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Review Article

Update on bacterial skin infections: CA-MRSA

細菌性皮膚感染新知：社區甲氧西林抗藥性金黃色葡萄球菌

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Staphylococcus aureus remains the commonest bacterial pathogen that causes skin and soft tissue infections. These strains evolve, were once susceptible to penicillin and cloxacillin, but are manifesting with methicillin (cloxacillin) resistance (MRSA). In some countries, these disseminate in the community, to be the so called, CA-MRSA, that possess unique genes encoding the panton-valentine leukocidin (PVL) toxins, which produce necrotising and recurrent abscesses. CA-MRSA is presenting as a major public health concern worldwide.

金黃色葡萄球菌是引起皮膚和軟組織感染最常見的細菌。由於基因的轉變，一些一向受制於青霉素和氯唑西林的品株開始產生對甲氧西林抗藥性。在一些國家裡，這種對甲氧西林抗藥性金黃色葡萄球菌蔓延到社區中，所謂社區甲氧西林抗藥性金黃色葡萄球菌(CA-MRSA)，它們擁有獨特製造panton-valentine leukocidin (PVL)毒性的基因，能夠引起復發壞死性膿腫，做成全球性的社會衛生問題。

Keywords: CA-MRSA, methicillin-resistant *Staphylococcus aureus* (MRSA), panton valentine leukocidin (PVL) gene, *Staphylococcus aureus*

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Introduction

Skin and soft tissue infections (SSTIs), from minor pyoderma to severe cellulitis, are the cause of considerable morbidity in both the community and hospital settings. *Staphylococcus aureus* is the commonest bacterial pathogen that causes SSTIs, whilst it also produces a wide spectrum of systemic diseases ranging from bacteraemia and septicaemia to toxin-producing illnesses leading to life-threatening infections (Table 1).

In August 2006, methicillin-resistant *Staphylococcus aureus* (MRSA) made headlines in the United States (Reuters Health Information, New York, 2006) for becoming the most frequent identifiable cause of SSTIs in major US Cities. This followed from results of a multicentered study[1] that included 422 patients with SSTIs managed at 11

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Table 1. Infections caused by *Staphylococcus aureus*

Skin and Soft Tissue
Impetigo
Furunculosis
Folliculitis
Erysipelas
Pyoderma
Cellulitis
Scalded skin syndrome
Toxic shock syndrome
Necrotising fasciitis
Surgical site infections
Other Sites
Bacteraemia and sepsis
Abscesses
Osteomyelitis and arthritis
Pyomyositis
Pneumonia
Endocarditis
Catheter associated infections
Infections of prosthetic devices
'Food poisoning'

hospital emergency departments across 11 metropolitan areas across the US. Seventy-six percent of the cases yielded *Staphylococcus aureus*, and of these, 78% (249/320) were due to MRSA. The isolation of MRSA in these emergency departments ranged from 15% in New York to 74% in Kansas City. Characterisation of these MRSA indicated these belonged predominantly to the USA300 strain, a community-acquired MRSA that typically possessed the SCC*mec* type IV and the panton-valentine leukocidin (PVL) toxin gene.[2]

MRSA first emerged as a nosocomial pathogen (HA-MRSA) and had become endemic in hospitals in many countries in the early 1980s, including Australia, USA, South America and South East Asia. It is prevalent among hospitals in Hong Kong and in the Asia Pacific region.[3,4] HA-MRSA is considered resistant to all β-lactam agents due to modified proteins (PBP2a) on the cell wall that have little affinity to β-lactam antibiotics. These proteins are encoded by the *mec* gene, which is located in a large gene cassette chromosome, the SCC*mec*. HA-MRSA belongs to a number of clonal complexes by molecular characterisation of the SCC*mec* type and the genomic profiles. In Hong Kong, the predominant HA-MRSA clone possess SCC*mec* type III, had multi-locus sequence type (MLST) ST239; and were multidrug-resistant to tetracycline, erythromycin, clindamycin, gentamicin, tobramycin, and ciprofloxacin.[5] This MRSA clone had been suggested to be widespread in many countries in SE Asia. This lineage included numerous clones of the British epidemic MRSA (eMRSA1,-4,-7,-9,-11), Brazilian, Portuguese, and Viennese clones.

