Emergence of community-acquired meticillin-resistant Staphylococcus aureus strain USA300 as a cause of necrotising community-onset pneumonia

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Meticillin-resistant Staphylococcus aureus (MRSA), usually known as a nosocomial pathogen, has emerged as the predominant cause of skin and soft-tissue infections in many communities. Concurrent with the emergence of community-acquired MRSA (CA-MRSA), there have been increasing numbers of reports of community-acquired necrotising pneumonia in young patients and others without the classic health-care-associated risk factors. Community-onset necrotising pneumonia due to CA-MRSA is now recognised as an emerging clinical entity with distinctive clinical features and substantial morbidity and mortality. A viral prodrome (e.g., influenza or influenza-like illness) followed by acute onset of shortness of breath, sepsis, and haemoptysis is the most frequent clinical presentation. The best treatment of this partly toxin-mediated disease has not been clearly defined. Whereas cases of CA-MRSA pneumonia have now been reported from almost every continent, the overall burden of disease of this emerging syndrome remains incompletely described. We report two related cases of community-onset pneumonia due to the MRSA USA300 genotype and review the literature regarding the emergence of CA-MRSA pneumonia.

Case presentation

Case 1

A 45-year-old white woman presented to the hospital during the height of the influenza season with complaints of shortness of breath, fever, chills, and a cough that produced brown sputum of 1 week’s duration. She denied haemoptysis, but gave a history of recurrent folliculitis for the past several months. She reported a preceding influenza-like illness (fever, myalgias, headache, and upper respiratory symptoms) 5 days before the onset of her current symptoms. Her medical history was notable for asthma, hypertension, hypothyroidism, adrenal insufficiency, and methadone maintenance for previous opiate dependence. She denied a history of alcohol use, but said that she smoked cigarettes. She had not received an influenza vaccination.

On admission, her blood pressure was 166/99 mm Hg, pulse rate was 103 beats per min, respiratory rate was 19 breaths per min, and temperature was 38.2°C. She...
seemed to be in moderate respiratory distress. On cardiopulmonary examination she was found to have diffuse rhonchi and crackles, but no heart murmurs. No skin lesions were noted. The rest of her examination was unrevealing. Laboratory data included a white blood cell count of 8.7 × 10⁹ cells per L (87% neutrophils), haematocrit of 43%, and platelet count of 299 × 10⁹/L. Her chest radiograph showed bilateral opacities with a right middle lobe dense consolidation (figure 1).

The patient was admitted with presumed community-acquired pneumonia. Several hours later, her dyspnoea worsened, and she required intubation and mechanical ventilatory support. Broad-spectrum antibiotic coverage with piperacillin–tazobactam and vancomycin were initiated after initial blood cultures were drawn. HIV serology and a legionella urinary antigen test were negative. Multiple sets of blood cultures (including the initial set obtained on admission) were culture negative. A culture of respiratory secretions obtained by mini bronchoalveolar lavage from the day of admission grew MRSA that was resistant to β-lactam antibiotics and erythromycin, but susceptible to clindamycin, fluorquinolones, rifampicin, co-trimoxazole (trimethoprim-sulfamethoxazole), and tetracycline. The D-test for inducible clindamycin resistance was negative. PFGE by use of methods previously described revealed the isolate to be the USA300 genotype of MRSA. Other molecular tests by PCR showed that the isolate contained the genes for PVL and the staphylococcal chromosomal cassette mec (SCCmec) element type IV.

On hospital day 4, the patient was continuing to require ventilatory support with 60–70% inspired oxygen. A bronchoscopy done on day 6 of her hospital stay revealed haemorrhagic vesicles (figure 2). An infectious diseases consultation was obtained on that day; clindamycin was added to her antibiotic regimen, vancomycin was continued, and piperacillin–tazobactam was discontinued. A repeat bronchoscopy on day 11 (5 days after the addition of clindamycin) showed resolution of these bronchial lesions. The patient began to improve clinically within 48 h after the addition of clindamycin and was extubated on hospital day 11. Respiratory herpes simplex virus culture and influenza cultures were negative. After 23 days in hospital, the patient eventually recovered and was discharged home. 2 years after presentation, the patient remains with mild residual dyspnoea on exertion, which has been attributed to secondary lung scarring; she is otherwise symptom free.

