A CLUSTER OF FULMINANT, FATAL NECROTIZING COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS PNEUMONIAS

By Aparajita Sohoni, MD, Colin Feeney, MD, Larry Lambert, MPH, and Robert McCabe, MD

Abstract

Community-associated methicillin-resistant Staphylococcus aureus is a frequent cause of skin and soft-tissue infections and is increasingly identified as a cause of pneumonia in immunocompetent patients. Panton-Valentine leukocidin, one of several leukocytotoxic peptides secreted by these cocci, is associated with increased virulence. A cluster of 3 unrelated patients with fatal pneumonia presumably caused by community-associated methicillin-resistant S aureus positive for Panton-Valentine leukocidin were treated in a 3-week period. Despite aggressive care and appropriate, timely administration of antibiotics, all 3 patients died. This article reviews the clinical and laboratory features suggestive of this lethal isolate, including unique findings on Gram stains of sputum.


T he dramatic emergence of community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) since the 1990s has resulted in a worldwide increase in skin and soft-tissue infections, prompting a large increase in evaluations in emergency departments and in hospital admissions. CA-MRSA infections are not limited to skin and soft tissue; any organ can be involved. Alameda County Medical Center, Oakland, California, was compelled to change evaluation and treatment algorithms to address this outbreak, which has become endemic. Unlike hospital-associated MRSA and methicillin-susceptible S aureus, CA-MRSA often produces toxins such as Panton-Valentine leukocidin (PVL), an exotoxin that enhances virulence and produces necrosis. PVL causes formation of pores in cells, especially white blood cells, resulting in cell death.

We describe 3 unrelated patients with fulminant CA-MRSA pneumonia who were treated at Alameda County Medical Center during a 3-week period.
CA-MRSA infections can be rapidly fatal and can cause outbreaks of community-acquired pneumonia.

Case Reports

The MRSA isolates from all 3 patients perfectly matched the cultural, biochemical, and antibiogram profiles of previous PVL-confirmed isolates that were characterized by using polymerase chain reaction and were reported in previous publications.1,3

Patient 1

NR was a 30-year-old woman who came to the emergency department in February 2008 because she had had dyspnea, fever, chills, and mild hemoptysis for 3 days. She had no risk factors for pneumonia other than a childhood history of asthma. Physical examination indicated that she was in severe respiratory distress, with respirations 60/min, blood pressure 140/80 mm Hg, pulse rate 120/min, and body temperature 39.4°C (103°F). A rapid test for human immunodeficiency virus was negative for the virus. Her initial white blood cell (WBC) count was 9500/µL; serum level of sodium was 132 mmol/L, and serum level of lactic acid was 6.2 mmol/L (to convert to milligrams per deciliter, divide by 0.111). A chest radiograph showed an infiltrate in the right middle lobe.

Levofloxacin 750 mg, piperacillin/tazobactam 4.5 g, and vancomycin 1 g were administered intravenously within the first hour, but NR's respiratory status worsened and she was intubated. A Gram stain of sputum showed gram-positive cocci in clusters, and linezolid 600 mg and clindamycin 900 mg were added to the medications given intravenously. The vancomycin trough level was 23 µg/mL (desired level, 15-20 µg/mL). The WBC count decreased dramatically to 1100/µL on hospital day 2. Chest radiography revealed acute respiratory distress syndrome. Vasopressor-refractory hypotension and kidney and liver failure developed, and the patient died on hospital day 7. Cultures of sputum, nasal specimens, and blood showed growth of MRSA susceptible in vitro to clindamycin. This susceptibility was determined by D test, a double-disc diffusion assay used to detect inducible clindamycin resistance typically missed when conventional minimum inhibitory concentration (MIC) methods are used. The E test, a specialized disc diffusion assay (AB Biodisc) that most accurately determines the MIC of an antibiotic to inhibit growth of an organism in vitro, indicated an MIC of 1.5 µg/mL for vancomycin.

