



Clinical Aspects and Treatment of CA-MRSA Infections

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Introduction

Community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection refers to an MRSA infection with onset in the community in an individual without established MRSA risk factors such as recent hospitalisation, surgery, dialysis, residence in a long-term care facility, presence of a permanent indwelling catheter or previous isolation of MRSA. CA-MRSA differs from their health care-associated (HA) counterparts from an epidemiological, genotypic, and phenotypic perspective. CA-MRSA strains have disproportionately affected children and young adults and have easy transmission in settings where people are in close contact such as households^{1,2,3}. Furthermore, the community isolates have high prevalence of genes encoding Panton-Valentine leukocidin (PVL), which is rarely identified in HA-MRSA isolates^{1,3,4,5,6}. PVL is an exotoxin associated with skin abscess formation and necrotising pneumonia although its role in the pathogenesis of CA-MRSA infection has not been fully elucidated^{7,8}. PBP2a, a penicillin-binding protein with decreased affinity to penicillin, is encoded by the gene *mecA*, which is carried on a mobile genetic element called staphylococcal cassette chromosomal (SCC) *mec*. At least 6 types of SCC*mec* have been identified and were numbered from I to VI. HA-MRSA strains harbour SCC*mec* type I, II and III, which are often resistant to multiple non-beta-lactam antibiotics whereas CA-MRSA isolates mostly harbour the SCC*mec* type IV and V, which are typically susceptible to multiple non beta-lactam antibiotics, including co-trimoxazole, doxycycline, minocycline and clindamycin^{1,2,3,4,9}. The spectrum of disease caused by CA-MRSA appears to be similar to that of MSSA. Skin and soft tissue infections (SSTIs) represent the majority of the CA-MRSA diseases burden. Less commonly, it has been associated with severe and invasive infections, including necrotising fasciitis and necrotising pneumonia.

Clinical Presentations

Skin and Soft Tissue Infections

Abscesses and furuncles with or without accompanying cellulitis are the commonest reported presentations of CA-MRSA infection. The skin lesions may sometimes be confused with spider bites by the patients and the physicians. It is characterised by the development of primary necrotic lesions of the skin and soft tissues that progress to abscesses formation later. CA-MRSA

associated impetigo and folliculitis have also been reported. The severity of CA-MRSA SSTIs varies from mild superficial infection to deeper soft tissue infection requiring hospital admission^{2,4,9,10}. Severe complications such as necrotising fasciitis, osteomyelitis, bacteraemia and sepsis syndrome have been reported although most of the infections usually remain confined to the skin and soft tissues (Figure 1). It is noteworthy that recurrent skin infections and clustering within the household are relatively common phenomena seen in CA-MRSA SSTIs^{1,3}.



Figure 1. Clinical photo of a patient with a MRSA abscess

Necrotising Pneumonia

Severe necrotising pneumonia is another clinical manifestation strongly associated with CA-MRSA stains^{5,6,11}. It is commonly seen in children and healthy young adult. Unlike HA-MRSA pneumonia, this disease is characterised by leucopenia, haemoptysis, high fever and multiple lobar infiltrate. Rapid progression to septic shock, acute respiratory failure and death are commonly seen. Diffuse necrotic haemorrhagic pneumonic change was frequently seen in autopsies. Preceding influenza or influenza-like prodrome was commonly associated with the disease. In fact, the relation between influenza and severe staphylococcal pneumonia has been well recognised. Influenza and other viruses can damage the respiratory epithelium and predisposes to staphylococcal infections.

Clinical Management

The emergence of MRSA in the community heralds a



need for new approaches to the management of SSTIs and other syndromes compatible with *S. aureus* infection such as necrotising pneumonia following an influenza-like illness^{12,13}. The suspicion of CA-MRSA should be particularly heightened by a history of a household contact or failed response to the first line antibiotic treatment although many of them have none of these risk factors.

For SSTIs, clinicians are encouraged to collect specimens for culture and susceptibility testing from patients with abscesses or purulent skin lesions, particularly those with **NARES** (Not responsive to first-line antibiotic; Atypical body site or clinical features; Recurrent SSTI; Extensive infection in multiple sites; Spread of infections among close contacts)¹². Culture and susceptibility results are not only useful for management of individuals but also help to determine local prevalence of CA-MRSA and monitor trends in susceptibility of *S. aureus* to non-beta-lactam agents.

