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Epidemiology, clinical features and management of infections due to community methicillin-resistant *Staphylococcus aureus* (cMRSA)

I. B. GOSBELL[1,2]

[1]*Department of Microbiology and Infectious Diseases, South Western Area Pathology Service, Liverpool and* [2]*Department of Pathology, School of Medical Sciences, Faculty of Medicine, University of New South Wales, Kensington, New South Wales, Australia*

Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) was initially confined to hospitals, but in the late 1970s appeared in the community in the USA, primarily among intravenous drug users. In the 1990s, community MRSA (cMRSA) strains appeared in multiple areas of the world, and spread extensively. Initially, there were problems with the definition of 'community-acquired', which was exacerbated by the fact that if a time-based definition was used without stratification for risk factors, patients with healthcare-associated MRSA would be counted. Some cMRSA strains have entered the hospital environment to cause outbreaks of infection, which has added to the difficulty in separating the two types. cMRSA strains usually possess genes for Panton-Valentine leukocidin (PVL), which is associated with furunculosis and necrotizing pneumonia, and sometimes possess other virulence genes such as those for toxic shock syndrome or exfoliative toxins. Antimicrobial resistance to commonly used topical and oral agents is now appearing in certain cMRSA strains, which is complicating therapy. While cMRSA strains are usually susceptible to most non-β-lactam antimicrobials, there is a lack of clinical trial data indicating which drugs have superior clinical efficacy. DNA fingerprinting methods have become more sophisticated over the last decade, and have determined that cMRSA strains have probably arisen from virulent methicillin-susceptible strains, most likely by horizontal transfer of methicillin-resistance genes from coagulase-negative staphylococci to *S. aureus* on a limited number of occasions, and these clones have spread extensively throughout the world by person-to-person transmission. In Australia, the dominant cMRSA clones are the Western Australia, Oceania and Queensland strains. (Intern Med J 2005; 35: S120–S135)

Key words: *Staphylococcus aureus*, antibiotic susceptibility, community-acquired infections, epidemiology, methicillin resistance.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) was originally a predominantly hospital organism,[1] and remained so until the late 1970s when an epidemic occurred among intravenous drug users (IVDUs) in Detroit.[2] Community MRSA (cMRSA) infections were unique to this group until the 1990s, when multiple epidemics began in geographically disparate areas of the globe, including the USA,[3,4] Canada,[5] Western Australia,[6] the Northern Territory,[7] New Zealand,[8] Papua New Guinea,[9] Turkey[10] and eastern Australia.[11]

The emergence of methicillin-resistance in community *S. aureus* isolates bears a striking resemblance to the emergence of penicillin-resistance in this species two decades earlier – it first emerged only in hospital strains, was then occasionally seen in the community, and then over a decade was found in >90% of community strains.[1] It is expected that methicillin-resistance will also become ubiquitous in community strains of *S. aureus*.

cMRSA epidemics have steadily progressed since the 1990s, moving beyond the original demographic groups,[12,13] and sometimes even into hospitals. cMRSA strains are virulent, perhaps more so than nosocomial MRSA strains,[14] occasioning appreciable morbidity and some mortality.[15] They are resistant to all β-lactam agents, which are the most frequently prescribed class of antimicrobials, and they acquire resistance to many non-β-lactams currently used in therapy.[16–18] At present, there is little surveillance in most areas of the world for this phenomenon, and no standardization of which non-β-lactams should be incorporated in antimicrobial susceptibility testing algorithms. Moreover, little is known about the therapeutic efficacy of the majority of non-β-lactams that one might consider for therapy. For all these reasons, cMRSA strains are very important to the general public, clinicians, laboratory technologists, infection control practitioners, health policy makers and researchers.