**Case 2**

The partner of case 1, a 36-year-old white man with a past medical history of schizophrenia, hepatitis C virus infection, and methadone maintenance for previous opiate dependence, was admitted to hospital 5 days later with similar symptoms (shortness of breath, fever, chills, and productive cough). He also reported a preceding influenza-like illness 1 week before the onset of his current symptoms, and a history of recurrent episodes of folliculitis.

On admission, his blood pressure was 107/65 mm Hg, pulse rate was 82 beats per min, respiratory rate was 16 breaths per min, oxygen saturation was 96% on room air, and temperature was 37.4°C. Lung examination revealed diffuse crackles with left-sided egophony. No heart murmurs or skin lesions were noted. The rest of his physical examination was normal. Laboratory tests revealed a white blood cell count of 17.9 × 10¹² cells per L (89% neutrophils), a haematocrit of 37%, and a platelet count of 283 × 10⁹/L. A CT scan of the chest revealed a multi-loculated cystic consolidation in the left upper lobe with cavitations and a right upper lobe consolidation (figure 3). HIV serological and legionella urinary antigen tests were negative.

**Figure 2:** Bronchoscopy of case 1 on hospital day 6
Haemorrhagic vesicles are shown.

**Figure 3:** Chest CT scan of case 2
Left lower lobe, multi-loculated consolidation with cavitations are shown.
Treatment with ceftriaxone and doxycycline was initiated after initial blood cultures had been drawn. However, due to persistent fevers, antibiotics were switched to vancomycin and piperacillin–tazobactam on hospital day 3. An infectious diseases consultation was obtained on hospital day 7 because of persistent fever, prompting the addition of clindamycin to the antibiotic regimen; vancomycin was continued and piperacillin–tazobactam was discontinued at this time. Three sets of blood cultures obtained on separate days were negative (including the initial set drawn on admission). Bronchoscopy was done on hospital day 7 and a bronchoalveolar lavage culture grew MRSA, which had the same antibiogram as the isolate recovered from case 1. Molecular studies revealed the isolate recovered from this patient was identical to that recovered from his partner (MRSA USA300, SCCmec IV, and PVL positive). The patient had resolution of fever and symptomatic improvement within 48 h of clindamycin initiation. He was discharged after 14 days to complete a 21-day course of antibiotics. 2 years after this episode, he remains in good health.

**Discussion and review of the published work**

**CA-MRSA**

Meticillin resistance in *S aureus* emerged roughly 45 years ago, but MRSA infections were primarily confined to the health care setting until recently. The first report of community-onset infections with MRSA came from Australia in 1993. In the USA, reports of CA-MRSA necrotising pneumonia in healthy children appeared in the late 1990s, and were followed by reports of outbreaks of CA-MRSA skin and soft-tissue infections among prison inmates, homosexual men, native Americans, and sports teams. Transmission of CA-MRSA infections among these high-risk groups, from infected patients to household contacts, and transmission of nasal colonisation within families were then reported. As a result, CA-MRSA infections are no longer restricted to certain risk groups or to the geographic areas where outbreaks first occurred. They now occur widely both in the community as well as health care facilities, and have been reported in nearly every continent.

The spectrum of disease caused by CA-MRSA occurs worldwide and primarily encompasses skin and soft-tissue infections, but deep-seated infections such as pyomyositis, osteomyelitis, septic arthritis, and severe infections such as necrotising pneumonia and bacteraemia have also been reported. The prevalence and incidence of invasive CA-MRSA infections probably varies geographically. In the USA, for example, 6% of CA-MRSA infections cause invasive disease (pneumonia accounting for 2% overall), and 14% of all invasive MRSA infections are due to CA-MRSA (14% of these invasive infections are CA-MRSA pneumonia).

