitting diagnoses; of note, these patients did not belong to populations traditionally thought to be at risk. In the 13 patients with unsuspected TB, the chest radiograph findings were as follows: upper lobe infiltrate and/or cavitation (n = 6), lower lobe infiltrate (n = 2), bilateral diffuse infiltrate (n = 2), pulmonary nodule (n = 1), pleural effusion (n = 1), and bilateral apical scarring (n = 1).

Table 3 shows when to suspect TB as a cause of CAP,

<table>
<thead>
<tr>
<th>Table 3</th>
<th>When to suspect tuberculosis as a cause of community-acquired pneumonia</th>
</tr>
</thead>
</table>
| ● Patients from endemic areas  
● Chest x-ray: upper lobe infiltrate, cavitation, miliary pattern  
● Hemoptysis or >1 mo of any of the following: cough, fever, malaise, weakness, night sweats, or significant weight loss  
● Nursing home patients, homeless, prison dweller, alcoholism  
● Human immunodeficiency virus  
● Exposure to tuberculosis |

Adapted from *Respir Care Clin North Am.*

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and Figure 5 shows worldwide endemic areas for TB. To avoid misdiagnosing TB as CAP, it is recommended that the following patients be considered suspect for TB: (1) patients with a chest radiograph showing upper lobe infiltrate, cavitation, and a miliary pattern; (2) patients with hemoptysis or \( \geq 1 \) month of any cough, fever, malaise, weakness, night sweats, or significant weight loss; (3) patients failing or relapsing after empirical therapy; and (4) any patient with HIV, regardless of CD4 count, with a known history of positive tuberculin skin test, previous TB, or recent exposure to TB, who presents with CAP.\(^1\)

Fluoroquinolones should not be used as first-line therapy to treat CAP in areas of endemic TB or in the other conditions listed in Table 2. These drugs are likely to both mask active TB and select for quinolone resistance in the infecting mycobacteria.\(^2\) Thus, clinicians should be aware of risk factors associated with TB pneumonia and avoid using a fluoroquinolone empirically in these patients owing to the risk of promoting fluoroquinolone resistance.

As observed in the present case, several studies have demonstrated delays in the treatment of TB in patients treated empirically with fluoroquinolones.\(^2\) In a retrospective study of 33 patients with culture-confirmed TB at Johns Hopkins Hospital in Baltimore, Maryland, 16 (48\%) patients received fluoroquinolones for presumed CAP.\(^2\) The median time between presentation to the hospital and initiation of TB treatment was 21 days in those patients treated with fluoroquinolones compared with 5 days in those patients who did not receive fluoroquinolone therapy (\(P = 0.04\)). This delay in treatment may be ascribed to partial symptom resolution, as observed in the present case. Although the patient in this case recovered fully, empirical treatment with fluoroquinolones with the consequent delay in treatment has been associated with poorer outcomes as compared with patients who do not receive fluoroquinolones.\(^2\) Monotherapy with an empirical fluoroquinolone in patients with suspected CAP who have TB may be associated with an initial partial response, but it is followed by gradual worsening of symptoms leading to poorer outcomes.

In a study by Ginsburg and colleagues,\(^2\) 2 of 55 \(M\) \(tuberculosis\) isolates were found to have decreased susceptibility to fluoroquinolones, compared with 0 of 36 isolates from nonfluoroquinolone-treated patients. However, this was in a relatively small sample and more recent studies have questioned whether empirical treatment with fluoroquinolones is a concern in terms of increased \(M\) \(tuberculosis\) resistance.\(^2\) For example, Huang and coworkers\(^2\) found that fluoroquinolone resistance was restricted to multidrug resistant (MDR) strains and was a consequence of treating patients with MDR TB strains rather than empirical use in the community setting. In a study of 420 \(M\) \(tuberculosis\) isolates from January 2004 to December 2005 in endemic areas of Taiwan, it was found that neither previous use of fluoroquinolones nor duration of fluoroquinolone exposure was correlated with fluoroquinolone susceptibility of the isolates.\(^2\)

