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# Community-associated MRSA (CA-MRSA): an emerging pathogen in infective endocarditis

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**Over the last decade, a novel methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged, primarily associated with healthy individuals within the community. This organism is distinct from healthcare-associated MRSA (HA-MRSA) in terms of epidemiology, microbiology and clinical manifestation and as such has been defined as community-associated MRSA (CA-MRSA). Given that *S. aureus* is a major aetiological agent of infective endocarditis (IE), particularly associated with the iv drug user population, reports of IE attributed to CA-MRSA are now emerging in the literature. The aims of this article are to (i) define and contrast CA-MRSA with HA-MRSA; (ii) review the published cases of CA-MRSA IE to date; and (iii) evaluate the current international recommendations for antibiotic prophylaxis and treatment regimens for IE in relation to CA-MRSA.**

Keywords: community-acquired MRSA, PVL, Panton-Valentine leucocidin

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has now emerged on five continents (Europe, Asia, Australia, North America and South America)[1,2] over the last decade, but particularly in the USA, where there have been several seminal publications on this organism.[3–5] CA-MRSA has distinctly different microbiological, epidemiological and molecular characteristics from those of healthcare-associated MRSA (HA-MRSA), and based on these differences (Table 1), new definitions have been published in an attempt to differentiate between these two organisms.[6]

CA-MRSA is usually associated with young healthy individuals in the community, who have no risk factors for acquisition of HA-MRSA. Several reports have documented CA-MRSA infections affecting individuals in prisons, military personnel, athletic populations, male homosexuals and ethnic populations (native Alaskans and American Indians, Hawaiian islanders). CA-MRSA is primarily associated with skin and soft tissue infections (abscesses, cellulitis and furunculosis); however, there have been severe cases of CA-MRSA infection associated with septic shock, bacteraemia and necrotizing pneumonia. For a comprehensive review on CA-MRSA, see Zetola *et al.*[7] It remains unclear as to whether CA-MRSA evolved historically from the acquisition of SCC*mec* elements conferring methicillin resistance, through an altered penicillin-binding protein (PBP2′) in the bacterial cell wall, within methicillin-susceptible *S. aureus* (MSSA) in the community or if CA-MRSA was originally derived from HA-MRSA.

More recently, infective endocarditis (IE) due to the involvement of CA-MRSA has been described. In order to identify cases of CA-MRSA IE, a thorough interrogation of the PubMed Search Engine was carried out by using several key words including 'endocarditis', 'MRSA' and 'community', seeking articles that were in print by July 2007 and which described clinical cases of IE associated with CA-MRSA. The determination of CA-MRSA was made by the original authors of the cases discussed, to include epidemiological, microbiological and molecular characteristics of each case, and a summary of these 23 published cases is detailed in Table 2. To date, reports of CA-MRSA IE have been limited to highly industrialized and developed regions including North America, Europe, Asia and Australia, though the majority (68%) of cases have originated in the USA. As yet, there have been no reports from developing nations, although this may reflect reporting bias and/or the absence of high-quality microbiological characterization. From the known epidemiological information recorded, CA-MRSA IE has been primarily acquired within the community and associated with a young, healthy population with no known risk factors for the acquisition of IE. It should be noted, however, that a large proportion of cases have a documented history of some form of skin lesion, including furunculosis, cellulitis and/or iv drug abuse. All cases reported to date have been associated with native valves, predominately the tricuspid valve (Table 3).

Where there has been sufficient epidemiological information provided, a comparison of clinical characteristics and outcome

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**Table 1.** Comparison of clinical, epidemiological and microbiological characteristics of CA-MRSA and HA-MRSA