**Differences between health-care-associated MRSA and CA-MRSA**

Genotypic characterisation of MRSA isolates by lineage, the type of genetic element that encodes meticillin resistance, and toxin production profile are important for epidemiological purposes to differentiate between health-care-associated MRSA (HA-MRSA) and CA-MRSA. The predominant lineage of MRSA isolates, as characterised by multilocus sequence typing (MLST) or PFGE, and toxin gene expression varies geographically, whereas SCCmec does not.

Typing for SCCmec, the mobile genetic element that carries the *mecA* gene that encodes meticillin resistance, is usually done worldwide to describe MRSA isolates. SCCmec is classified into types I–VII (based on the *mec* and *ccr* complex) and each type is further classified into subtypes based on differences in the junkyard (J) region. HA-MRSA usually carry SCCmec types that are larger (types I, II, and III), whereas CA-MRSA isolates carry a much smaller staphylococcal cassettes (SCCmec types IV, V, or VII). The smaller size of SCCmec elements in CA-MRSA isolates may represent an evolutionary advantage, allowing horizontal spread of this element across bacterial species. However, the larger SCCmec elements associated with HA-MRSA isolates represent additional carriage of non-β-lactam resistance genes that probably confer their ability to survive in the hospital environment. With the exception of SCCmec VI, which seems to be confined to one geographic area (Portugal), the different MRSA SCCmec types associated to either HA-MRSA or CA-MRSA have all been initially isolated from a specific region and subsequently spread worldwide. Characterisation of the genetic lineage of MRSA can be done mainly by MLST or PFGE. Outside the USA, description of MRSA isolates is done by their sequence type based on MLST. In Europe, the predominant CA-MRSA clone reported has been sequence type ST80, whereas ST30 is an important clone in Asia and Oceania. In Denmark, for example, ST80 causes 60% of community-onset infections compared with 28% of health-care-associated infections. In the USA, molecular typing has often been done using PFGE, which has shown that USA300, USA400, USA1000, and USA1100 (which correlate with sequence types ST8, ST1, ST59, and ST30, respectively) are the most common genotypes recovered among patients with CA-MRSA infections. With MRSA USA300 accounting for up to 97–99% of cases. By contrast, traditional HA-MRSA genotypes in the USA most commonly include USA100 and USA200.

The presence of PVL genes is more common among CA-MRSA than HA-MRSA isolates. However, the prevalence of PVL among CA-MRSA isolates varies geographically. In the USA, PVL genes are present in 40–95% of CA-MRSA isolates and nearly all USA300
isolate contain PVL.65 However, the prevalence of PVL-positive CA-MRSA in the UK is significantly lower than in the USA,66 and in Japan, Korea, and Western Australia, the predominant CA-MRSA clones are PVL negative.67–69

Finally, from a clinical standpoint, CA-MRSA infections most commonly involve skin and soft tissues,14–16,44,70 and tend to affect younger patients than does HA-MRSA.5,14–16,47–49 CA-MRSA isolates are also characteristically susceptible to a greater number of non-β-lactam antibiotics such as clindamycin, macrolides, co-trimoxazole, tetracyclines, and fluoroquinolones.52–54 However, carriage of antimicrobial resistance genes may vary by the sequence type of CA-MRSA isolate and therefore susceptibility to these non-β-lactam antibiotics cannot be implied.55

Clinical presentation, laboratory findings, radiological features, and outcomes of patients with CA-MRSA pneumonia

