Pleuropulmonary Complications of Panton-Valentine Leukocidin-Positive Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

Importance of Treatment With Antimicrobials Inhibiting Exotoxin Production

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Four patients with pleuropulmonary complications attributed to community-acquired methicillin-resistant *Staphylococcus aureus* (CAMRSA) positive for Panton-Valentine leukocidin (PVL) are described. These patients presented to Barnes-Jewish Hospital with severe necrotizing pneumonia, empyema, ARDS-complicating pneumonia, and ventilator-associated pneumonia-complicating acute pancreatitis, respectively. The first three patients had influenza-like illnesses preceding their PVL-positive CAMRSA infections. In all four cases, PVL-positive CAMRSA was isolated from respiratory secretions, and from blood cultures in three of the individuals. Antimicrobial therapy was inappropriate initially in all four patients. Three patients failed to respond to subsequent treatment with vancomycin, including two patients with persistent bacteremia despite at least 48 h of treatment with vancomycin. These patients were subsequently treated with antimicrobials inhibiting exotoxin production (linezolid or clindamycin) with good clinical results. Clinicians should be aware of PVL-positive CAMRSA due to the rapid and severe progression of pleuropulmonary complications associated with this infection. Additionally, specific antimicrobial therapy directed against CAMRSA differs from the traditional antimicrobial agents prescribed for community-acquired pneumonia. Antimicrobial agents that specifically inhibit exotoxin production appear to be the preferred treatment agents.

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**Key words:** empyema; infection; Panton-Valentine leukocidin; pneumonia; *Staphylococcus aureus*

**Abbreviations:** CAMRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; PCR = polymerase chain reaction; PVL = Panton-Valentine leukocidin

Staphylococcus aureus accounts for 20 to 30% of all cases of hospital-acquired pneumonia, and the proportion of resistant isolates continues to increase.1 Nosocomial strains of methicillin-resistant *S aureus* (MRSA) are distributed worldwide, and data from the National Nosocomial Infections Surveillance System Report show that MRSA now accounts for >55% of *S aureus*-related infections in the intensive care setting.2,3 Along with Pseudomonas aeruginosa and Acinetobacter, MRSA is also a common cause of late-onset pneumonia, particularly in patients requiring mechanical ventilation.1

MRSA has also moved beyond the hospital setting and is emerging as a community-acquired pathogen among patients without established risk factors. The MRSA strains originating in the community are microbiologically distinct from hospital-acquired MRSA and thus have been labeled as community-acquired MRSA (CAMRSA). While CAMRSA is primarily associated with skin and soft tissue infections, it is increasingly causing more invasive infections, including a severe form of necrotizing pneumonia.4

This case series describes four adult patients who presented to Barnes-Jewish Hospital with CAMRSA pleuropulmonary infections over a 4-month period (November 2004 to February 2005). The CAMRSA isolates from these patients were all positive for Panton-Valentine leukocidin (PVL), a potent inflam-
matory mediator linked to necrotizing infections in humans. The goal of this report is to familiarize clinicians with PVL-positive CAMRSA in order to avoid misdiagnosis of this important community-acquired respiratory infection and to minimize delays in the administration of appropriate antimicrobial treatment.

**Case Reports**

**Case 1**

A 45-year-old man had influenza-like symptoms with arthralgias, myalgias, rhinorrhea, fatigue, and a mild cough for 5 days. He had no recent hospitalizations or chronic medical conditions and lived on a horse ranch in Missouri. He was hospitalized at a local hospital for community-acquired pneumonia and treated with ceftriaxone and azithromycin. His condition worsened over 24 h, requiring mechanical ventilation, and his antibiotics were broadened to include vancomycin (1 g bid) on the second hospital day following a positive blood culture finding for Gram-positive cocci, subsequently identified to be MRSA. His chest radiograph worsened with bilateral infiltrates, and he was transferred to Barnes-Jewish Hospital on the fourth hospital day due to increasing oxygen requirements. Blood culture specimens were obtained on transfer to Barnes-Jewish Hospital and BAL was performed, both yielding PVL-positive CAMRSA (> 105 cfu/mL from the BAL fluid) [Table 1] despite having received vancomycin, 1 g bid, for the previous 3 days (vancomycin serum levels are not available). Antibiotics were changed to linezolid and rifampin after 24 h at Barnes-Jewish Hospital for a total treatment course of 14 days. A nasal swab for influenza virus was negative, but a conventional tube culture was positive for influenza virus type A. The chest radiograph at transfer revealed bilateral dense infiltrates, and CT showed severe necrotizing pneumonia with cystic changes in both lungs (Fig 1). The peak positive end-expiratory pressure level was 18 cm H2O with a fraction of inspired oxygen of 100% for 48 h after transfer to Barnes-Jewish Hospital despite the administration of inhaled prostacyclin. Normal left ventricular function without an intracardiac shunt was found on echocardiography, and the patient underwent tracheostomy on hospital day 16 after improvement in oxygenation. He was subsequently weaned from mechanical ventilation and transferred to a long-term care facility for physical rehabilitation.