| Characteristic | HA-MRSA | CA-MRSA |
|---|---|---|
| Population affected | patients or residents in hospitals or nursing homes, the elderly, pre-term neonates, immunocompromised | young healthy individuals in the community with no risk factors for acquisition of HA-MRSA, prisoners, military personnel, athletes, male homosexuals, ethnic populations (native Alaskans and American Indians, Hawaiian islanders) |
| Site of infection | bacteraemia and wound infections also symptomatic infections of respiratory and urinary tracts | mainly skin [abscesses and cellulitis, furunculosis, severe skin and soft tissue infections (sSSTIs)] in severe cases, septic shock and bacteraemia, necrotizing pneumonia |
| Risk factors | indwelling devices, catheters, lines, haemodialysis, prolonged hospitalization, long-term antibiotic use | close physical contact, abrasion injuries, activities associated with poor communal hygiene (e.g. sharing towels) |
| Transmission | (i) person-to-person spread via healthcare staff (e.g. nurses, doctors, surgeons and physiotherapists), visitors and patients (ii) environment-to-patient spread e.g. via hospital equipment | (i) person-to-person via shared facilities (e.g. sports equipment, towels, pools, etc.) (ii) environment |
| Microbiological characteristics | | |
| susceptibility to methicillin | no | no |
| susceptibility to other antibiotic agents (fluoroquinolones, aminoglycosides, erythromycin and clindamycin) | no | yes (in the majority of cases) |
| presence *pvl*[a] gene | low (<5%) | high (>95%) |
| SCC*mecA* type | predominantly subclasses I, II or III | mainly IV (and subtypes a–h), V |
| *agr*[b] genotype | predominantly II | predominantly I and III |

[a]*pvl* (Panton-Valentine leucocidin).
[b]*agr* (accessory gene regulator).

of these cases of CA-MRSA IE (Table 3) has been made with collated cases of native valve MSSA IE and native valve MRSA IE, taken from the merged database of the International Collaboration on Endocarditis (ICE), as previously published.[18] This comparison shows a close correlation of CA-MRSA IE to MSSA IE, particularly in terms of age, acquisition in the community, vegetation location and embolic complications. Mortality associated with CA-MRSA IE has been shown, to date from the limited numbers of cases reported, to be markedly lower at 13%, in comparison with either HA-MRSA IE or MSSA IE, which is 37.2% and 23.2%, respectively (Table 3), whereas associated mortality due to *Propionibacterium* and *Candida* endocarditis has been 13.3% and 37%, respectively, as reported previously by ICE.[19,20]

Although CA-MRSA IE resembles MSSA IE more closely than MRSA IE, the antibiotic management of CA-MRSA IE requires a similar approach to treatment as MRSA IE, as a result of the resistance of CA-MRSA to β-lactam agents. Although CA-MRSA tends to be more susceptible to antibiotic agents than HA-MRSA, treatment should follow current international guidelines as described by the British Society for Antimicrobial Chemotherapy (BSAC),[21] the European Society for Cardiology (ESC)[22] and the American Heart Association (AHA)[23] (Table 4). In all the CA-MRSA IE cases described, patients received vancomycin, frequently combined with a second agent (rifampicin, gentamicin, linezolid, co-trimoxazole, daptomycin and clindamycin). In the majority of cases, the patients were treated solely by antimicrobial therapy; however, surgical intervention was performed in five cases, four of which had valve replacement and one case had a vegectomy. The mortality rate of 13% was markedly lower than that in MSSA IE or HA-MRSA IE (23% and 37%, respectively) (Table 3). As CA-MRSA is relatively more susceptible to treatment than HA-MRSA, this may eventually lead to a new set of specific treatment guidelines for CA-MRSA, as its antibiotic susceptibility may allow several novel combinations of agents to be used. However, it is difficult to evaluate such novel approaches, until clinical experience evolves. At present, we are not aware of any CA-MRSA that is resistant to vancomycin and, therefore, we do not believe that CA-MRSA should be regarded as being different in terms of the BSAC, AHA and ESC antibiotic guidelines. However, this is a situation that requires careful monitoring, as antibiotic susceptibility patterns may begin to evolve, if this organism becomes more endemic in healthcare settings, as is the case in the USA, with the associated diversity and quantity of anti-infectives used in the hospital setting.

Given that CA-MRSA is an organism that resides on skin and outer epithelial surfaces, this location may play a significant