Low and colleagues\(^2\) propose that increasing empirical use of fluoroquinolones to treat CAP may not necessarily lead to increased numbers of resistant \(M\) \(tuberculosis\) clones in the future. This supposition is based on the use of fluoroquinolones in combination therapy and by the use of

![Figure 5](https://example.com/figure5.png)

Figure 5 Cases of tuberculosis per 100,000 population (2000). (Courtesy of University of California at Santa Cruz.)
fluoroquinolones at doses that exceed the resistance levels of spontaneous mutants to thereby prevent their amplification. In any event, fluoroquinolones should not be given as first-line empirical treatment when TB is suspected.

**Treatment**

The patient had confirmed miliary TB with positive sputum and bone marrow cultures. She was administered isoniazid, rifampin, pyrazinamide, and ethambutol for 7 days per week for 8 weeks, followed by isoniazid and rifampin 7 days per week for 24 weeks.

**Outcome**

The patient responded well to the drug regimen.

**CASE 3**

**Presentation**

On a late afternoon in mid-November, a 33-year-old corrections officer was brought by her husband to their primary care practitioner. The husband stated that his wife had come home from work late that morning not feeling well and developed a high fever and difficulty breathing over the course of the afternoon. She had been to visit the primary care practitioner 5 days prior for a respiratory virus and had been experiencing a lingering and severe cough that had been deteriorating over time.

**History and Physical Examination**

The patient was moderately overweight (body mass index, 28.5). She had smoked cigarettes since age 15 (approximately 2.5 packs per day) and drank beers liberally (~6 beers per night). Aside from her recent visit for flu-like symptoms, she had visited her primary care practitioner over the previous year for minor lacerations and a job-related shoulder separation. She had no history of chronic disease, but had a family history of hypertension and coronary artery disease. Her father had a fatal myocardial infarction at age 54.

Her vital signs were as follows: temperature, 101.3°F (38.5°C); pulse, 135 beats per minute; and respiratory rate, 33 breaths per minute. On auscultation, bilateral coarse rhonchi could be heard in both the left and right lung fields.

The primary care practitioner was concerned about the condition of this patient based on the results of the examination. Although the patient had no history of methicillin-resistant *Staphylococcus aureus* (MRSA) infections or colonizations, her job in the prison environment was a risk factor suggestive of community-acquired MRSA (CA-MRSA) pneumonia—particularly as a potential secondary bacterial infection postinfluenza. As a consequence, the patient was referred immediately to the local university medical center emergency department (ED), where she was met by an attending pulmonologist colleague of her primary care practitioner.

CA-MRSA as the causative pathogen in patients with CAP is becoming more common, such that practitioners should be aware of local prevalence patterns and associated risk factors. Under such conditions, patients presenting with severe CAP should be urged by their primary care practitioner to seek immediate medical attention at a local ED. As in this patient, CA-MRSA pneumonia should be suspected in young, previously healthy adults who have had a flu-like illness—particularly those who participate in close-contact settings (sports participants [e.g., football players, wrestlers, fencers], prisoners in correctional facilities, children in day care and other institutional centers, military recruits), male homosexuals, and people in the general population who travel to MRSA endemic areas. Clinicians should determine from the patient (and caretaker, if necessary) social and family history, history of recurrent infections, any recent contact with healthcare facilities, or if any family members have a history of skin abscesses or cellulitis or are carriers of MRSA. The key to rapid diagnosis of CA-MRSA is a high level of suspicion.

**ED Visit (Diagnostic Testing)**

Upon initial examination of the patient, the pulmonologist ordered a chest radiograph (Figure 6) and measurement of arterial blood gases. Bilateral infiltrates were observed throughout both lung fields. Blood gas measurements (partial pressure of oxygen [PO<sub>2</sub>] = 42 mm Hg) confirmed that the patient had severe hypoxia.

