Methicillin-resistant *Staphylococcus aureus* as a Cause of Community-acquired Pneumonia

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New pathogens have emerged that now complicate the management of community-acquired pneumonia (CAP). Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged as a potential cause of CAP, particularly complicated CAP. In this literature review, the incidence, invasiveness, and antimicrobial management of CA-MRSA is discussed. Based on existing data and the rising incidence of CA-MRSA, we recommend a change in antibiotic selection for complicated CAP.

Introduction

Community-acquired pneumonia (CAP) is typically defined as an acute infection of the lung parenchyma in a patient who has not been hospitalized within 14 days or a resident of a long-term care facility within 1 year of symptom onset. In the United States, there are 4 to 5 million cases of CAP annually, and approximately 25% require hospitalization [1]. Pneumonia is the seventh leading cause of death overall. It is the leading cause of death from an infectious etiology in the United States and carries a 14% mortality rate [1,2]. Traditionally, the antibiotic management of patients with CAP and the selection of antibiotics have been straightforward. However, new pathogens have recently emerged that tend to complicate the management of patients with CAP. These new entities are: the coronavirus responsible for severe acute respiratory syndrome, human metapneumovirus, and community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). This review focuses on CA-MRSA and its impact on CAP.

Background

Most cases of CAP occur during the winter. Patients diagnosed with CAP may have a wide variety of complaints including varying degrees of fever, cough, chest pain, shortness of breath, rigors, or diaphoresis. Nonspecific complaints such as fatigue, myalgia, and headache may be present as well. Most patients may have either auscultatory findings of pneumonia on exam or the presence of an acute infiltrate on chest radiograph.

The more common pathogens causing CAP, their incidence, and preferred antibiotic choices, are listed in Table 1. Guidelines for the management of CAP have been published by the American Thoracic Society and the Infectious Diseases Society of America on a regular basis since 1993; however, the organizations differ in their approach to the management of CAP. The Infectious Diseases Society of America recommends pathogen-specific treatment, whereas the American Thoracic Society does not [3]. These latest practice guidelines published by the American Thoracic Society and the Infectious Diseases Society of America in 2000 and 2003, do not mention CA-MRSA as a possible etiologic agent for CAP, and recommendations for management are lacking [1,3].

CA-MRSA

The first patient infected with MRSA was described in 1968, but it was not until 1980 that the first case of CA-MRSA infection was documented [4]. In the past, CA-MRSA was more prevalent in certain patients with predisposing conditions such as a history of chronic disease, intravenous drug abuse, recent surgery or hospitalization, or residency at a chronic care facility. Evidence in recent literature suggests that CA-MRSA now infects previously healthy patients without predisposing factors. A rise in the number of cases of CA-MRSA during the past 5 years has been documented in several studies [5,6•,7••,8]. A 2-year study performed in Memphis, TN showed that 46 of 122 MRSA isolates were due to CA-MRSA in the beginning of the study. During the final

Table 1. Causes of CAP in immunocompetent patients in the United States

Pathogen	Percentage of CAP	Preferred antibiotic
Most common		
Streptococcus pneumoniae	20%–60%	Penicillin, ceftriaxone, cefotaxime, fluoroquinolones
NTHI	3%–10%	Cephalosporin (second or third generation), doxycycline, β-lactam plus β-lactamase inhibitor
Moraxella catarrhalis	3%–10%	Cephalosporin (second or third generation), doxycycline, β-lactam plus β-lactamase inhibitor
Atypical		
Mycoplasma pneumoniae	13%–37%	Doxycycline, macrolides, fluoroquinolones
Chlamydia pneumoniae	4%–19%	Doxycycline, macrolides, fluoroquinolones
Legionella pneumoniae	1%–13%	Macrolide with or without rifampin, fluoroquinolones
Aspiration		
Anerobes	6%–10%	Clindamycin, β-lactam plus β-lactamase inhibitor
Other causes		
Gram-negative *bacilli*	3%–10%	Cephalosporin (second or third generation), doxycycline
MSSA	3%–5%	Nafcillin/oxacillin, with or without rifampin or gentamicin
CA-MRSA	?	Clindamycin with or without rifampin or gentimicin, trimethoprim-sulfamethoxazole, vancomycin
Viruses	2%–45%	
Other	3%–5%	

CA-MRSA—community-acquired methicillin-resistant *Staphylococcus aureus*; CAP—community-acquired pneumonia; MSSA—methicillin-susceptible *S. aureus*; NTHI—nontypeable *Haemophilus influenzae*.
(*Data from* American Thoracic Society [1] and Michelow et al [30].)