**Table 2.** Documented cases of IE due to CA-MRSA

| Sex, age | History/underlying medical condition[a]/ risk factor | Country | Valve | SCC*mec* type | *pvl* | Sequence type/genotype | Antibiotic susceptibility | Embolism/CNS event | Treatment | Outcome | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M, 37 years | recurrent CA-MRSA furunculosis, posterior neck abscess | USA | mitral | IV | + | NK | S: VAN, CIP, SXT, RIF R: ERY, TET | brain lacunar infarct | VAN | asymptomatic at 3 m | Bahrain *et al.*[8] |
| M, 44 years | healthy, soft tissue abscess on left knee, furunculosis | USA | aortic | IV | + | NK | S: VAN, CIP, SXT, RIF, TET R: ERY | septic lung emboli | VAN | asymptomatic at 3 m | Bahrain *et al.*[8] |
| F, 44 years | diabetic, furunculosis | USA | TOE negative | IV | + | NK | S: VAN, CIP, SXT, RIF R: ERY, TET | large epidural abscess in L2–L5 region, bilateral nodular infiltrates | VAN | asymptomatic at 6 m | Bahrain *et al.*[8] |
| M, 19 years | recurrent skin boils, furunculosis | USA | TOE not performed | IV | + | NK | S: VAN, CIP, SXT, RIF R: ERY, TET | left-sided thrombus of the brain, multiple lung lesions | VAN and RIF | asymptomatic at 6 m | Bahrain *et al.*[8] |
| M, 47 years | diabetic, boil left thigh, furunculosis | USA | TOE negative | IV | + | NK | S: VAN, CIP, SXT, RIF R: ERY, TET | left lower lung lobe infiltrate | VAN and GEN | asymptomatic at 10 m | Bahrain *et al.*[8] |
| M, 28 years | IVDU | Singapore | tricuspid | IVa | − | ST78 | S: VAN, CIP, SXT, TET, GEN, FUS R: ERY, OXA, CLI | ND | VAN and valve replaced | cured | Hsu *et al.*[9] |
| M, 22 years | left elbow cellulitis, drainage of knee inflammation, abscess near distal femur; worked at military base | USA | aortic | IV | + | ST8 | S: VAN, SXT, MIN, LZD | septic lung emboli | VAN and LZD | cured | Crum[10] |
| M, 34 days | pre-term neonate 31 w gestation; gastroschisis repaired, respiratory distress syndrome | USA | NK | IV | NK | NK | S: VAN, SXT, GEN R: ERY, PEN, OXA, CLI | none | VAN, GEN, RIF | cured | Healy *et al.*[11] |
| F, 14 days | pre-term neonate 24 w gestation; respiratory distress syndrome | USA | NK | IV | NK | NK | S: VAN, GEN, SXT, ERY, CLI R: PEN, OXA | none | VAN, GEN, RIF, SXT | died: multiple co-morbidities including pleural empyema, pneumatoceles and renal failure | Healy *et al.*[11] |