The treatment of SSTI depends on an assessment of the type and severity of the clinical presentation (Figure 2). In general, incision and drainage continue to be the mainstay therapy for abscesses and furuncles. Empirical antimicrobial therapy is recommended as an adjunct to surgical incision and drainage to some patients with purulent SSTI and presence of the following factors: 1) severe and rapid progression of the infection 2) presence of systemic symptoms and signs 3) presence of associated cellulitis 4) presence of co-morbidities 5) extremes of age, 6) location of the abscess which cannot be drained easily or that can be associated with severe complications such as face and periorbital areas. As MSSA is still more prevalent than MRSA in Hong Kong, the choices for empirical therapy of uncomplicated SSTIs in outpatient settings includes penicillinase-resistant penicillin (e.g. cloxacillin), first generation cephalosporin and oral beta-lactam/beta-lactamase inhibitor combinations (such as amoxicillin-clavulanate), which have good coverage for both MSSA and Group A streptococcus. When there is no or only little clinical improvement, culture should be obtained (if not taken yet) and alternative antibiotic therapy with CA-MRSA coverage should be considered. However, the optimal antibiotic therapy for suspected or confirmed CAMRSA is not clear^{9,14,15}. Local susceptibility data should be used to guide to the antibiotic treatment. A study in Hong Kong reported that 25 of 29 CA-MRSA isolates were susceptible to all but 1 or 2 antibiotic agents in addition to cloxacillin but all 29 isolates were susceptible to cotrimoxazole, minocycline, doxycycline, and vancomycin. In the same study, clindamycin resistance displaying constitutive phenotype was found in a few isolates but none had inducible MLSB phenotype, which can be detected by the D-zone test. Isolates with inducible MLSB phenotype that are erythromycin resistant and are initially susceptible to clindamycin can develop clindamycin resistance during the course of clindamycin therapy. Treatment failure with clindamycin may happen in infection with inducible MLSB isolate.

Table 1 lists oral agents that are useful in outpatient management of uncomplicated CA-MRSA SSTIs.

Cotrimoxazole (trimethoprim-sulfamethoxazole) has been reported to be useful in the treatment of *S. aureus* infections, including MRSA¹⁶. However, Group A streptococcus (GAS), one of the commonest organisms causing SSTIs, is usually resistant to cotrimoxazole. Thus clinicians should avoid using cotrimoxazole as the sole empirical therapy for SSTIs of unknown cause. In addition, cotrimoxazole is contraindicated in women in the third trimester of pregnancy or in infants less than two months of age. Doxycycline and minocycline are long-acting analogues of tetracycline and possess much better activity and susceptibility profile for staphylococcus than tetracycline. Therefore, they are recommended for MRSA SSTIs. Like co-trimoxazole, they are not recommended as empirical monotherapy for SSTIs of unknown cause because of their limited activities against GAS. They are contraindicated in pregnant women and young children. Clindamycin has been widely used in SSTIs, including necrotising fasciitis because of its good soft tissue penetration, good activity against gram positive coccus such as beta-haemolytic streptococci and staphylococcus, and potential inhibition of toxin production. As mentioned above, D-zone test should be performed to detect the inducible MLSB phenotype. In fact, increasing clindamycin resistance has been reported recently. Moxifloxacin, a newer fluoroquinolone, has enhanced potency against *S. aureus* as compared with ciprofloxacin and levofloxacin. However, a major limitation of fluoroquinolone use is that MRSA strains readily develop resistance which may lead to treatment failure and relapse¹⁷. In addition, fluoroquinolone is not recommended in pregnant women and young children. Linezolid, an oxazolidinone, is indicated for the treatment of SSTIs and hospital-acquired pneumonia due to MRSA. However, its use is limited by high cost and potential haematological side effects.

Patients with severe CA-MRSA infections require hospital admission and intravenous antibiotic therapy^{12,13}. Vancomycin is still considered the first line treatment for severe infections caused by MRSA. Other potentially useful intravenous antibiotics include clindamycin, minocycline, linezolid and daptomycin (Table 2).