Patient 2

RM was a 54-year-old man who came to the emergency department in February 2008 because he had had cough, fever, chills, dyspnea, pleuritic chest pain, and progressive hemoptysis for 3 days. He had a history of congestive heart failure and cocaine, cigarette, and alcohol use. On physical examination, he was coughing up copious blood. Vital signs included blood pressure 113/73 mm Hg, pulse rate 144/min, respirations 40/min, body temperature 37.4°C (99.3°F). The initial WBC count was 3600/µL, the serum level of sodium was 136 mmol/L, and the lactic acid level was 2.5 mmol/L. Chest radiography showed consolidation in the left upper lobe and air bronchograms.

RM was given vancomycin 1 g, piperacillin/tazobactam 4.5 g, and doxycycline 100 mg intravenously within the first 4 hours. The hypoxemia worsened, and he was intubated. A Gram stain of sputum showed intracellular gram-positive cocci with loss of cytoplasmic granules (see Figure). Linezolid 600 mg every 12 hours was added to the intravenous medications he was receiving. On day 2, the WBC count was 1400/µL. A chest radiograph showed extensive disease in the right lung. Cultures of sputum and blood had growth of MRSA with in vitro susceptibility to clindamycin (D test negative) and an E test MIC of 1.5 µg/mL for vancomycin. Despite maximal interventions, renal failure, disseminated intravascular coagulation, and acidosis developed. The patient died of vasopressor-refractory shock on day 2.

Patient 3

DW was a 53-year-old man who came to the emergency department in the first week of March 2008 because he had had pleuritic chest pain, night sweats, myalgias, nausea, and cough with pink-tinted sputum for 7 days. He had a history of type 2 diabetes mellitus and chronic diarrhea. He smoked cigarettes, but he said that he did not abuse drugs or alcohol.

Physical examination revealed blood pressure 105/82 mm Hg, pulse rate 166/min, respirations 18/min, body temperature 36.7°C (98°F). The WBC count was 9500/µL with 12% bands. The initial

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Three unrelated patients with fulminant community-acquired MRSA and pneumonia were seen during a 3-week period.
Evidence has accumulated that CA-MRSA isolates have become more resistant to vancomycin therapy, as evidenced by MIC “creep.” Greater concentrations of vancomycin are required to inhibit growth in vitro, and these concentrations are close to the upper breakpoint susceptibility cutoff of 2 µg/mL. At Alameda County Medical Center, 90% of MRSA isolates tested before 2007 had an MIC of less than 1 µg/mL. Recently, a vancomycin concentration of 1.5 µg/mL was needed to inhibit the growth of 90% of isolates. This reduced susceptibility has been linked to clinical and microbiological failures, which have prompted the use of other antibiotics, especially linezolid and daptomycin, and recommendations for higher serum trough levels of vancomycin, although neither of these strategies has altered clinical outcomes. Of note, daptomycin should not be used for bacterial pneumonia because this antibiotic is inactivated by surfactant.

Increased virulence of CA-MRSA has been attributed to production of toxin, leading to greater interest in antibiotics that inhibit toxin production, such as linezolid and clindamycin.

Although the results of 2 studies suggested that clinically and microbiologically linezolid was better than vancomycin for treatment of MRSA pneumonia, both studies were limited by use of retrospective analysis, small groups, inclusion of pathogens other than MRSA, and suboptimal dosing of vancomycin. In a recent prospective, randomized, multicenter, double-blind trial of treatment of MRSA nosocomial pneumonia that avoided some of these criticisms, compared with patients treated with vancomycin, patients treated with linezolid had significant (P = .04) improvement in clinical outcome at the end of the study and fewer instances of nephrotoxic effects. The 2 groups did not differ in 60-day mortality.

A potentially important issue is the use of combinations of antibiotics that might be antagonistic in vivo. Clinical data are lacking, but antibiotic combinations and their potential interactions have been reviewed by Deresinski.