Correspondence to: Iain Gosbell, Department of Microbiology and Infectious Diseases, South-western Area Pathology Service, Locked Bag 7090, Liverpool BC 1871, New South Wales, Sydney, Australia. Email: i.gosbell@unsw.edu.au

DEFINING COMMUNITY MRSA

The definition of 'community-acquired MRSA' is problematic. Generally, it is considered the converse of 'nosocomial' infection, which is usually taken as an infection developing beyond 48–72 h of hospital admission. The revolution in how healthcare is provided in the last decade has resulted in blurring of the distinctions between hospital and community – for example, into which category nursing homes, ambulatory care units, day-stay units, doctors' surgeries, and so on fit.[19] Also, modern hospital patients frequently return to hospital repeatedly. MRSA can be acquired during a prior encounter, and can be carried for years. We have found that many patients with cMRSA had some 'risk factors' associated with nosocomial MRSA acquisition – they kept presenting for medical care and had multiple courses of antibiotics, and the fact that they had MRSA was unrecognized.[20] Others have found that patients with 'community-onset' MRSA, as defined by the time definition, have usual risk factors for MRSA acquisition and are really not cMRSA cases.[21–24] These cases are generally adults from geographical areas with a low prevalence of true cMRSA epidemic clones.

The literature on cMRSA is bedevilled with other problems. The majority of studies are very small, and usually retrospective. Important groups such as IVDUs have often been excluded. Also, a 'nursing home' in the US may be the equivalent of a small acute care hospital in Australia.

In addition, the majority of studies do not report full isolate antibiograms or provide typing data. There is no standardization of typing, apart from recent efforts with pulsed-field gel electrophoresis (PFGE)[25] and composite analysis involving multilocus sequence typing (MLST) combined with staphylococcal cassette chromosome *mec* typing (MLST/SCC*mec* typing),[26] and most typing work is not coupled to comprehensive clinical and epidemiological data. However, recent data from MLST/SCC*mec* typing have assisted greatly in delineating epidemic MRSA clones,[26] and typing is probably an essential part of any high-quality investigation of the epidemiology of cMRSA.

The solutions to this problem are to stratify patients and to include standardized typing methodologies (either PFGE using 'Harmony' conditions[25] or MLST/SCC*mec* typing[26]) into future investigations. The following stratification into four groups has been suggested:[19]

1 Discharged hospital patients with MRSA
2 MRSA in nursing and residential homes
3 MRSA spreading to non-hospitalized patients
4 Community-acquired MRSA arising *de novo*.

US workers have suggested stratification into two groups based on the presence or absence of nosocomial MRSA risk factors.[3] Recently, the US Centers for Disease Control and Prevention (CDC) suggested that 'a case of community-acquired MRSA was defined as illness compatible with staphylococcal disease, in which MRSA was cultured from the site of infection . . . in an outpatient setting or <48 h after hospital admission, and with none of the following healthcare risk factors: hospitalization, surgery, dialysis, or residence in a long-term-care facility <1 years before the onset of illness; permanent indwelling catheter or percutaneous medical device; or a previous positive MRSA culture.'[27] Recent US surveys have found that the majority of 'community-acquired' MRSA cases are in patients with multiple risk factors, generally underlying medical problems, and multiple readmissions to hospital.[22] It should be noted that all of these surveys have come from urban US centres (and that the experience elsewhere is different), and that not enough typing was done to allow determination of which clones where responsible.

Australian workers have suggested that, at least for bloodstream infections, infectious states can be stratified into healthcare-associated, community-associated or maternally acquired.[28] Community-associated infections are defined as not healthcare-associated, not maternally acquired, and not manifesting more than 48 h after hospital admission (excluding infections due to organisms with prolonged incubation periods). Healthcare-associated infections are those acquired during hospitalization and not present or incubating on admission, those occurring as a complication of an indwelling medical device and/or within 30 days of surgery, invasive instrumentation, or an incision related to the bloodstream infection was performed less than 48 h prior to the onset of the infection, and/or an infection associated with cytotoxic drug-induced neutropenia. Healthcare-associated infections can be further categorized into inpatient and non-inpatient events.

An earlier version of these definitions contained the above plus infection developing within 10 days of hospital discharge as being hospital inpatient-associated.[20]

HISTORY OF COMMUNITY MRSA

As noted above, 'community-acquired' MRSA was first described in intravenous drug users in Detroit, USA.[2] These individuals were less likely to have traditional risk factors for MRSA acquisition, such as hospital admission, but they were frequently exposed to antibiotics, most often cephalosporins sourced from the street. This strain entered the local hospitals, and nosocomial transmission was described.[30] Limited antimicrobial data were reported, but strains were less resistant to non-β-lactam antimicrobials than hospital MRSA strains.