**Case 2**

A 40-year-old woman with HIV had an upper respiratory tract infection with rhinorrhea, a dry cough, and fatigue. She had an allergy to trimethoprim-sulfamethoxazole manifested by severe erythoderma and was treated 6 months earlier for an episode of *Pneumocystis carinii* pneumonia with dapsone. She was seen by her primary care physician and received 7 days of azithromycin before presenting to the emergency department of Barnes-Jewish Hospital with 24 h of progressive shortness of breath, fever, and dyspnea with mild exertion. A chest radiograph showed a large right-sided pleural effusion (Fig 2). Arterial oxygen saturation on room air was 86%, and supplemental oxygen was administered. On transfer to the medical ICU, two drainage tubes were placed into the right chest cavity by the thoracic surgery service, revealing purulent appearing fluid with a positive Gram stain from Gram-positive cocci in clusters. The pleural fluid culture grew out PVL-positive CAMRSA, and the patient completed a 30-day course of vancomycin with removal of both chest tubes after 7 days.

**Case 3**

A 34-year-old man with a history of cocaine and heroin use was admitted to Barnes-Jewish Hospital with 3 days of cough, fever, and dyspnea following 1 week of influenza-like symptoms. A chest radiograph in the emergency department revealed a right upper lobe infiltrate (Fig 3), and the patient was started on antimicrobial therapy with ceftriaxone and azithromycin. He was transferred to the medical ICU, where his condition deteriorated over 24 h requiring tracheal intubation and mechanical ventilation due to hypoxemia and respiratory distress. Chest radiograph findings worsened as did his oxygenation, requiring 14 cm H2O of positive end-expiratory pressure and a fraction of inspired oxygen of 80% for

| Table 1—Antimicrobial Susceptibility and Appropriateness of Initial Antimicrobial Therapy* |
|---------------------------------------------------------------|---|---|---|---|
| Antimicrobials | Case No. | 1 | 2 | 3 | 4 |
| Antimicrobial susceptibility | | | | | |
| Oxacillin | R | R | R | R |
| Fluoroquinolones | R | S | R | I |
| Erythromycin | R | R | R | R |
| Vancomycin | S | S | S | S |
| Linezolid | S | S | S | S |
| Clindamycin | S | S | S | S |
| Cephalosporin | R | R | R | R |
| Trimethoprim-sulfamethoxazole | S | S | S | S |
| Inappropriate initial | | | | |
| Antimicrobial treatment | Yes | Yes | Yes | Yes |
| Vancomycin treatment failure | Yes | No | Yes | Yes |
| *R = resistant; S = sensitive; I = intermediate. | | | | |

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24 h. Blood cultures and BAL revealed PVL-positive CAMRSA as the only identified pathogen. The patient was initiated on vancomycin, 1 g bid, but switched to linezolid, 600 mg bid, after 72 h due to his worsening clinical condition manifest by progressive infiltrates, hypoxemia, fever, and leukocytosis. After 4 days of linezolid therapy, the pulmonary condition and WBC count had improved. However, the patient was switched back to vancomycin with the addition of clindamycin, 900 mg q8h, due to development of a severe rash while receiving linezolid that was suspected to be a drug reaction. The CAMRSA isolate was shown to be susceptible to clindamycin based on in vitro testing. The patient completed a 14-day course of antibiotics and underwent a tracheostomy on hospital day 11. He was subsequently transferred to a long-term ventilator facility for weaning and physical therapy.

Case 4

A 40-year-old man with a 6-year history of insulin-dependent diabetes mellitus and abuse of alcohol and cocaine was admitted to Barnes-Jewish Hospital with altered mental status and abdominal pain. The patient’s blood sugar was 1,755 mg/dL, with a sodium concentration of 116 mmol/L and an anion gap of 34 mmol/L. A diagnosis of diabetic ketoacidosis was made, and the patient was transferred to the medical ICU, where he was treated with IV fluids and insulin. CT of the abdomen was performed, revealing severe acute pancreatitis without evidence of necrosis or pseudocyst formation. As part of the routine surveillance carried out in the medical ICU, a nasal swab culture was performed and found to be positive for CAMRSA. The patient was treated with imipenem for the pancreatitis and was intubated on the third hospital day for respiratory failure attributed to noncardiogenic pulmonary edema with the presence of new pulmonary infiltrates. Acute renal failure also developed on the third hospital day necessitating hemodialysis. On the fourth hospital day, vancomycin, 1.5 g bid, was empirically added to his medical regimen due to progression of the radiographic infiltrates. Over the next 4 days, vancomycin trough levels were obtained that were 18.0 g/mL, 18.5 g/mL, and 35.3 g/mL, respectively. A chest radiograph on the ninth hospital day revealed a cavitary lesion within the right-side infiltrate that was confirmed by CT (Fig 4). Blood culture findings and BAL performed after receiving 3 days and 7 days of