*Continued*

**Table 2.** *Continued*

| Sex, age | History/underlying medical condition[a]/ risk factor | Country | Valve | SCC*mec* type | *pvl* | Sequence type/genotype | Antibiotic susceptibility | Embolism/CNS event | Treatment | Outcome | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| F, 45 years | recent cellulitis, congestive heart failure, hernia repair 10 m previously, IVDU | USA | aortic | IV | + | USA 300 | S: VAN, CLI, GEN, MXF, SXT<br>R: ERY, OXA | subarachnoid haemorrhage | VAN and GEN and valve replacement with bioprosthetic valve | died ~11 m following discharge, due to subarachnoid haemorrhage and *S. aureus* bacteraemia | Haque *et al*.[12] |
| F, 18 years | recent pneumonia, IVDU | USA | tricuspid | IV | + | USA 300 | S: VAN, CLI, GEN, MXF, SXT<br>R: ERY, OXA | septic emboli of thorax and abdomen | VAN and GEN | blood cultures clear at discharge; patients lost to follow-up | Haque *et al*.[12] |
| M, 67 years | endocarditis previously (1980), myocardial infarction, hepatitis, IVDU | USA | tricuspid | IV | + | USA 300 | S: VAN, CLI, GEN, SXT<br>R: ERY, OXA | septic emboli of thorax | VAN and GEN | developed renal failure, attributed to the gentamicin; asymptomatic at 6 m | Haque *et al*.[12] |
| F, 44 years | IVDU | USA | mass proximal to pulmonic valve and distal to tricuspid valve | IV | + | USA 300 | S: VAN, CLI, GEN, MXF, SXT, ERY<br>R: OXA | none | VAN and GEN | status unknown, did not return for follow-up | Haque *et al*.[12] |
| F, 41 years | IVDU | USA | tricuspid | IV | + | USA 300 | S: VAN, CLI, GEN, SXT<br>R: ERY, OXA | lung abscess | VAN and GEN; changed to DAP due to renal failure; discharged on CLI | no signs of infection 1 w post-discharge | Haque *et al*.[12] |
| M, 53 years | erythematous area on upper chest, prior IE 3 years earlier | USA | aortic | IV | + | USA 300 | S: VAN, CLI, GEN, MXF, SXT<br>R: ERY, OXA | none | VAN | status unknown, did not return for follow-up | Haque *et al*.[12] |
| F, 36 years | IVDU, endocarditis 3 w prior, multiple abscesses in right buttock and surrounding muscles requiring drainage | USA | tricuspid | IV | + | USA 300 | S: VAN, CLI, GEN, SXT<br>R: ERY, OXA | septic lung emboli | prior treatment with DAP; current treatment with VAN and RIF; on discharge oral CLI | asymptomatic at 2 m | Haque *et al*.[12] |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| M, 41 years | IVDU | USA | tricuspid | IVd | − | NK | S: VAN, CLI, GEN, ERY, SXT, DAP, LZD, RIF, CIP, MXF, LVX, MIN<br>R: NK | septic lung emboli | VAN, RIF and valve replacement | asymptomatic on day 77 | Tsigrelis *et al.*[13] |
| F, 38 years | IVDU | Australia | tricuspid | IV | NK | NK | S: GEN, CLI, CIP, CHL, TET, RIF, SXT, Q/D, LZD<br>R: MET and two or less non-β-lactams | NK | VAN and RIF | survived | Murray *et al.*[14] |
| NK | NK | Australia | aortic | NK | NK | NK | S: GEN, CLI, CIP, CHL, TET, RIF, SXT, Q/D, LZD<br>R: MET and two or less non-β-lactams | NK | VAN | survived | Murray *et al.*[14] |
| NK | NK | Australia | mitral | NK | NK | NK | S: GEN, CLI, CIP, CHL, TET, RIF, SXT, Q/D, LZD<br>R: MET and two or less non-β-lactams | NK | valve replacement and VAN | died: cause of death not stated | Murray *et al.*[14] |
| M, 36 years | admitted due to presumed aspiration pneumonia, developed empyema, spondylitis | Greece | mitral | NK | + | NK | S: macrolides, CLI, RIF, SXT, Q/D<br>R: NK | none | VAN and GEN; CLI and SXT for 10 w following discharge | cured | Pefanis *et al.*[15] |
| M, 20 years | soldier, healthy | Taiwan | mitral | NK | NK | NK | S: NK<br>R: OXA | septic embolism with total obstruction of right popliteal artery | VAN and removal of vegetation | cured, well at 2-year follow-up | Lin *et al.*[16] |
| M, 47 years | healthy | Italy | mitral | NK | NK | Italian clone (II::B::E) | S: AMK, SXT, VAN, TEC, TET<br>R: CLI, CIP, RIF, GEN, TOB | multiple areas of cerebritis, splenic infarction | VAN, LZD and valve replacement | cured | Pistella *et al.*[17] |

IVDU, intravenous drug user; m, month; ND, not determined; NK, not known; S, susceptible; TOE, transoesphageal echocardiography; R, resistant; w, week; AMK, amikacin; CHL, chloramphenicol; CIP, ciprofloxacin; CLI, clindamycin; DAP, daptomycin; ERY, erythromycin; FUS, fusidic acid; GEN, gentamicin; LVX, levofloxacin; LZD, linezolid; MET, methicillin; MIN, minocycline; MXF, moxifloxacin; OXA, oxacillin; PEN, penicillin; Q/D, quinupristin/dalfopristin; RIF, rifampicin; SXT, co-trimoxazole; TEC, teicoplanin; TET, tetracycline; TOB, tobramycin; VAN, vancomycin.
[a]With relevance to IE.

**Table 3.** Comparison of clinical characteristics and outcomes for patients with MSSA native valve IE (NV-IE), those with MRSA NV-IE and those with CA-MRSA NV-IE

| | MSSA NV-IE[18] ($n = 248$) | MRSA NV-IE[18] ($n = 43$) | CA-MRSA NV-IE ($n = 23$) |
|---|---|---|---|
| Age (years) | 33 (25–58) | 60 (44–73) | 34.8 (0.04–67) |
| Male sex (%) | 66.1 | 48.8 | 62.0 |
| Diabetes (%) | 7.3 | 27.9 | 9.5 |
| Intravenous drug use (%) | 54.8 | 14.0 | 42.9 |
| Community acquisition (%) | 83.9 | 18.6 | 81.0 |
| Vegetation location (%) | | | |
| aortic | 17.3 | 7 | 29.4 |
| mitral | 18.2 | 39.5 | 29.4 |
| tricuspid | 42.7 | 23.3 | 41.2 |
| pulmonary | 0.8 | 0 | 0 |
| Pulmonary embolism (%) | 49.0 | 16.3 | 52.6 |
| Total embolism (%) | 63.7 | 44.2 | 68.4 |
| CNS event (%) | 20.4 | 20.5 | 21.1 |
| Death (%) | 23.2 | 37.2 | 13.0 |