The patient in this case had bilateral infiltrates. Patients with CA-MRSA pneumonia characteristically exhibit bilateral consolidation and multilobular cavitating alveolar infiltrates, and possibly the presence of pleural effusion. Cavitation possibly caused by the Panton-Valentine leukocidin toxin associated with CA-MRSA pneumonia may not show on a chest radiograph initially, but may develop rapidly. A computed tomography scan or magnetic resonance imaging are suggested for the optimal evaluation of the radiologic changes.

**Initial Treatment**

As a consequence of the severe hypoxia, the patient was intubated and placed on a mechanical respirator. Prior to intubation, she was administered a third-generation cephalosporin and azithromycin. At the time of intubation a Gram stain of endotracheal aspirate showed many polymorphonuclear leukocytes and many gram-positive cocci in clusters (see Gram stain under “Laboratory Testing” below). Intravenous vancomycin (15 mg/kg every 12 hours) was initiated.

The IDSA/ATS guidelines recommend the use of vancomycin or linezolid in cases of suspected CA-MRSA pneumonia. Susceptibility data show that CA-MRSA isolates are becoming more resistant to multiple drugs/drug classes, including clindamycin, fluoroquinolones, mupirocin, and macrolides. Moreover, clindamycin and linezolid may act to reduce or suppress Panton-Valentine leukocidin production through protein synthesis inhibition.
Laboratory Testing
A Gram stain of endotracheal secretions (Figure 7) revealed gram-positive cocci in clusters typical of *S. aureus*. According to the IDSA/ATS 2007 guidelines, a Gram stain should be obtained from patients at risk for CA-MRSA pneumonia. If the Gram stain and culture results of an adequate respiratory specimen are negative, these results alone should be adequate to withhold or stop treatment for CA-MRSA pneumonia.

Diagnosis
The patient was diagnosed with CA-MRSA. Evidence supportive of the diagnosis in this patient included the patient’s preceding influenza-like illness, Gram stain evidence of gram-positive cocci clusters, chest radiograph with bilateral infiltrates, and laboratory findings.

Additional Treatment
Based on the results of the Gram stain, treatment with vancomycin was maintained. The patient’s WBC count was 4,100/μL (4.1 × 10^9/L).

Outcome
Despite urgent care, the patient’s condition deteriorated and she died 12 hours after presentation to the hospital. There was evidence of multiple organ failure (abnormal coagulation studies, elevated liver function tests, and anuria). Endotracheal aspirate cultures exhibited heavy growth of MRSA. Follow-up typing of the pathogen led to its identification as the Panton-Valentine leukocidin–positive USA300 MRSA strain indicative of CA-MRSA.

The patient died of virulent CA-MRSA pneumonia that carried the Panton-Valentine leukocidin gene and isolate banding patterns consistent with the USA300 pulsed-field type as described by Francis and associates. Recent reports of 2 case series of 50 patients in France and 51 patients in the United States show mortality to be ~50% in patients with CA-MRSA pneumonia. A total of 14 of 20 patients with confirmed Panton-Valentine leukocidin–secreting CA-MRSA died despite being treated with appropriate therapy. The illness is typically characterized by severe respiratory symptoms, hemoptysis, high fever, leukopenia, and hypotension. Risk factors for mortality include influenza, requirement for intubation, need for inotropic...
support, acute respiratory distress syndrome, hemoptysis, and leukopenia.\textsuperscript{32,36} Although early reports of CA-MRSA pneumonia suggest a high association with necrotizing infection with high mortality, it is quite likely that less severe cases also occur.