12 months of the study, CA-MRSA was the cause of 106 of 167 MRSA-positive cultures [7••]. Martinez-Aguilar et al. [9] examined all *Staphylococcus*-positive cultures from February 2000 to January 2002 and showed that the proportion of CA-MRSA increased from 35% to 67% of all isolates during this time period [9]. Similar results have been cited in many other cities in the United States, Europe, and Latin America.

CA-MRSA differs from its hospital-acquired counterpart from a genotypic and epidemiologic standpoint. A clear genetic distinction exists between the two. All MRSA strains are resistant to β-lactam antibiotics including cephalosporins. Before the evolution of drug-resistant *S. aureus*, patients infected with *S. aureus* were treated with β-lactam antibiotics. β-lactam antibiotics bind to an enzyme on the cell wall of the bacteria called transpeptidase (PBP). PBP works by catalyzing the cross-linking of structural molecules in the bacterial cell wall. When β-lactam antibiotics bind to PBP, this cross-linking is inhibited, resulting in a weaker cell wall, which eventually lyses [8]. *S. aureus* has evolved and acquired a new gene, the *mecA* gene. This gene sequence is located on a mobile genetic element known as the staphylococcal cassette chromosome *mec* (SCC*mec*). The *mecA* gene codes for the penicillin-binding protein 2a (PBP-2a), which is also expressed on the cell wall. However, β-lactam antibiotics have a low affinity for PBP-2a, which results in a *S. aureus* strain insensitive to β-lactam antibiotics, including cephalosporins [10].

CA-MRSA strains differ when compared to hospital-acquired strains by carrying only one antibiotic resistance gene (*mecA*) and a smaller SCC*mec*. Hospital-acquired MRSA is multidrug resistant, whereas CA-MRSA is typically resistant to β-lactam antibiotics but sensitive to clindamycin, trimethoprim-sulfamethoxazole, gentamicin, and vancomycin.

CA-MRSA seems to act differently than methicillin-sensitive *S. aureus* (MSSA). Both pathogens most commonly cause skin and soft tissue infections; however, data indicate that the prevalence of invasive infections caused by CA-MRSA is increasing [11]. This fact was highlighted in a recent study performed in Houston. The authors compared sites of infection between patients infected with *Staphylococcus*. They found that the sites of infection were similar when comparing the MRSA and MSSA groups, except pneumonia: 24% of patients in the CA-MRSA cohort had pneumonia when compared to 5% in the MSSA group ($P = 0.001$) [9].

Pneumonia

Data regarding CA-MRSA as a cause for uncomplicated CAP is scarce. This paucity of data can be easily explained by the fact that biologic samples for culture are

not routinely obtained from patients with uncomplicated pneumonia. However, data does exist describing CA-MRSA as a cause of complicated pneumonia with effusion or empyema [6•,12•,13].

Effusion and Empyema

Evidence shows that the bacterial cause of pleural effusion and empyema has been changing over the past several years, which has been attributed to the widespread administration of the heptavalent pneumococcal conjugate vaccine. Some reports have shown a decrease in the incidence of parapneumonic effusions since 2000, with a significant decrease in effusions caused by *Streptococcus pneumoniae*. As effusions caused by *Streptococcus* have diminished, *S. aureus* has emerged as the most likely cause of effusion and empyema [5]. However, there is conflicting data. Other reports show an increase in the prevalence of complicated parapneumonic effusions. In a 10-year retrospective study conducted by Alfaro et al. [13], an etiology for complicated pneumonia was found in 28 of the 54 enrolled patients. All of the *Staphylococcus* isolates were methicillin resistant and occurred in the final 2 years of the study, 2002 and 2003 [13].