CA-MRSA pneumonia generally affects young and previously healthy patients.9–13,15–21,25,27–30,32,72 Severe cases of CA-MRSA pneumonia have been reported during influenza seasons, or associated with a preceding influenza illness in 33–71% of patients.12,20 Clinical presentation is usually that of a severe pneumonia with rapid progression to septic shock and requirement for ventilatory support (table). By contrast with other bacterial pneumonias in which leucocytosis is a prominent feature, leucopenia can be observed in a substantial proportion of cases and has been found to be one of the predictors of poor outcome (in addition to erythroderma and airway bleeding; table).14–16,19 More than a quarter of patients with CA-MRSA pneumonia are reported to have multilobar infiltrates and/or cavitation in imaging studies (table),9,12,16,20 which correlates with pathological examination that usually reveals a haemorrhagic necrotising pneumonia with high bacterial counts.9,11,14,16–18,22 Substantial morbidity and mortality have thus been reported due to CA-MRSA pneumonia, but mortality varies widely.10–16,20 However, despite reporting bias, many reports from the USA and Europe have noted mortalities greater than 50%.9,11,14

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CDC=Centers for Disease Control and Prevention; †=data not available. *As shown by pathology or radiographic imaging. ††The other two patients died before ventilatory support. †††Includes four patients described by Frazee et al. †‡Data available for 16 patients. §§Data available for 49 patients. **100% of CA-MRSA pneumonia isolates were PVL positive and 78% of meticillin-sensitive S aureus isolates were PVL positive. †‡‡Data available for 45 patients.
integrity of the airway epithelium, whereas recombinant PVL alone cannot.73 Thus, either pre-existing airway damage is required or an unknown staphylococcal exotoxin must mediate the initial epithelial damage for bacterial adhesion to take place.

The inflammatory cascade is then mediated by binding of protein A to a receptor for tumour necrosis factor (TNFR1), which is widely distributed in the airway epithelium.73 Protein A is a major staphylococcal surface protein that has been implicated in pathogenicity in other infection models.73 It induces production of interleukin 8 (a polymorphonuclear neutrophil chemokine), binds to TNFR1, and causes the receptor’s mobilisation and shedding to the epithelial surface; the shed receptor binds tumour necrosis factor and protein A to generate a negative feedback loop and protects the host’s airway from further damage caused by the inflammatory cascade.73 This protein A–TNFR1 pathway has been shown to mediate the inflammatory response and virulence in murine models of pneumonia.73 Both TNFR1-null mice and mice infected with protein A-null mutant S aureus had substantially less pneumonia, bacteraemia, and mortality.73

Role of PVL and other virulence factors

The staphylococcal toxin that has received the most interest is PVL, which is present in most CA-MRSA isolates but is rarely (<5%) present in HA-MRSA isolates.80,81 PVL has been shown to cause lysis and apoptosis of neutrophils,79 tissue necrosis,76 and has been found in the pulmonary lesions in murine models of pneumonia.76,80 Its role as a potential virulence factor in invasive S aureus infections was found to have more sepsis and haemoptysis (probably as a surrogate marker of the degree of necrosis),81 and higher mortality. However, only recently has its role in the pathogenesis of invasive S aureus infections been studied in detail.41 In a murine model of acute primary MRSA pneumonia, mice infected with the PVL-positive strains showed evidence of inflammation and tissue necrosis compared with neutrophil infiltration alone for mice infected with PVL-negative strains.80 When plasmid-encoded PVL was introduced to the PVL-negative strains, massive tissue damage and substantial mortality was observed within 24 h. In addition, administration of the toxin components LukS-PV and LukF-PV caused tissue necrosis and mortality in a dose-dependent fashion. PVL was also shown to induce the expression of protein A and downregulate the expression of secreted proteins.82 Thus, the ability of PVL to lyse neutrophils and boost the inflammatory cascade could partly explain the progressive tissue necrosis observed.