Worldwide, there are concerns with the emergence of MRSA in the community setting (CA-MRSA).[2,6] One of the early reports that drew much attention was of four paediatric deaths due to MRSA necrotising pneumonia in 1997-99. The children acquired the infection from the community and had no risk factors or previous healthcare contact.[7] Subsequently, there were numerous reports of clusters of CA-MRSA infections in certain populations, including atheletes, prison inmates, children, Native Americans, and military recruits.[8-11] A classical history of 'a spider bite' was suggestive of infection due to CA-MRSA in the clinical presentations.[12] Often the lesion begins with small papules, and develop into larger pustules or abscesses with areas of necrosis and surrounding erythema, and be confused with spider bites. Most CA-MRSA cases involve SSTIs, the most frequently being furunculosis and cellulitis.[6]

CA-MRSA infection is defined as one with a diagnosis of MRSA made in the outpatient setting or by a culture positive for MRSA within 48 hours of hospital admission (CDC definition: www.cdc.gov/ncidod/hip/Aresist/ca_clinician.htm). The patient should not have a medical history of previous MRSA infection / colonisation, or medical history in the past year of hospitalisation;

admission to a nursing home or institution; dialysis; surgery; permanent indwelling catheters or medical devices. Often, CA-MRSA is found in healthy people with skin infections eg boils/ abscess. Transmission is through close skin-to-skin contact. The CA-MRSA isolates are characterised by two unique genes: the SCCmec type IV or V and the panton-valentine leukocidin (PVL) locus.[2] The strains are typically resistant to oxacillin but tends to be more susceptible to antimicrobial agents outside of the β-lactam class. The characteristerics of HA- and CA-MRSA are listed in Table 2.

In Hong Kong, the first reported case of CA-MRSA infection[13] was in a previously healthy 50 years old male who had a one week history of fever and a carbuncle 4 cm in size in the neck. The patient was managed with incision and drainage of the carbuncle, together with 7 days of treatment with ampicillin and cloxacillin. The culture of the drained pus grew *Staphylococcus aureus* that was resistant to oxacillin but sensitive to gentamicin, erythromycin, clindamycin, fusidic acid, ciprofloxacin, co-trimoxazole, tetracycline, chloramphenicol, rifampicin and vancomycin. No previous risk factors of MRSA were identified and the case fulfilled the CDC definition. Since then, a series of 25 episodes in 23 patients with CA-MRSA infections was also documented in Hong Kong for the period from January 2004 to December 2005.[14] These included 24 episodes of skin and soft tissue infections, and one episode of meningitis. The mean age of these patients was 28.1±21.1 years (range 13 months-91 years) and included 7 children (<16 years) and 16 adults. There was an ethnic association, with 14 Chinese, 3 Filipino, 2 British, 2 Nepalese, 2 Japanese in the series. All, but 4 cases, had no underlying disease. Three children suffer from eczema and 1 patient was known to be a hepatitis B carrier. The commonest clinical presentations were furuncle or carbuncle, followed by perianal abscess, deep-seated thigh infection, infected sebaceous cyst, and a scalp abscess. Fourteen cases had incision and drainage, and no

Table 2. Characteristics of Hospital (HA-) and Community acquired (CA-) MRSA

HA-MRSA	CA-MRSA
Healthcare contact	No healthcare contact
Mean age >50 years old	Younger age <20 years old
Bacteraemia	SSTIs, necrotising pneumonia
Resistant to β-lactams	Resistant to β-lactams
Multidrug resistant to erythromycin, clindamycin, fluoroquinolones	Susceptible to other classes, occas resistant to erythromycin, gentamicin, fluoroquinolone, fusidic acid
SCC*mec* I, II or III	SCC*mec* IV or V
PVL rare (5%)	PVL positive (95%)
Other toxin genes e.g. *tst, sea, seb*, etc.	Occas *tst*
Clonal type ST239, 5	Clonal type ST30, ST80, ST59