Optimal antimicrobial therapy of CA-MRSA pneumonia is not well defined. The recent IDSA/ATS guidelines recommend vancomycin or linezolid for severe pneumonia. In our case, the patient rapidly deteriorated despite vancomycin therapy; however, it is unlikely that any alternative intervention in the ED in the context of her clinical condition would have resulted in survival. Therapeutic failures with vancomycin may be a result of the greater prevalence of \textit{S. aureus} infections with increasing minimal inhibitory concentrations (MICs).\textsuperscript{38} Other limitations associated with vancomycin that may lead to therapeutic failure include its poor penetration into the epithelial lining fluid\textsuperscript{39} and its slow bactericidal activity against high-MIC, yet susceptible, MRSA strains.\textsuperscript{40,41} Higher dosing of vancomycin (>4 g/day) to achieve higher trough serum concentrations may not be feasible because vancomycin is potentially nephrotoxic.\textsuperscript{39,42}

Because of the lack of randomized controlled trials in CA-MRSA pneumonia, guidelines are unable to provide strong recommendations beyond use of either vancomycin or linezolid, particularly because these agents are moderately recommended based on level III evidence. (Such evidence comes from case studies and expert opinion. In some instances therapy recommendations come from antibiotic susceptibility data without clinical observations.\textsuperscript{8}) In fact, the IDSA/ATS guidelines acknowledge that vancomycin does not decrease Panton-Valentine leukocidin or other toxin production, suggesting the addition of clindamycin or linezolid may be more beneficial for the treatment of necrotizing pneumonias.\textsuperscript{8} The Canadian guidelines suggest that linezolid may be preferred over empirical therapy with vancomycin based on clinical trial data of adults with healthcare-associated MRSA and improved penetration in the lung parenchyma.\textsuperscript{43,44} The United Kingdom guidelines acknowledge that “there is as yet no unequivocal clinical evidence to support combination” therapy for CA-MRSA pneumonia, yet they list the use of combination therapy with linezolid plus clindamycin and also acknowledge support for the use of rifampin.\textsuperscript{31} Investigational agents that may fulfill the promise of treating CA-MRSA pneumonia include the cephalosporins (ceftobiprole, ceftaroline fosamil)\textsuperscript{45,46} and the lipoglycopeptides (telavancin).\textsuperscript{47} The association of influenza and secondary CA-MRSA pneumonia is another reason to promote universal influenza vaccination.

(This illustrative case study is a variation of a case recently reported in a CME-accredited MRSA monograph.\textsuperscript{48})

\textbf{COMMENTARY}

The case studies in this article—a typical case of CAP, a case of TB initially treated as CAP, and a severe case of CA-MRSA—have been described to provide the primary care practitioner with some insight into case management beyond that available by being merely informed of current guideline recommendations. However, what must remain
foremost in the mindset of the primary care practitioner is the prevention of lower respiratory tract infections. These avenues to improve outcome are well characterized; they include smoking cessation, timely administration of vaccines (both pneumococcal and influenza), reducing the effect of comorbidities (e.g., controlling congestive heart failure, hyperglycemia, reducing swallowing disorders [e.g., when brushing teeth]), and pandemic preparation.3,49

Moving forward, continuing improvements in the delineation of performance measures will also be instrumental in improving care of patients with CAP. Deviation from performance measures can be deemed acceptable based on individual characteristics because “specific performance measures cannot cover all host settings.”50 Finally, measures should be evaluated for “unintended” consequences, as was observed with the overuse of vancomycin associated with requiring blood cultures for all patients with CAP who were admitted to the hospital (with a consequent high number of false-positive results), as well as forced timing of antimicrobial delivery that led to antibiotic overuse before a firm diagnosis was in place.50 The Centers for Medicare and Medicaid Services provide performance measures for antibiotic treatment of CAP, underscoring the need for adequate blood culture collection, oxygenation assessment, influenza and pneumococcal immunization, and smoking cessation counseling.51

ACKNOWLEDGMENTS
Medical writing support for the preparation of this article was provided by Ira Mills, PhD, and Craig Ornstein, PhD, of Embryon; LLC, A Division of Advanced Health Media, LLC formerly Medesta Publications Group, A Business of Advogen).

AUTHOR DISCLOSURES
The author of this article has disclosed the following industry relationships:


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