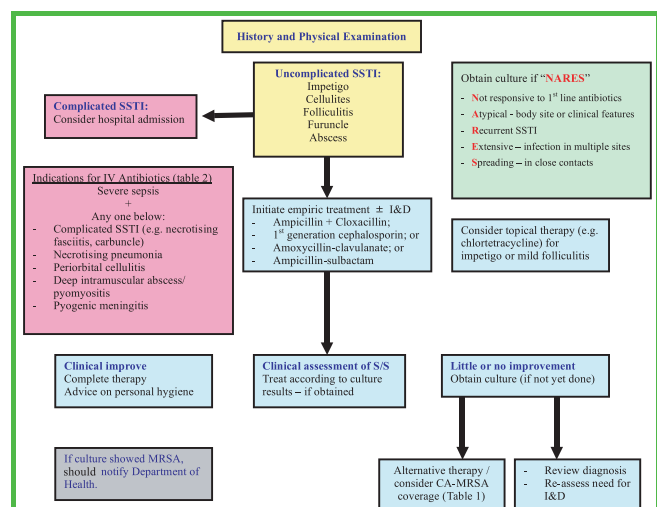


Figure 2. Guideline for clinical management of skin and soft tissue infections (SSTIs) and clinical syndromes compatible with staphylococcal infections.



Conclusion

MRSA is well known as a cause of hospital associated infection and is now emerging as an important infection in the community with the strains distinct from nosocomial ones in term of epidemiology, genotype and phenotype. The community strains are commonly harbouring gene encoding PVL and SCCmec IV and V. Unlike hospital strains, CA-MRSA strains are usually susceptible to many non-beta-lactam antibiotics. SSTIs represent the majority of CA-MRSA disease burden. Severe and invasive diseases caused by community strains are less commonly seen, including necrotising pneumonia, necrotising fasciitis, pyomyositis, and osteomyelitis and sepsis syndrome. A decreased in the threshold for obtaining cultures to document MRSA is warranted especially for those with risk factors (i.e. NARES). Purulent skin and soft tissue infections can generally be managed with surgical incision and drainage with or without oral antibiotics. Patients with severe infection require in-patient care and intravenous antibiotic therapy.

Table 1. Oral Antimicrobial agents for outpatient therapy of uncomplicated CA-MRSA SSTI

Agents-note (1)	Potential advantages	Precautions	Usual dose for adult Usual	Usual Dose for Children
Cotrimoxazole	Oral	Not for patients with sulfur allergy, women in the third trimester and infants less than 2 months	960mg BD	Trimethoprim, 8-12mg/kg/day, and sulfamethoxazole, 40-60mg/kg/day, in two divided doses
Doxycycline	High skin concentration	Not for children <12yrs or pregnant women	200mg once, then 100mg BD	-
Minocycline	As above	As above	100mg BD	-
Clindamycin	Inhibit toxin production	Diarrhoea caused by <i>C. difficile</i> Note (2)	300-450mg TDS	30mg/kg of body weight/day, in three or four divided doses
Moxifloxacin	Oral	Resistance may develop during therapy	400mg QD	-

(1) Clinicians should consult complete drug prescribing information. Antibiotic therapy should be modified according to results of culture and susceptibility testing. Information available at present showed that most CA-MRSA isolates in HKSAR are susceptible to the above oral antibiotics. The duration of therapy for most SSTI is 5 to 7 days; longer therapy may be necessary depending on severity of infection and clinical response. Oral antibiotics are not indicated for MRSA carriage/colonisation.

(2) If clindamycin is considered, isolate resistant to erythromycin but apparent "sensitivity" to clindamycin should undergo laboratory testing for inducible clindamycin resistance using the "D" test. Organisms that show flattening of the clindamycin zone adjacent to the erythromycin disk should be reported as resistant to clindamycin.

Abbreviations: BD, twice daily; QD, once daily; TDS, three times daily.

Table 2. Parenteral Antimicrobial agents for severe CA-MRSA infection

Agents (note 1)	Potential advantages	Precautions	Usual dose for adult Usual	Usual dose for children
Vancomycin	Long experience of use	Red-man syndrome	1gm Q12H	40mg/kg/day, in three to four divided doses
Clindamycin (Note 2)	Inhibit toxin production	Diarrhoea caused by <i>C. difficile</i>	300mg Q8H	30mg/kg/day, in three divided doses
Minocycline	High skin concentration	Not for children <12yrs or pregnant women	100mg Q12H	-
Linezolid	High tissue concentration	Myelosuppression, mostly with prolonged use	600mg Q12H	10 mg/kg every 8-12 hr

(1) Clinicians should consult complete drug prescribing information. Antibiotic therapy should be modified according to results of culture and susceptibility testing.

(2) If clindamycin is considered, isolate resistant to erythromycin but apparent "sensitivity" to clindamycin should undergo laboratory testing for inducible clindamycin resistance using the "D" test. Organisms that show flattening of the clindamycin zone adjacent to the erythromycin disk should be reported as resistant to clindamycin.