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22032/)

**Figure 1.** Chest radiograph and CT of patient with necrotizing pneumonia due to CAMRSA positive for PVL expression.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22032/)

**Figure 2.** Chest radiograph demonstrating a right-sided empyema attributed to PVL-positive CAMRSA.
vancomycin, respectively, were positive for PVL-positive CAMRSA (> 105 cfu/mL from the BAL fluid). Transesophageal echocardiography findings were negative for any lesions on the heart valves. The patient was switched to linezolid, 600 mg bid, and rifampin, 300 mg q8h. His medical condition gradually improved while completing a 14-day course of linezolid and rifampin, and he underwent a tracheostomy after 11 days of mechanical ventilation. He was subsequently transferred to a long-term care facility for weaning of mechanical ventilation and physical rehabilitation.

**Materials and Methods**

**Microbiologic Assays**

Oxacillin resistance among isolates of *S aureus* was determined by disk diffusion susceptibility testing using a 30-µg cefoxitin disk...
as recommended by the Clinical Laboratory Standards Institute. This was confirmed by growth on screening agar containing 6 μg/mL of oxacillin (Becton-Dickinson Microbiology Systems; Cockeysville, MD).

To obtain purified bacterial DNA for polymerase chain reaction (PCR) analysis, individual clinical isolates were grown overnight in trypticase soy broth. The cells were centrifuged, and the DNA was purified from the pellets using a modified version of the extraction method described by Kalia et al7 in combination with a genomic DNA extraction kit (QIAamp; QIAGEN; Chatsworth, CA). Amplification of PVL genes was accomplished by the method of Lina et al8 using luk-PVL-1 (5′-ATCATTAGGAATAATGTCTGGACATGATCCA-3′) and the luk-pv-2 (GCATCAASTGTATTGGATAGCAAAAGC-3′) primers. All amplified PCR products were visualized following electrophoresis in 1.5% agarose gels run at 100 V with ethidium bromide staining and comparison to molecular weight standards (phiX174 DNA-Hae III Digest markers; Promega; Madison, WI) [Fig 5]. PVL-positive strains yielded an amplification product of 433 base pairs.

Discussion

Over the past 2 decades, the prevalence of MRSA strains has steadily increased in hospitals in the United States and abroad. A number of factors are associated with a higher risk for MRSA infection among hospitalized patients, including lengthy hospitalization, ICU stay, prolonged antimicrobial therapy, surgical procedures, and close proximity to a hospitalized patient with MRSA infection or colonization.9–12 The spread of MRSA among healthy community dwellers lacking established risk factors has been characterized by clusters of cases or outbreaks that have occurred among diverse groups of people. Recent outbreaks have included Pacific Islanders, native American populations, athletic teams, and prison inmates.13–16

In a study17 that compared the epidemiologic and microbiological characteristics of CAMRSA and health-care–acquired MRSA among patients from Minnesota, community-associated cases comprised 12% of 1,100 MRSA infections. Skin and soft tissue infections accounted for 75% of all CAMRSA cases and were far less likely than health-care–acquired strains to involve the respiratory or urinary tract. CAMRSA isolates also tended to possess different exotoxin gene profiles than the health-care–acquired isolates. However, in contrast to health-care–acquired MRSA strains, which are generally multidrug resistant, CAMRSA strains tended to be susceptible to agents other than β-lactams.

All MRSA strains contain a mecA gene and regulatory sequences that encode for the production of penicillin-binding protein 2a, which is not found in methicillin-susceptible S aureus isolates.18 The presence of penicillin-binding protein 2a renders S aureus insensitive to all β-lactams that have been developed, including cephalosporins, cefamycins, and carbapenems. Hospital-acquired strains also tend to be multidrug resistant and may exhibit reduced susceptibility or complete resistance to erythromycin, clindamycin, aminoglycosides, and fluoroquinolones. Conversely, CAMRSA isolates usually exhibit resistance only to β-lactams, and are susceptible to many non–β-lactam agents.5

S aureus strains can express many potential virulence factors, including surface proteins that promote colonization of host tissues, exotoxins, and superantigens that cause tissue damage and the symptoms of septic shock, and invasins that promote bacterial spread in tissues (leukocidin, kinases, hyaluronidase). PVL is a cytotoxin produced by < 5% of S aureus strains and has been associated with primary skin infections and severe necrotizing pneumonia.5,18 In a study8 that screened 172 S aureus strains, PVL genes were detected in 93% of strains associated with furunculosis, and in 85% of those associated with severe necrotic hemorrhagic pneumonia, both of which were community acquired. PVL genes were not detected in strains causing other types of infections, such as hospital-acquired pneumonia, toxic-shock syndrome, infective endocarditis, or mediastinitis.