From 1989 onwards, cMRSA strains were reported from other areas of the world.[3–11] Despite occurring in vastly separated regions, there were certain common features: the strains were often susceptible to most non-β-lactam antimicrobials, they were associated with poor and often indigenous peoples, and they showed striking epidemic potential and were strongly associated with skin and soft tissue suppuration.

Unusual non-multiresistant MRSA strains were isolated from patients presenting to Perth hospitals in the early 1990s.[6,31,32] The epidemics of cMRSA in Western Australia are some of the best described in the literature,[6,12,31–35] no doubt reflecting the fact that MRSA

is a notifiable condition in that state. These patients were often from remote areas in the Kimberley and Goldfields regions of Western Australia. They had not been in hospitals outside of the state, and where not known to carry MRSA. Subsequently, these MRSA strains have spread steadily, and are now seen in the eastern states of Australia.[35]

The strains were originally noted to have different phage and PFGE types to the multiresistant MRSA strains that were occasionally imported from other states. Recent MLST/SCC*mec* typing has shown that there are multiple distinct clones among the Western Australian isolates,[35–37] implying that there are multiple concurrent epidemics of cMRSA in that state.

At the same time, an outbreak of cMRSA began in New Zealand.[38] Again, recognition of the outbreak was facilitated by having MRSA a notifiable condition and having all MRSA isolates sent to a central laboratory. These strains were non-multiresistant, and fell into two groups by phage typing – the Western Samoan Phage Pattern-1 (WSPP1) and Western Samoan Phage Pattern-2 (WSPP2). Subsequent work by others has shown these strains are the same clone.[35] The epidemic was most intense in the Auckland area, and the organisms spread widely, including to Australia.[11,14,20,39] In Australia, they are also known as the South-western Pacific[39] or Oceania strain.[40]

Multiple case reports and two small series[3,41] were reported from the USA during this period. The most detailed study by Herold *et al.*,[3] was a seminal one in being the first sizeable series to examine clinical and epidemiological factors, and the first to stratify patients according to the presence or absence of risk factors. These researchers found a real increase in presentations in patients without risk factors, and most cases were infections and not colonization. However, only limited antibiogram and typing data were presented; the community isolates were somewhat less resistant and the PFGE patterns of the three community strains actually typed were different to hospital strains of MRSA.

The publication of a report on four fatal paediatric cMRSA infections intensified interest in this phenomenon.[15] The children had bacteraemia and died from severe sepsis. The strains were non-multiresistant and typing showed they were related to each other but were distinct from nosocomial strains.

Laboratories in Brisbane, Melbourne and Sydney reported the isolation of non-multiresistant, cMRSA strains in the late 1990s.[11] Most patients were Polynesians and presented with skin and soft tissue infections. Phage and PFGE typing showed that multiple strains were responsible, including the Oceania strain.

A later study from Queensland of gentamicin-susceptible MRSA showed that 23 of 35 patients had community-acquired infections, and 16 of these 23 patients lacked risk factors associated with nosocomial MRSA acquisition.[39] The strains were non-multiresistant, most were fully susceptible to non-β-lactams and closely related to New Zealand WSPP strains, and most patients were Polynesians. Subsequent work from New South Wales showed that WSPP strains were usually associated with skin and soft tissue infections, but that the infections were much more severe than infections with methicillin-susceptible *S. aureus* (MSSA) or multiresistant MRSA strains and the majority of patients required hospital admission and surgery.[14] Polynesians were again over-represented in this cMRSA group.

A second clone of cMRSA was recently reported from Queensland.[42,43] This clone was initially seen around Ipswich, and most patients were Caucasians. Apart from causing boils, it also caused bacteraemia and pneumonia. PFGE typing revealed a unique pulsotype, and subsequent work showed that this strain is common in Queensland, New South Wales and Victoria.[18,36,37,44] It was also responsible for a substantial outbreak in Aboriginals in rural New South Wales.[44]

The most extensive data on the Australian cMRSA situation derives from the work of the Australian Group on Antimicrobial Resistance (AGAR).[36,37] This group has representatives in major hospital laboratories in the capital cities of all Australian states, and each November, 100 consecutive isolates of *S. aureus* are collected for antimicrobial susceptibility testing and strain differentiation. Surveys performed in 2000 and 2002 concentrated on 'community' patients, as defined by the 48-h cutoff. In 2000, 10% of *S. aureus* strains were resistant to methicillin, and this rose to 19% in 2002. In both surveys, approximately 50% of MRSA strains were non-multiresistant.