PVL kills leukocytes by forming pores in the cell membrane, leading to release of inflammatory mediators. Because the action of PVL on neutrophils can be blocked by specific antibodies to the leukocidin found in commercial preparations of intravenous immunoglobulin, early adjunctive therapy with the immunoglobulin should be considered in addition to antibiotics in life-threatening cases. Some clinical evidence supports use of intravenous immunoglobulin, and the recent practice guidelines of the Infectious Diseases Society of America state that intravenous immunoglobulin can be considered for some patients, such as those with severe sepsis or necrotizing pneumonia.

Greater concentrations of vancomycin are required to inhibit growth in vitro.

Discussion

These 3 unrelated patients with fatal presumptive PVL-positive CA-MRSA severe necrotizing pneumonia were treated at Alameda County Medical Center during a 3-week period. We are unaware of any reports of a similar case series. Although we did not analyze these patients’ MRSA isolates for the SCCmec IV allele or for genes for PVL, the biochemical profile, antibiogram, and cultural characteristics of the isolates were identical to those characterized by using pulsed-field gel electrophoresis and polymerase chain reaction. In both studies, 99% of CA-MRSA isolates had the SCCmec IV allele and PVL genes and belonged to the USA300 pulsed-field type.

The optimal treatment for severe MRSA infections is not known, although guidelines have been published. Evidence has accumulated that CA-MRSA isolates have become more resistant to vancomycin therapy, as evidenced by MIC “creep.” Greater concentrations of vancomycin are required to inhibit growth in vitro, and these concentrations are close to the upper breakpoint susceptibility cutoff of 2 µg/mL.

Intravenous administration of vancomycin 1 g and piperacillin/tazobactam 4.5 g were started within the first 5 hours of DW’s time in the emergency department. The hypoxemia worsened, and the WBC count was 2600/µL on day 2. A Gram stain of sputum showed clusters of gram-positive cocci, and linezolid was added to the medications administered. Cultures of sputum and nasal specimens had growth of MRSA with in vitro susceptibility to clindamycin (D test negative) and an E test MIC of 1.5 µg/mL for vancomycin. Blood cultures were negative for growth of any organisms. Despite maximal interventions, progressive lactic acidosis and vasopressor-refractory shock developed. The patient died on day 4.

Figure Gram stain of sputum from patient 2 shows intracellular gram-positive cocci in clusters in blue, with surrounding cytoplasmic clearing and an absence of normal intracellular organelles.
The role of PVL as the principal staphylococcal toxin has been debated because animal models have been inconclusive, perhaps because rodent neutrophils are relatively resistant to the lytic effect of PVL, whereas rabbit (and human) polymorphonuclear leukocytes are susceptible. Interest has also focused on phenol-soluble modulins, another type of cytolytic peptides secreted preferentially by CA-MRSA. Whether the toxin is PVL or phenol-soluble modulins, the marked lytic effect on neutrophils can be seen directly, as indicated by the cytoplasmic clearing we observed in the Gram stain of our patient’s sputum (see Figure). This lysis provides direct visualization of toxin-mediated cellular destruction that correlates with a fulminant clinical course.

Conclusion

These 3 cases of fatal CA-MRSA pneumonia illustrate the lethality of this MRSA isolate. As highlighted in our case series, features such as hemoptysis, rapid progression of signs and symptoms in an otherwise healthy or immunocompetent person, and an initial normal or low WBC count that subsequently decreases further, are suggestive of this disease. In these 3 patients, the Gram stains of sputum were the first results received to suggest CA-MRSA. Clusters of gram-positive cocci with cytoplasmic clearing and the absence of normal intracellular organelles strongly suggest PVL-positive MRSA. Increased awareness of CA-MRSA pneumonia, with associated administration of appropriate antibiotics and, possibly, intravenous immunoglobulin, is important to maximize a patient’s chances of survival.

FINANCIAL DISCLOSURES

None reported.

REFERENCES


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