References

- Ho PL, Cheung C, Mak GC, Tse WS, Ng TK, Cheung HY, Que TL, Lam R, Lai WM, Yung WH & Yuen KY. Molecular epidemiology and household Transmission of community-associated methicillin-resistant *Staphylococcus aureus* in Hong Kong. *Diagn Microbiol Infect Dis.* 2007; 57, 145-51.
- Fridkin SK, Hageman JC, Morrison M, Sanza LT, Sabetti KC, Jernigan JA, Harriman K, Harrison LH, Lynfield R & Farley MM. Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med.* 2005; 352, 1436-44.
- Davis SL, Perri MB, Donabedian SM, Manierski C, Singh A, Vager D, Haque NZ, Speirs K, Muder R, Robinson-Dunn B, Hayden MK & Zervos MJ. Epidemiology and outcomes of community-associated methicillin-resistant *Staphylococcus aureus* infection. *J Clin Microbiol.* 2007; 45, 1705-11.
- Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB & Talan DA. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med.* 2006; 355, 666-74.
- Francis JS, Doherty MC, Lopatin U, Johnston CP, Sinha G, Ross T, Cai M, Hansel NN, Perl T, Ticehurst JR, Carroll K, Thomas DL, Nuermberger E & Barlett JG. Severe community-onset pneumonia in healthy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton-Valentine leukocidin genes. *Clin Infect Dis.* 2005; 40, 100-7.
- Labandeira BE, Hulten KG, Dishop MK, Lamberth LB, Hammerman WA, Mason EO & Kaplan SL. Pulmonary manifestations in children with invasive community-acquired *Staphylococcus aureus* infection. *Clin Infect Dis.* 2005; 41, 583-90.
- Labandeira-Rey M, Couzon F, Boisset S, Brown EL, Bes M, Benito Y, Barbu EM, Vazquez V, Hook M, Etienne J, Vandenesch & Bowden MG. *Staphylococcus aureus* Panton-Valentine leukocidin causes necrotizing pneumonia. *Science* 2007; 315, 1130-3.
- Voyich JM, Otto M, Mathema, Braughton KR, Whitney AR, Welty D, Long RD, Dorward DW, Gardner DJ, Lina G, Kreiswirth BN & DeLeo FR. Is Panton-Valentin Leukocidin the major virulence determinant in community-associated methicillin-resistant *Staphylococcus aureus* disease? *Clin Infect Dis.* 2006; 194, 1761-70.
- Ruhe JJ, Smith N, Bradsher RW & Menon A. Community-onset methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections: impact of antimicrobial therapy on outcome. *Clin Infect Dis.* 2007; 44, 777-84.
- Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS, tang AW, Phung TO & Spellberg B. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. *N Engl J Med.* 2005; 352, 1445-53.
- Severe methicillin-resistant *Staphylococcus aureus* community acquired pneumonia associated with influenza-Louisiana and Georgia, December 2006-January 2007. *MMWR* 2007; 56, 325-329.
- Hospital Authority. Fact sheet on community associated methicillin resistance *Staphylococcus aureus*. 2007
- Gorwitz RJ, Jernigan DB, Powers JH & Jernigan JA. Strategies for clinical management of MRSA in the community: summary of an experts' meeting convened by the Centers for Disease Control and Prevention. 2006
- Miller LG, Quan C, Shay A, Mostafaie K, Bharadwa K, Tan N, Matayoshi K, Cronin J, Tan J, Tagudar G & Bayer AS. A prospective investigation of outcomes after hospital discharge for endemic, community-acquired methicillin-resistant and -susceptible *Staphylococcus aureus* skin infection. *Clin Infect Dis.* 2007; 44, 483-92.
- Lee Michael C, Rios AM, Aten MF, Mejias A, Cavuoti DD, Mccracken GH & Hardy RD. Management and outcome of children with skin and soft tissue abscesses caused by community-acquired methicillin-resistant *Staphylococcus aureus*. *Pediatr Infect Dis J.* 2004; 23, 123-7.
- Jemni L, Hmouda H & Letaief A. Efficacy of trimethoprim-sulfamethoxazole against clinical isolates of methicillin-resistant *Staphylococcus aureus*: a report from Tunisia. *Clin Infect Dis.* 1994; 19, 202-203.
- Blumberg HM, Rimland D, Carroll DJ, Terry & Wachsmuth IK. Rapid development of ciprofloxacin resistance in methicillin-susceptible and resistant *Staphylococcus aureus*. *J Infect Dis.* 1991; 163, 1279-1285.