Typing of isolates from the 2000 survey revealed the presence of several major epidemic clones of non-multiresistant MRSA (i.e. several strains of WA MRSA, the Oceania strain, the Queensland strain, four other epidemic clones and a small number of sporadic isolates).[36,37] WA MRSA strains were mainly seen in the western and central states, the WSPP strains mainly in the east, and the Queensland strain mainly in Queensland. The 2002 survey showed these epidemic clones were moving, the western ones to the east, and *vice versa*.

CLINICAL FEATURES OF INFECTIONS WITH COMMUNITY MRSA

Virtually all studies reporting clinical manifestations have found that cMRSA infection is most often manifest by skin and soft tissue suppuration.[3,11,14,39,45–48]

Common presentations

A study from New South Wales sought to compare the clinical features of infections with non-multiresistant MRSA, multiresistant MRSA, and methicillin-susceptible *S. aureus* (MSSA).[14] Compared with the other two groups, patients with non-multiresistant MRSA were younger, more likely to be Polynesian, less likely to have the usual risk factors for MRSA acquisition, more likely to present with boils and abscesses, and more likely to need admission and surgery. Bacteraemia was rare and other kinds of infections such as bone and joint infection were uncommon in the non-multiresistant MRSA group. The majority of the non-multiresistant MRSA isolates were WSPP1 or 2, and all the multiresistant MRSA

strains were classified as AUS-2 MRSA-2.[40] The methicillin-susceptible isolates were not typed.

Serious infections with community MRSA

Serious infections are uncommon but often appear in the literature as case reports, for example, as bacteraemia,[15] osteomyelitis[4] and pneumonia,[49] and a small series where 10 MRSA bacteraemias occurred in persons without the usual risk factors for acquisition of MRSA.[50] In one report, 9% of WA MRSA infections were found to be bacteraemias.[48] Intravenous drug users with cMRSA frequently have bacteraemia, often with complications such as endocarditis and osteomyelitis.[2]

The published studies are too small to indicate whether these more serious infections constitute a significant part of the disease burden of cMRSA, or whether they are more or less common than infections with other *S. aureus* strains. No study has compared the clinical features of infections caused by different strains of cMRSA – for example, whether Oceania or Queensland strains are more likely to cause deep-seated infections.

Interest in cMRSA in the USA increased substantially with the deaths of four children from serious infectious with cMRSA.[15] Subsequently, the number of reports of serious, sometimes fatal infections with cMRSA has increased, and this has included several from Australia.[11,51–54]

VIRULENCE OF COMMUNITY MRSA

The pathogenicity of *S. aureus*, like that of most pathogenic bacteria, is dependent on the balance between the host and the organism.[55] A myriad of virulence factors have been described in this species.[55] Given the important advances being made in strain differentiation, especially with MRSA, there is, paradoxically, little information about how these virulence factors might vary between strains of *S. aureus*. Important epidemic clones of MRSA are being sequenced, including the strain from the fatal US paediatric cases (MW-2);[56] important information about pathogenicity genes and their control will hopefully emerge from this work.

A study of US and Australian cMRSA strains found the mean doubling times of the two strains were 28.79 ± 7.09 and 28.24 ± 2.48 min, respectively, which was significantly faster than the mean doubling time of 38.81 ± 7.01 min for nosocomial strains.[12] The authors suggested this might give cMRSA strains a competitive advantage in colonizing likely hosts.

There has been much recent interest in the production of Panton–Valentine leukocidin (PVL) by *S. aureus* strains. This cytotoxin was discovered in 1894 by van de Velde[57] and distinguished from haemolysins in 1932 by Panton and Valentine.[58] Gamma haemolysins and PVLs form a two-component exotoxin, which is synergistically toxic to human neutrophils, monocytes and macrophages.[59] The genes for PVL enter *S. aureus* via a bacteriophage.[60] PVL is a potent dermonecrotic toxin,[61] and appears to be strongly associated with *S. aureus* strains that cause skin and soft tissue infections such as impetigo and boils.[62–64] Strains of *S. aureus* possessing PVL are also associated with necrotizing pneumonia, and patients with this infection have a high mortality.[65] One group of investigators found that *S. aureus* strains possessing PVL genes showed greater affinity for collagen and laminin than PVL-negative strains, and they hypothesized that this might permit binding of such strains to damaged respiratory epithelia.[66]

