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

Curt Stankovic, MD, Prashant V. Mahajan, MD, MPH, MBA, and Basim I. Asmar, MD

**Corresponding author**
Curt Stankovic, MD
Division of Emergency Medicine, Children’s Hospital of Michigan, 3901 Beaubien, Detroit, MI 48201, USA.
E-mail: cstankov@dmc.org

*Current Infectious Disease Reports* 2007; 9:223–227
Current Medicine Group LLC ISSN 1523-3847
Copyright © 2007 by Current Medicine Group LLC

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.

**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...
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 (SCCmec). 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 SCCmec. 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

| 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 gentamicin, 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].)
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 macrodiles, 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.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. American Thoracic Society: Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. Am J Resp Crit Care Med 2001, 163:1730–1754.

2. Mokdad AH, Marks JS, Stroup DF, et al.: Actual causes of death in the United States, 2000. JAMA 2004, 291:1238–1245.

3. Mandell LA, Bartlett JG, Dowell SF, et al.: Infectious Diseases Society of America. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003, 37:1405–1433.

4. Barrett FF, McGehee RF Jr, Finland M: Methicillin-resistant Staphylococcus aureus at Boston City Hospital: bacteriologic and epidemiologic observations. N Engl J Med 1968, 279:441–448.

5. Buckingham SC, King MD, Miller ML: Incidence and etiologies of complicated parapneumonic effusion in children, 1996 to 2001. Pediatr Infect Dis J 2003, 22:499–504.

6. Schultz KD, Fan LL, Pinsky J, et al.: The changing face of pleural empyemas in children: epidemiology and management. Pediatrics 2004, 113:1735–1740.

The authors argue that performing VATS less than 48 hours post-admission reduces the hospital stay and duration of fever.
7. Buckingham SC, McDougall LK, Cathey LD, et al.: Emergence of community-acquired methicillin-resistant Staphylococcus aureus at a Memphis, Tennessee Children's Hospital. *Pediatr Infect Dis J* 2004, 23:619–624.

This retrospective study evaluated the etiology of parapneumonic effusion in patients in the pre- and post-pneumococcal-vaccine era. They found that the overall number of effusions decreased in the post-vaccination era; however, the proportion caused by CA-MRSA increased significantly.

8. Katayama Y, Zhang H, Chambers HF: PBP 2a mutations producing very-high-level resistance to beta-lactams. *Antimicrob Agents and Chemother* 2004, 48:453–459.

9. Martínez-Aguilar R, Hammerman WA, Mason EO Jr: Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus in children. *Pediatr Infect Dis J* 2003, 22:593–598.

10. Foster TJ: The Staphylococcus aureus "superbug." *J Clin Invest* 2004, 114:1693–1696.

11. Stankovic C, Mahajan PV: Healthy children with invasive community-acquired methicillin-resistant Staphylococcus aureus infections. *Pediatr Emerg Care* 2006, 22:361–363.

12. Mishan AM, Mason EO Jr, Martínez-Aguilar G, et al.: Emergence of a predominant clone of community-acquired Staphylococcus aureus among children in Houston. *Pediatr Infect Dis J* 2005, 24:201–206.

13. Alfar C, Fergie J, Purcell K: Emergence of community-acquired methicillin-resistant Staphylococcus aureus in complicated parapneumonic effusions. *Pediatr Infect Dis J* 2005, 24:274–276.

14. Honeybourne D, Tobin C, Jevons G, et al.: Intrapulmonary penetration of linezolid. *Chest* 2002, 122(Suppl):159a.

15. König B, Prevost G, Piemont Y, et al.: Effects of Staphylococcus aureus leukocidins on inflammatory mediator release from human granulocytes. *J Infect Dis* 1995, 171:607–613.

16. Lina G, Piemont Y, Godail-Gamot F, et al.: Involvement of Panton-Valentine leukocidin-producing Staphylococcus aureus in primary skin infection and pneumonia. *Clin Infect Dis* 1999, 29:1128–1132.

17. Gonzalez C, Rubio M, Romero-Vivas J, et al.: Bacteremic pneumonia due to Staphylococcus aureus: a comparison of disease caused by methicillin-resistant and methicillin-sensitive organisms. *Clin Infect Dis* 1999, 29:1171–1177.

18. The Centers for Disease Control and Prevention: Four pediatric deaths from community-acquired methicillin-resistant Staphylococcus aureus-Minnesota and North Dakota, 1997-1999. *JAMA* 1999, 282:1123–1126.

19. Gillet Y, Issartel B, Vanhems P, et al.: Association between Staphylococcus aureus trains carrying gene for Panton-Valentine leukocidin and highly lethal necrotizing pneumonia in young immunocompetent patients. *Lancet* 2002, 359:753–759.

20. Frazee BW, Salz TO, Perdereau-Remington F: Fatal community-associated methicillin-resistant Staphylococcus aureus pneumonia in an immunocompetent young adult. *Ann Emerg Med* 2005, 46:401–404.

21. Abramson JS, Lewis JC, Lyles DS, et al.: Inhibition of neutrophils lysosome-phagosome fusion associated with influenza virus infection in vitro. Role depressed bactericidal activity. *J Clin Invest* 1982, 69:1383–1397.

22. Hageman JC, Uyeki TM, Francis JS, et al.: Severe community-acquired pneumonia due to Staphylococcus aureus, 2003-04 influenza season. *Emerg Infect Dis* 2006, 12:894–899.

23. Rello J, Diaz E, Bodi M: Appropriate treatment of pneumonia. *Clin Infect Dis* 2000, 31:1313–1315. [Comment on: Clin Infect Dis 1999, 29:1171–1177.]

24. Gonzalez C, Rubio M, Romero-Vivas J, Picazo JJ: Reply. *Clin Infect Dis* 2000, 31:1314–1315.

25. Cruciani M, Gatti G, Lazzarini L, et al.: Penetration of vancomycin into human lung tissue. *J Antimicrob Chemother* 1996, 38:865–869.

26. Conte JE Jr, Golden JA, Kipps J, et al.: Intrapulmonary pharmacokinetics of linezolid. *Antimicrob Agents Chemother* 2002, 46:1475–1480.

27. Como-Sabetti K, Glennen A, Barkus J, et al.: Inducible clindamycin resistance among erythromycin resistant community-onset methicillin resistant Staphylococcus aureus isolates in Minnesota, 2000-2001 [abstract 92]. Program and abstracts of the Infectious Disease Society of America 40th Annual Meeting. Chicago: Infectious Disease Society of America; 2002:61.

28. Frank AL, Marcinak JF, Mangat PD, et al.: Clindamycin treatment of invasive Staphylococcus aureus infections in children. *Pediatr Infect Dis J* 2002, 21:530–534.

29. Meehan TP, Fine MJ, Krumholz HM, et al.: Quality of care, process and outcomes in elderly patients with pneumonia. *JAMA* 1997, 278:2080–2084.

30. Michelow IC, Olsen K, Lozano J, et al.: Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. *Pediatrics* 2004, 113:701–707.