These trends are similarly reported in patients with empyema. An analysis of 219 patients with empyema over a period of 10 years revealed that the prevalence of *S. pneumoniae* identified from pleural fluid culture decreased from 66% to 27% after universal pneumococcal conjugate vaccine. *S. aureus* was the most common pathogen isolated from patients in this study as well, with 78% of the *S. aureus* strains being methicillin resistant [6•]. One report from Houston described a single clone of *S. aureus* responsible for more than 90% of CA-MRSA infections. From 2001 to 2003, they found a 65% increase in the number of patients diagnosed with empyema caused by CA-MRSA [12•].

Invasiveness

The majority of the patients infected with CA-MRSA suffer from skin and soft tissue infections. However, recently a surge has been seen in the number of invasive diseases caused by CA-MRSA such as septic arthritis, septic shock, osteomyelitis, and pneumonia [11,14]. Panton-Valentine leukocidin (PVL) has been blamed for the invasive capability of CA-MRSA resulting in severe pneumonia, including necrotizing pneumonia. PVL is a toxin that causes lytic pores in the cell membranes of neutrophils, causing leukocyte destruction and the release of chemotactic factors that result in a massive inflammatory response [15]. This inflammatory response is the cause of tissue necrosis. In one report of CAP due to *S. aureus* carrying the PVL gene, six of eight patients died [16]. This toxin has been found in numerous patients who developed hemorrhagic pneumonia [10], including a 16-month-old girl without risk factors who died from septicemia [17]. This toxin, as well as the enterotoxins B and C, have been isolated from CA-MRSA strains in Minnesota, Nebraska, and North Dakota. These toxins are super antigens, and have been responsible for at least four pediatric deaths from 1997 to 1999 [18].

In another report, hemoptysis, purulent expectoration, and temperature above 39°C were more common in patients with PVL-positive *S. aureus* pneumonia when compared to PVL-negative *S. aureus* pneumonia. No difference was noted in hypotension, tachycardia, tachypnea, or cyanosis between groups. Initial radiographic findings were also similar in both cohorts, but the PVL-positive group was more than twice as likely to develop infiltrates consistent with acute respiratory distress syndrome. The 48-hour survival rate was 62.5% in the PVL-positive patients and 94% in the PVL-negative patients [19]. Another report describes a previously healthy 31-year-old man diagnosed with CAP who was treated with oral levofloxacin because of a 2-day history of fever, chills, nausea, and cough. The patient returned 15 hours later with shortness of breath and hemoptysis and was managed with vancomycin, other antibiotics, and inotropic support. The patient died 38 hours later and MRSA was identified in blood culture with resistance patterns consistent with community-acquired strains. Genotyping revealed the presence of the PVL gene [20].

Influenza and CA-MRSA

Staphylococcal pneumonia has been reported to occur this past century during influenza epidemics. *S. aureus* has been associated with severe illness and death in patients with influenza. Recently, cases of CA-MRSA–associated pneumonia have been reported in patients with flu-like symptoms. Influenza is believed to increase host susceptibility to Staphylococcal superinfection by reducing phagocytic killing of neutrophils and increasing adhesion to the respiratory tract [21]. In one recent review of 17 cases of influenza-like illness complicated with *S. aureus* pneumonia during the 2003 to 2004 influenza season, 88% of the patients had CA-MRSA CAP. A PVL gene was detected in 85% of isolates, and 80% of all deaths were due to CA-MRSA. All the isolates were resistant to macrolides, and one half were resistant to fluoroquinolones. The authors concluded that management of pneumonia during or following an influenza season should include antimicrobial coverage for MRSA [22].