Nearly all cMRSA strains studied possess the PVL gene, including the Oceania and Queensland strains.[43] These most probably arose by insertion of methicillin resistance elements into strains of methicillin-susceptible *S. aureus* that already possessed the PVL gene.[26,67] At least four epidemic WA MRSA clones were not found to possess the PVL gene,[36] although a WA MRSA-1 strain recently detected in New South Wales was shown to possess the gene.[44] In another study in which virulence genes were examined in 100 isolates of cMRSA isolated from children in New South Wales,[18] only 68% of strains possessed PVL genes, 4% possessed the toxic shock syndrome toxin-1 and 25% possessed one or more enterotoxin genes. Thus, PVL is clearly not a universal marker of cMRSA strains, contrary to frequent claims in the literature.

Exfoliative toxin genes have been detected in cMRSA strains isolated in Japan[68] and Switzerland.[69] These strains were PVL gene-negative, and were associated with impetigo, as opposed to PVL gene-positive, exfoliative toxin gene-negative strains, which were associated with boils and abscesses. Staphylococcal toxic shock syndrome toxin-1 (TSST-1) was detected in 4% of paediatric cMRSA isolated in Sydney,[18] and was also described in a strain causing sepsis in a neonate in France.[70]

A recent report has described *in vitro* work on virulence factors of the Oceania cMRSA strain by comparing it with UK EMRSA-15, UK EMRSA-16 and AUS-2 MRSA.[71] It was found that Oceania strains were more tolerant to sodium chloride, but equally tolerant to fatty acids, ultraviolet light and desiccation. They were better at attaching to HEp2 cells, were egg yolk opacity factor-negative and exhibited high levels of α- and β-haemolysin activity. The authors noted that α-haemolysin activity was correlated with pore formation and membrane damage in host leucocytes. They also noted that β-haemolysin activity is usually found in strains of animal origin.[71]

In another study, virulence genes and genetic backgrounds were analysed in 117 cMRSA strains from the US, France, Switzerland, Australia, New Zealand and Western Samoa.[43] All strains were found to possess PVL genes and SCC*mec* IV, and most had an *agr*3 background. Of the other genes sought, *luk*E-*luk*D was present in 116 (99%), haemolysin G in 13 (11%), variant haemolysin G in 100 (85%), haemolysin B in 1 (1%), Enterotoxin A in 23 (20%), Enterotoxin B in 9 (8%), Enterotoxin C in 20 (17%), Enterotoxins D-J in 3 (3%), Enterotoxin H in 29 (25%) and Enterotoxin K in 24 (21%), while the enterotoxin gene cluster was present in 13 (11%). The distribution of genes other than SCC*mec* and PVL was specific to the dominant strain from each geographical region. It was also found

that the cMRSA strains in each region were genetically distinct from local nosocomial strains.

Given that PVL genes and SCC*mec* are widely separated on the genome,[56] it is unlikely these markers of cMRSA strains were acquired together.[43]

RISK FACTORS FOR ACQUISITION OF COMMUNITY MRSA

It is becoming clear that the risk factors for acquiring healthcare-associated and community MRSA are markedly different, as summarized in Table 1. The evidence for specific cMRSA risk factors is examined below. It is important to note that for most of these, the specific risk factor has not been specifically elucidated as part of univariate or multivariate analysis, and this is an area for further study.

Injectable drug use

The first reports of cMRSA were in IVDUs in Detroit.[2,30] Subsequently, many reports on cMRSA, especially from the USA,[41,72–74] but also from other countries, have described many patients as IVDUs. However, this is not universally the case, as most Australian studies have not shown this association.[11,14,20,39] Nevertheless, there is recent evidence of the emergence of cMRSA in IVDUs in Queensland,[75] and in New South Wales (Gosbell IB; unpublished data).