SSTIs: Skin and soft tissue infections; PVL: panton-valentine leukocidin

antibiotics were given in 4 of the cases. CA-MRSA infection or carriage was present in 13% of the 46 household contacts. The commonest strain type identified represented the ST30, the Southwest Pacific clone of CA-MRSA[2] which was first reported in Australia, New Zealand, and later in Singapore and parts of Europe and United States.

The PVL toxin was first described in 1932. The PVL gene is common among CA-MRSA strains and had been associated with chronic, recurrent soft tissue infections, necrotising pneumonia, fasciitis, and osteomyelitis with multiple abscesses.[6] It is a membrane toxin that targets leukocytes, and causes lysis of white blood cells, dermal necrosis and increases adhesions to matrix proteins, collagen, laminin. The PVL has also been shown to upregulate expression of Protein A that binds to TNF-alpha receptors and mimics a B-cell superantigen. Other virulence factors associated with CA-MRSA have also been documented and listed in Table 3.

Table 3. Virulence factors of community-acquired *Staphylococcus aureus*

Virulence factor	Characteristics	Clinical syndrome
Resistance determinants		
SCC*mec* type IV	Resistance to methicillin	
SCC_{476}	Resistance to fusidic acid	
Adherence		
Collagen-adhesin protein (CNA)	Greater adherence to host tissues	Epidemic furunculosis, necrotising pneumonia, arthritis, osteomyelitis
Colonisation		
Bacteriocin	Intra- and inter-species competition	Epidemic furunculosis
Unknown	Greater tolerance to salt	Epidemic furunculosis
Superantigens		
Staphylococcal enterotoxins A, B, C, G, H, K, L, O	Activation of T cells	Epidemic furunculosis, necrotising pneumonia, toxic shock syndrome-like illness
Exotoxins		
Staphylococcal exotoxin T	Possible defence against immunity	
Pore-forming toxins		
PVL (LukSPV + LukFPV)	Necrosis, oedema	Epidemic furunculosis, necrotising pneumonia,
LukE + LukD	Destruction of intestinal microvilli	Postantibiotic diarrhoea
LukEv + LukDv	Necrosis	Epidemic furunculosis,
α-Haemolysin	Necrosis, vascular leakage, shock	Necrotising pneumonia, bullous impetigo
Exfoliative toxins		
Exfoliative toxin A and B		

Aadapted from Zetola N, Francis JS, Nuermberger EL, Bishai WR. Community-acquired meticillin-resistant *Staphylococcus aureus*: an emerging threat. Lancet Infect Dis 2005;5:275-86.[6]

Guidelines for the management of CA-MRSA infections have been published http://www.cdc.gov/ncidod/dhqp/ar_mrsa_ca_prevention.html. The most up to date recommendation locally is available in the Centre for Health and Protection website http://www.chp.gov.hk. A mainstay of therapy is adequate incision & drainage of the abscess and to obtain material for culture when possible. If outpatient antibiotic therapy is deemed necessary; the choices may include cotrimoxazole, doxycycline or minocycline, clindamycin (if susceptible to both macrolides and clindamycin). Macrolides and fluoroquinolones are often not suggested because of increased risk for development of resistance. Infection control with contact precautions together with good hand and personal hygiene are indicated. CA-MRSA infection has from 5th January, 2007, been made a statutory notifiable disease in Hong Kong. The case definition is available at www.chp.gov.hk/ceno and further information is available on the CHP website at http://www.chp.gov.hk/content390e.htmllang=en&info_id=5392&id=24&pid=9.

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