Fatal bacteraemic pneumonia due to community-acquired methicillin-resistant Staphylococcus aureus

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ABSTRACT
The recent worldwide surge in the incidence of fatal pneumonia caused by community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) has generated renewed interest in this well-known organism. We describe two cases of fulminant bacteraemic pneumonia due to CA-MRSA at the National University Hospital in Singapore and provide further epidemiological descriptors of this potentially-deadly disease. The first patient was an 83-year-old woman while the second was a 71-year-old man, none of whom had risk factors for hospital-acquired MRSA colonisation. Clinicians should be aware of the possibility of severe community-acquired pneumonia caused by this organism. Adequate empirical antimicrobial coverage for this important pathogen should be considered.

Keywords: bacteraemic pneumonia, community-acquired methicillin-resistant Staphylococcus aureus, pneumonia, Staphylococcus aureus

INTRODUCTION
Staphylococcus aureus (S. aureus) is an important pathogenic organism capable of diverse disease manifestations in the human, ranging from mild superficial skin infection to toxic shock syndrome and life-threatening bacteraemia(1). The wide use of penicillin, although resulting in marked improved prognosis in severe S. aureus infections, had inevitably promoted increased antibiotic resistance. From the time of its first described occurrence in the United Kingdom in 1961, methicillin-resistant S. aureus (MRSA) infections had been largely confined to patients with well-described risk factors in healthcare facilities. However, the rising incidence of community-acquired methicillin-resistant S. aureus (CA-MRSA) infections following the first report in the United States in 1980 had since challenged that notion(2).

The true prevalence of CA-MRSA remains unknown. There are significant regional variations(3). Recent reports have described an increasing incidence in both adult and paediatric patients without the usual risk factors for MRSA infection and colonisation(4,5). Unlike healthcare-associated MRSA strains which infect mainly the respiratory or urinary tract, CA-MRSA infections tend to involve the skin and soft tissue. The recent emergence of rapidly fatal cases of haemorrhagic necrotising pneumonia caused by CA-MRSA in previously-healthy children and young adults is unusual and clearly demonstrates the invasive nature of the organism. This have raised considerable concern that this presentation is becoming a particular feature of CA-MRSA and have sparked new debate on the adequacy of empirical antimicrobial coverage in severe community-acquired pneumonia (CAP)(6-9).

To our best knowledge, CA-MRSA pneumonia had not been described in Singapore. We report two cases of fatal CA-MRSA bacteraemic pneumonia in two elderly adults with comorbidities who were admitted to the National University Hospital and provide further expansion to the epidemiological characterisation of this potentially life-threatening disease.

CASE REPORTS
Case One
An 83-year-old Chinese woman with a history of hypertension and stroke was admitted with a three-day history of increasing dyspnoea and productive cough, and depressed mental status. The family gave a history of upper respiratory tract infection a week prior to admission. There was no history of immunosuppression, diabetes mellitus, human immunodeficiency virus (HIV) infection, alcoholism, asplenia, recent hospitalisation, instrumentation or having received antimicrobial therapy. She did not have any indwelling catheter or close household contact with anyone with an identified risk factor, nor was she a worker in a healthcare environment.
On presentation, she was septic, hypotensive and hypoxic. Chest radiograph showed bilateral diffuse airspace shadowing, consistent with bronchopneumonia. She was started on empirical intravenous ceftazidime and azithromycin. Despite treatment, she rapidly deteriorated and died from septic shock within 48 hours of admission. MRSA was subsequently isolated from both the blood and respiratory culture taken on admission. The strain was sensitive to gentamicin, amikacin, cotrimoxazole, clindamycin, rifampicin, fusidic acid, and vancomycin but was resistant to penicillin, cloxacillin, and erythromycin.

Case Two
A 71-year-old Chinese man had a history of nasopharyngeal carcinoma with curative radical radiotherapy three years ago, diabetes mellitus and hypertension. Similar to the first case, there was no risk factors for hospital-acquired MRSA colonisation elicited in the patient or his close contacts. He was admitted for a one-day history of fever and cough. He was febrile and hypoxic on presentation. Chest radiograph showed bilateral diffuse lower lobe consolidations. He developed shock, requiring high inotropic support, and went into acute respiratory distress syndrome that needed high oxygen and ventilatory support. Initial empirical antibiotics covered consisted of intravenous ceftazidime and levofloxacin.

Both sputum and blood culture taken within 72 hours of hospital admission subsequently grew MRSA which was sensitive to gentamicin, amikacin, cotrimoxazole, clindamycin, rifampicin, fusidic acid and vancomycin but resistant to penicillin, cloxacillin and erythromycin. The antibiotic regime was converted to intravenous vancomycin and amikacin. He continued to deteriorate despite treatment and died from multiorgan failure after ten days of illness. Intravenous ceftazidime was the empirical antibiotic of choice for severe CAP in the hospital during that period, due to a widespread outbreak of melioidosis in the country from the rainy season then.