Despite these observations, PVL’s direct role in the pathogenesis of CA-MRSA infections has been under debate.84 Relative insensitivity of murine polymorphonuclear leucocytes to the lytic effect of PVL has been recognised compared with that of human cells, making controversial the findings of mouse model-based studies. By contrast with previous findings, a rabbit model failed to show PVL’s contribution to CA-MRSA virulence by altering global gene or protein regulatory networks of S aureus.83 In addition, in murine sepsis and abscess models, PVL-positive strains have been shown to be as virulent as PVL-negative strains.84 The quantity of PVL produced in vitro from CA-MRSA strains obtained from patients with clinical infections also did not correlate with disease severity. Other virulence factors have also been postulated as responsible for mediating the virulence of this organism.85,86 For example, production of phenol-soluble modulins has been found to be higher in CA-MRSA than in HA-MRSA isolates. These toxins have been shown to recruit, activate, and lyse neutrophils; loss of their expression was found to reduce the virulence of CA-MRSA USA300 and USA400 strains in murine models of bacteraemia and abscess.87

Thus, although some data suggest an important pathogenetic role of PVL in MRSA pneumonia, debate remains about the importance of this toxin in the pathogenesis of CA-MRSA pneumonia or whether PVL is merely a marker of CA-MRSA infections.

Treatment

The use of vancomycin or linezolid has been recommended for empirical treatment of community-acquired pneumonia in cases in which CA-MRSA is a consideration.44 However, reported treatment failures for MRSA infections with minimum inhibitory concentrations (MICs) of vancomycin in both the susceptible and non-susceptible range remain an important concern.87–89 Whether optimisation of vancomycin pharmacokinetic parameters will improve outcomes for patients with MRSA pneumonia is not clear,90 but the American Thoracic Society/Infectious Disease Society of America guidelines for pneumonia recommend aiming for vancomycin trough concentrations of 15–20 mg/mL.89 Responses in patients with MRSA bacteraemia, for example, have been found to be better among those with isolates that have vancomycin MICs of at least 0.5 μg/mL compared with those with 1–2 μg/mL.90 Slightly contrasting with this observation, patients with MRSA pneumonia who attained vancomycin serum trough concentrations four times the MIC had improved responses at 72 h but not at the end of therapy.91

The optimum treatment for nosocomial and CA-MRSA pneumonia thus remains incompletely defined because of the lack of prospective clinical trials.92,93 Claims that linezolid is superior to vancomycin for the treatment of nosocomial MRSA pneumonia have been controversial,94 and criticised due to use of subgroup or post-hoc analysis.95,96 Ongoing prospective trials comparing linezolid versus vancomycin for the treatment of MRSA pneumonia will hopefully address and resolve this issue.
Among other available agents with MRSA activity, daptomycin should not be used for the treatment of staphylococcal pulmonary infections because the drug’s activity is inhibited by pulmonary surfactant and clinical data suggest that it is inferior to other antibiotics in the treatment of community-acquired pneumonia.44 The lack of data on the efficacy of tigecycline for MRSA pneumonia limit the use of this drug.10 Finally, the role of newer agents, including enhanced glycopeptides (dalbavancin, oritavancin, and telavancin) and anti-MRSA cephalosporins (cefobiprole and cefaroline fosamil), in the treatment of these infections will need to be studied in prospective trials before any recommendations on their use can be made.108,109

Concomitant use of antibiotics that suppress toxin production has been advocated for the treatment of severe and invasive CA-MRSA infections including pneumonia.10 The rationale for their use in CA-MRSA pneumonia includes (1) the presumed role of PVL (and perhaps other toxins) in pathogenesis, and (2) the striking morbidity and mortality observed. For example, clindamycin has been shown to decrease production of staphylococcal exotoxins in vitro and in vivo,104,105 enhance the organism’s phagocytosis,106 and selectively inhibit the transcription of spa and hla exoprotein genes.107 If consideration is given to its use, inducible clindamycin resistance should be ruled out by doing a D-test, because a substantial proportion of erythromycin-resistant isolates have shown clindamycin resistance despite appearing susceptible on initial testing.107 Another example is linezolid, which has been shown to potentiate the opsonisation and phagocytosis of S aureus at concentrations below the MIC.108 By contrast, β-lactam antibiotics have the potential to increase exoprotein synthesis, specifically that of PVL.108-110 Some clinicians therefore advocate the treatment of patients with CA-MRSA pneumonia with agents that suppress toxin production, and urge the avoidance of agents (ie, β-lactams) that can lead to increased production of PVL and other exotoxins.111