![Figure 5. Agarose gel electrophoresis demonstrating the results of PCR for PVL. Lane 1: molecular weight marker. Lane 2: positive PVL control strain of S aureus. Lane 3: negative PVL control strain of S aureus. Lane 4: negative clinical isolate of S aureus. Lane 5: patient isolate of S aureus demonstrating a positive PCR product representing PVL.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22032/ on 06/26/2017)
PVL is a synergohymenotropic toxin assembled from two component proteins.19,20 PVL creates lytic pores in the cell membranes of neutrophils and induces release of neutrophil chemotactic factors including interleukin-S and leukotriene B4.21 The inflammatory response in the lung associated with PVL is thought to be the mediator of tissue necrosis accounting for the clinical and radiographic presentation of patients with PVL-positive CAMRSA pneumonia.

Gillet et al22 compared 16 cases of PVL-positive S aureus pneumonia with 36 PVL-negative cases. Patients in the PVL-positive cohort tended to be much younger than those with PVL-negative S aureus infection. Twelve of 16 PVL-positive patients experienced an influenza-like illness during the 2 days prior to hospital admission, compared to only 3 individuals with PVL-negative strains. Rapid progression to severe pneumonia was also seen in PVL-positive patients, and 48 h after admission their survival rate was 63%, compared to 94% for PVL-negative individuals. Postmortem histopathologic examination of the lungs showed extensive necrotic ulcerations of the tracheal and bronchial mucosa and massive hemorrhagic necrosis of interalveolar septa.

Four well characterized healthy adult patients with severe community-acquired pneumonia caused by CAMRSA from Johns Hopkins University have recently been described.23 Two of the patients had documented influenza A infection, and at least two of these patients received inappropriate initial antimicrobial therapy directed against more traditional bacterial pathogens associated with community-acquired pneumonia. Like our patients, the four individuals in the Johns Hopkins report had necrotizing pneumonia with cavitary lesions and evidence of sepsis syndrome. Definitive antimicrobial therapy consisted of combination treatment with various agents including vancomycin, fluoroquinolones, clindamycin, linezolid, and rifampin. Our fourth case is unique in representing the first report of early-onset ventilator-associated pneumonia attributed to CAMRSA in a patient with documented colonization with this pathogen at the time of hospital admission.

For MRSA strains that produce toxins such as PVL, antimicrobial agents acting to inhibit protein synthesis such as linezolid or clindamycin may be a more appropriate selection. The α-toxin, encoded by the *hla* gene, is a major virulence factor of *S aureus*.18 In a study24 that evaluated the influence of subinhibitory doses of 31 antibiotics on the expression of the gene, vancomycin and teicoplanin did not have any effect. Conversely, low concentrations of clindamycin reduced *hla* expression by 98%, and other data25 have shown that clindamycin also inhibits production of toxic shock syndrome toxin 1. The inability of vancomycin to inhibit toxin production may explain the lack of clinical response seen in three of our patients treated with vancomycin and subsequently switched to other agents. Clindamycin has been used successfully to treat MRSA pneumonia, but concern over the possibility of inducible clindamycin resistance has discouraged some clinicians from prescribing that agent.26 The erythromycin-clindamycin “D-zone” test can separate strains that have the genetic potential to become resistant during therapy from strains that are fully susceptible to clindamycin.

The expression of virulence factors in *S aureus* has also been found to be vulnerable to subgrowth-inhibitory concentrations of linezolid. Bernardo et al27 tested subinhibitory concentrations of linezolid (12.5%, 25%, 50%, and 90% of minimum inhibitory concentration) in *S aureus* cultures. At all minimum inhibitory concentrations, linezolid reduced the secretion of several specific virulence factors, including staphylococcal enterotoxin A, bifunctional autolysin, autolysin, protein A, and α- and β-hemolysins.

In summary, PVL-positive CAMRSA appears to be an increasingly prevalent pathogen worldwide. Clonal expansion of this virulent pathogen appears to be increasing in North American, Australia, Asia, and Europe.17,20,22,28–30 Clinicians should be aware of PVL-positive CAMRSA as a potential pathogen in any patient presenting with severe community-acquired pneumonia. Many of these patients will have had a preceding influenza-like illness and radiographic evidence of lung necrosis. The presence of CAMRSA should be further suspected if the MRSA isolate shows susceptibility to non-β-lactam antibiotics including minocycline, fluoroquinolones, clindamycin, and trimethoprim-sulfamethoxazole. In such patients, initial empiric therapy directed against CAMRSA appears reasonable until this infection can be excluded microbiologically.

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