DISCUSSION
MRSA epidemiology is undergoing evolution\(^5\). Significant community transmission and infection has now been observed, with a distinct set of characteristics that differ from that of its hospital-acquired counterpart\(^4,7\). Genetic analysis had shown that the methicillin-resistance mechanism in CA-MRSA is predominantly associated with the staphylococcal cassette chromosome mec (SSCmec) type IV variant of the mec gene which being significantly (by 10-46 kbp) smaller than the three previously-described cassettes, is transported easily on a plasmid or bacteriophage to a susceptible recipient strain. This facilitated its spread, suggesting that the prevalence of methicillin resistance in the community will only increase, potentially even more quickly than it has in the hospital setting\(^6\). Accumulative evidence seems to suggest that CA-MRSA is not a hospital “escapee”. But it remains unclear whether this traditionally nosocomial pathogen is arising de novo in the community or merely being spread after initial transmission from hospitals or other high-risk facilities\(^9\).

The increased virulence associated with CA-MRSA has been attributed to the gene for Panton-Valentine leukocidin (PVL), a member of the recently-described family of synergohymenotropic toxins, which damage the membranes of host defense cells through the synergistic activity of two separately secreted proteins, leukocidin S-component protein (LukS) and leukocidin F-component protein (LukF)\(^10\). PVL-producing S. aureus has been shown to be strongly linked to cases of severe superficial abscesses and fatal pneumonia\(^6,5\). There are increased recent reports of PVL-positive CA-MRSA strains which caused rapidly-progressive haemorrhagic necrotising pneumonia in healthy children and young adults who lack risk factors associated with healthcare MRSA infections. These are often associated with high mortality rates.

However, the results of the recently-published largest population-based surveillance study to date have dispelled that belief indicating that susceptibility to severe CA-MRSA infections may not be truly related to age or absence of underlying co morbidities\(^11\). Similar to the epidemiological characteristics of our patients, a significant number of their patients were elderly (>65 years) with underlying chronic diseases, and lack the other features which typified nosocomial MRSA infections including recent hospitalisation, admission from another hospital, nursing-home residence, healthcare employment, injection drug use, and previous antimicrobial treatment, indwelling foreign bodies, and underlying immunocompromised states. This is not surprising, given that diseases do strike with greater lethality in those who are vulnerable, i.e. the extremes of age and those with impaired host defense. Therefore, age and presence/absence of co-morbidities may not serve well in providing further distinction of the disease.

One of our patients had pronounced “flu-like” prodromes. Most of the described lethal cases of
CA-MRSA pneumonia were preceded by influenza-like symptoms and thus, it has been highlighted that CA-MRSA could be a cause of community-acquired pneumonia, especially during the influenza seasons. Although influenza is a widely-recognised predisposing risk factor of S. aureus pneumonia, it is non-specific to CA-MRSA. We therefore believe this will not be a useful clinical indicator for reliable differentiation.

In contrast to hospital strains of MRSA which are frequently resistant to many other antimicrobial agents, most CA-MRSA appear to be resistant to beta-lactams only and are often susceptible to most other drug classes\(^{12}\). This may explain why these strains are not prevalent in the hospital environment where the antibiotic selective pressure is high. Most strains belong to Western Samoan phage patterns (WSPP1 or WSPP2) and pulotype A when typed by pulsed-field gel electrophoresis\(^{13}\). Similarly, the MRSA isolates from the respiratory and blood samples of our patients were sensitive to most antibiotics, including clindamycin, with the exceptions of beta-lactams (penicillin and cloxacillin) and erythromycin. Reported prevalence of erythromycin resistance among CA-MRSA varies from 38% to 86%\(^{12,14}\).

Several studies have shown that most CA-MRSA strains are susceptible to clindamycin and therefore, clindamycin has been advocated for treatment of CA-MRSA infections\(^{4,3}\). However, clinical failures associated with the development of clindamycin resistance have been reported lately\(^{15}\). The recent appearance of erythromycin and inducible clindamycin resistance in the south-west Pacific strain of non-multiresistant MRSA in eastern Australia has been reported. It has been recommended that microbiology laboratories should screen for inducible clindamycin resistance in erythromycin-resistant strains, and if found, an alternative antibiotic should be used for treatment\(^{15}\).

These findings have profound implications to the prescribing practice and use of antimicrobial agents. The significant increase in incidence would undeniably necessitate modifications to the prescribing guidelines for CA-MRSA infections and severe CAP. Although most CA-MRSA isolates were sensitive to several antibiotics, the choice of alternative agents will still rely on local susceptibility patterns. The clinicians should be aware that they can no longer depend on beta-lactam antimicrobials as empirical treatment for invasive CA-MRSA infections. The growing number of infections caused by CA-MRSA would markedly increase the widespread use of vancomycin therapy which may further promote the development of resistance. Healthcare institutions should screen and compare their local antibiotics sensitivity data. In the presence of existing high antimicrobial susceptibility, routine use of vancomycin should be discouraged and reserved mainly for invasive severe CA-MRSA infections.

These are the first reported cases of CA-MRSA causing severe CAP in Singapore. Although epidemiological features require clearer definitions, physicians should have a heightened awareness of this possibility in any patients presenting to the hospital with severe staphylococcal sepsis and pneumonia. Empiric therapy with agents active against MRSA strains may have to be considered in the future for severe CAP.

**REFERENCES**