role in the potential introduction to the host. Consequently, it is important to give careful consideration to this ecological niche in relation to antibiotic prophylaxis. When the published cases are examined, none of the patients with CA-MRSA IE had documented classical risk factors for the acquisition of IE, e.g. heart murmur, structural heart disease or prior rheumatic fever. These data suggest that a new 'at risk' group may be emerging, namely, patients with some form of CA-MRSA skin lesion coupled with iv drug abuse or diabetes mellitus. At present, it is difficult to draw definitive conclusions, not least as the overall role of antibiotic prophylaxis for IE is currently undergoing major reappraisal. However, with increasing reports, careful consideration should be given to this potential new 'at risk' group.

Cardiologists and microbiologists need to be aware of the growing significance of this organism and its potential to cause IE. CA-MRSA, although an organism with its origins in the community, has already emerged in nosocomial transmission within healthcare settings, particularly neonatal intensive care units, where it has been involved in several types of infections. Although a very rare event to date, the risk remains relating to the potential for nosocomial IE, from CA-MRSA acquired in the community, but spreading in the healthcare setting. Unlike conventional IE, CA-MRSA has a worrying trait, appearing to cause IE in otherwise healthy and young patients akin to its more common presentation with skin lesions. The combination of CA-MRSA in skin lesions and skin trauma through injection (iv drug abuse and diabetes mellitus) may represent a new susceptible

**Table 4.** Comparison of International Guidelines for the antibiotic management of IE caused by MRSA

| | BSAC[21] | ESC[22] | AHA[23] |
|---|---|---|---|
| Native valve | vancomycin (1 g iv, 12 hourly), modified according to renal function plus: rifampicin (300–600 mg by mouth, 12 hourly)[a] or gentamicin (1 mg/kg body weight, 8 hourly), modified according to renal function[a] or sodium fusidate (500 mg by mouth, 8 hourly)[a] | vancomycin 30 mg/kg/24 h iv divided into two doses for 6 weeks (infusion over at least 60 min) | vancomycin 30 mg/kg per 24 h iv in two equally divided doses for 6 weeks adjust vancomycin dosage to achieve 1 h serum concentration of 30–45 mg/L and trough concentration of 10–15 mg/L paediatric dose: vancomycin 40 mg/kg per 24 h iv in two or three equally divided doses |
| Prosthetic valve | vancomycin (1 g iv, 12 hourly), modified according to renal function plus: rifampicin (300–600 mg by mouth, 12 hourly)[a] and/or gentamicin (1 mg/kg body weight, 8 hourly), modified according to renal function[a] and/or sodium fusidate (500 mg by mouth, 8 hourly)[a] | vancomycin 30 mg/kg/24 h iv divided into two doses for 6 weeks (infusion over at least 60 min) plus rifampicin 300 mg/24 h iv divided into three doses plus gentamicin 3 mg/kg/24 h iv (maximum of 240 mg/day) divided into three doses, all for 6–8 weeks | vancomycin 30 mg/kg per 24 h iv in two equally divided doses for $\geq$6 weeks (adjust vancomycin dosage to achieve 1 h serum concentration of 30–45 mg/L and trough concentration of 10–15 mg/L) plus rifampicin 900 mg per 24 h iv/po in three equally divided doses for $\geq$6 weeks plus gentamicin 3 mg/kg per 24 h iv/im in two or three equally divided doses for 2 weeks. Paediatric dose: vancomycin 40 mg/kg per 24 h iv in two or three equally divided doses; rifampicin 20 mg/kg iv/po per 24 h in three equally divided doses up to adult dose; gentamicin 3 mg/kg per 24 h iv or im in three equally divided doses |

AHA, American Heart Association; BSAC, British Society for Antimicrobial Chemotherapy; ESC, European Society of Cardiology; iv, intravenously; im, intramuscularly; po, orally.
[a]According to susceptibility.

population for the acquisition of CA-MRSA IE. We therefore would encourage continued reporting and examination of the epidemiology of IE because of this causal organism in an attempt to define the optimal antibiotic treatment regimens, as well as the potential role (if any) for the prevention of this infection.

## Transparency declarations

None to declare.

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