A second adjunctive approach is the targeting of toxin production directly with anti-toxin antibodies. Intravenous immunoglobulin possesses anti-PVL antibodies that are able to prevent PVL-mediated cytopathic effects on cells in vitro.112 However, no clinical data exist to guide its use in vivo, but a higher dose of immunoglobulin might be required to neutralise staphylococcal toxins than for those of Streptococcus pyogenes.113 To date there is only one report of the successful use of intravenous immunoglobulin as salvage therapy.44

Given the potential severity of CA-MRSA infections, another important question is whether screening and treating of household contacts that are found to be colonised with MRSA should be advocated. Nasal colonisation with S aureus is a known risk factor for subsequent infection with this organism,114 a risk that seems higher with CA-MRSA.115 However, there are no formal recommendations for the surveillance and decolonisation of household contacts of patients presenting with CA-MRSA infections. Whereas antimicrobial/anti-septic regimens that were intended for the eradication of S aureus colonisation have been used in some community settings to prevent autoinfection of colonised patients and transmission to contacts, the effectiveness of this approach has not been established.116 Reports have indicated that the prevalence of household colonisation with CA-MRSA is higher than that among the general population.44 However, direct transmission probably does not account for all cases of household colonisation because only 50% of colonised household members carry the same strain as the contact.117 Therefore, treatment decisions are often made on an individual basis by the physicians who provide care to the patients and their families to prevent recurrent disease or intrafamilial spread.

In summary, there are no prospective clinical trials or evidence-based guidelines to direct the treatment of patients with CA-MRSA pneumonia. Options for therapy include vancomycin, which still remains the drug of choice, or linezolid. Given the high morbidity and mortality associated with the disease, adjunctive use of an antibiotic that suppresses protein synthesis or anti-toxin antibody (intravenous immunoglobulin) has been advocated in patients with severe disease.

Conclusion

CA-MRSA pneumonia has emerged as a cause of community-acquired pneumonia, generally after influenza or influenza-like illness and most often among previously healthy patients. The pathophysiology is incompletely understood, although some data suggest that PVL or other toxins, or both, might play an important part in the pathogenesis of the disease. CA-MRSA pneumonia manifests as a severe, necrotising pneumonia, associated with substantial morbidity and mortality. This entity should be suspected in patients presenting from the community with sepsis, haemoptysis, multilobar infiltrates, and leucopenia. In such patients, standard treatment of community-acquired pneumonia will be

Search strategy and selection criteria

We searched PubMed for English or Spanish language references published as of July, 2007, using combinations of the following terms: “Staphylococcus aureus”, “methicillin resistance”, “CA-MRSA”, “HA-MRSA”, “community acquired”, “hospital acquired”, “healthcare associated”, “Panton Valentine leukocidin”, “PVL”, “community acquired pneumonia”, “pneumonia”, “necrotizing pneumonia”, “epidemiology”, “influenza”, “pathogenesis”, “virulence”, and “treatment”. The bibliographies of the articles herein obtained, as well as those of review articles were also reviewed for inclusion of relevant publications. Spelling variants of the search terms were used.
appropriate, and an antibiotic with activity against MRSA (ie, vancomycin or linezolid) should be included in the empirical regimen until culture results are available. The two patients described in this report seemed to have failed to improve until treatment geared towards toxin suppression was instituted (ie, addition of clindamycin). Despite the lack of clinical trials to support such measures, in-vitro data coupled with a high case-fatality rate suggest the use of an antibiotic that decreases toxin production, and the adjunctive use of intravenous immunoglobulin may be indicated. Finally, since the emergence of CA-MRSA USA300 in hospitals, it is unclear whether severe health-care-associated pneumonias due to MRSA USA300 will also emerge.

Conflicts of interest
We declare that we have no conflicts of interest.

References