Management

Antibiotic therapy for patients infected with CA-MRSA–associated pneumonia is not well established. Most experts recommend the use of clindamycin or trimethoprim sulfamethoxazole for outpatient management. Inpatient therapy should consist of intravenous

clindamycin, whereas vancomycin should be reserved for critically ill patients who have a suspected CA-MRSA infection.

Vancomycin is considered the standard for critically ill patients with CA-MRSA. Opponents of vancomycin argue that tissue levels of vancomycin above minimum inhibitory concentration are far more predictive of clinical outcome. Therefore, they recommend a continuous infusion of vancomycin with the goal of maintaining blood levels that are greater than 20 μm/mL in an attempt to maintain adequate tissue levels of vancomycin [23,24]. Recent data also suggest that vancomycin may not be the optimal antibiotic due to poor tissue penetration. Cruciani et al. [25] measured vancomycin concentrations in lung tissue and blood at 1 and 12 hours in 30 patients with pleural effusions and demonstrated that the vancomycin level in the lungs was subtherapeutic despite adequate serum vancomycin levels. In a series of patients, Gonzalez et al. [17] demonstrated that patients with MSSA pneumonia who were treated with vancomycin had a higher mortality rate, 47% versus 0% in the cloxacillin cohort [17]. A case series of three patients published by Rello et al. [23] found positive MRSA growth in postmortem cultures despite vancomycin therapy. Alternatively, other authors have shown that the concentration of linezolid is higher in lung epithelial lining at 2, 4, 6, 10, and 12 hours when compared to blood [26,27]. These data suggest that vancomycin may not be the ideal antibiotic choice for pneumonia caused by CA-MRSA.

We suggest that the first-line antimicrobial choice for CA-MRSA should include clindamycin or trimethoprim-sulfamethoxazole. Reports have shown that clindamycin successfully treats CA-MRSA, MSSA, and penicillin-resistant *S. pneumoniae* infections. One retrospective study examined 46 patients with invasive CA-MRSA infections who were managed with clindamycin, vancomycin, or β-lactam antibiotics. All 39 patients who were treated with clindamycin had complete or substantial improvement [9]. If clindamycin is chosen as therapy, the erythromycin induction test (D-test) should be performed on MRSA isolates to check for the presence of inducible resistance. The presence of clindamycin resistance in different communities varies widely. Data from Texas showed that 83% of CA-MRSA isolates were resistant to erythromycin, but inducible clindamycin resistance was found in only 2.2% of strains [9]. However, other areas such as Chicago and Minnesota have reported positive D-tests in over 85% of isolates [27,28].

The management of empyema is also controversial. Antibiotics alone are adequate therapy for simple pneumonia or an early effusion. However, fluid drainage is necessary if the effusion is large or there is evidence of an empyema. There are many management choices for fluid drainage such as needle thoracostomy, tube thoracostomy, and video-assisted thoracoscopy (VATS).

The rapid initiation of treatment of CAP, pleural effusion, or empyema can not be overstated. The delayed use of antibiotics to which MRSA is susceptible may have contributed to the fatal outcome of four children with pneumonia [18]. One prospective study of 14,000 patients with pneumonia requiring admission showed that delay in antibiotic initiation exceeding 8 hours post-admission was associated with an increase in mortality [29]. Another report proposed the early use of VATS for initial management of empyema. The authors showed a reduced hospital stay of 11.49 days versus 15.18 days and a shorter duration of fever when VATS was performed within the first 48 hours of admission [6•].

Conclusions

The management of CAP is not as clear as it has been in the past. The exponential rise in the prevalence of MRSA strains and the changing resistance patterns make this condition challenging to treat. Although the management of uncomplicated patients remains unchanged, the addition of clindamycin to cover CA-MRSA in certain situations is recommended. We suggest managing patients who are diagnosed with pleural effusions, empyema, or other forms of complicated pneumonia with antibiotics targeted at CA-MRSA. Other circumstances where suspicion for CA-MRSA should be heightened include young patients or critically ill patients with pneumonia, or patients who have pneumonia associated with influenza. A need now seems to exist for a prospective multicenter analysis to evaluate the impact of CA-MRSA on CAP.

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