Ethnicity

Initial Australian reports of cMRSA described an association with being an Australian Aborigine.[7,31] Initially, the Queensland cMRSA strain was isolated in Caucasians,[42] but it was subsequently found to be the dominant clone in Aborigines in New South Wales.[18,44] The Oceania cMRSA strain is strongly associated with Polynesian ethnicity.[8,14,39]

American Indians are often represented in reports from the USA.[15,76] cMRSA is also associated with aboriginal peoples in Honolulu,[47] Alaska[77,78] and Canada.[70]

Contact sports

Playing contact sports is a risk factor for acquisition of cMRSA. In the UK, a British rugby team played a visiting team of Polynesians and shortly afterwards, several members of the British team came down with boils.[80] Isolates were found to be non-multiresistant, and by phage typing were WSPP-1 strains, although this was not recognized at the time. Subsequently, wrestlers,[81,82] fencers[82] and gridiron players,[82,83] have also been found to acquire non-multiresistant MRSA. Risk factors for acquisition include physical contact,[82,83] skin damage including turf burns[82] and skin shaving;[82] and sharing of towels,[82,83] equipment[82,83] and/or clothing.[82] However, a recent study did not show that shaving of the body, other than the face, was a risk factor, nor was the presence of turf burns *per se*, but overt infections were always found at the site of turf burns.[83] In two studies where fomites were sampled, MRSA contamination was not found,[81,83] but in one of these, the samples were taken after measures to increase hygiene were implemented.[83]

Prison incarceration

There have been several reports describing epidemics of non-multiresistant MRSA in US gaols.[84,85] Mainly boils and abscesses were seen, but there were also invasive infections. Strains are usually non-multiresistant, and the strain known as USA300 was the most common clone. Carriage by both inmates and gaolers was found to be common. Factors contributing to outbreaks included barriers to routine hygiene (such as implementation of security, mental health issues, poor access to laundering facilities), poor access to healthcare, a lack of recognition of MRSA (due to lack of awareness in healthcare workers, not taking swabs, and falsely attributing skin lesions to 'spider bites').[84] The US Centers for Disease Control and Prevention have identified MRSA in gaols as a priority area for investigation and control.

Military service

In a series of 67 cases of skin sepsis seen between 1994 and 1997 in military recruits, 24 were found to have MRSA and of these, nine did not have usual risk factors for MRSA acquisition.[86] An outbreak of cMRSA among military recruits has also been described.[87] The outbreak of boils involved 34 patients, and 22 of 206 recruits were colonized with cMRSA (the USA300 strain). Risk factors in this study were reported to be having a roommate with cMRSA infection or having a contact who was a healthcare worker.

Table 1 Risk factors for acquisition of healthcare-associated versus community MRSA

Healthcare-associated MRSA[146–150]	Community MRSA
Recent hospitalization	IVDU
Close contact with a person who has been hospitalized	Being indigenous
Recent surgery	Playing contact sports
Recent intubation	Incarceration in gaol
Renal dialysis	Being a military recruit
Chronic disease	Resident of institutions for developmentally disabled
Indwelling medical device	Being a client of steam baths
Previous antimicrobials	Being a man who has sex with men
	Previous antimicrobials

IVDU, intravenous drug use; MRSA, methicillin-resistant *S. aureus*.

Homosexuality

Outbreaks of non-multiresistant MRSA have also been reported from the USA, in men who have sex with other men.[88,89] Again, boils were the usual manifestation and these patients were often HIV antibody-positive. Investigations of this are in progress, and further information will be published shortly.

An investigation of cMRSA in a day-care centre in Toronto undertaken after the discovery of an index case of infection found only one positive child out of 164 tested children and 38 tested adult contacts.[90] In two other day-care centre investigations, higher cMRSA carriage levels of 3% and 24% were found and two strains were demonstrated by PFGE typing.[91] Another day-care centre study undertaken after a severe case of cMRSA infection had been discovered noted that 10% of contacts (15 of 143) were MRSA carriers, including 7% of the contact healthcare workers (5 of 76), although none of the positive contacts was carrying the index strain.[92] It would seem from these three studies that transmission of cMRSA strains from an index case in the day-care centre setting is rare.

For people with intellectual disabilities, however, the situation may be quite different. An outbreak of boils caused by cMRSA in such an institution has been reported, with 20 of the 28 residents having 73 infections over a 9-month period;[93] 68% of the residents and 32% of the healthcare personnel were found to harbour cMRSA. The outbreak was terminated by institution of hygiene measures and treatment of nasal carriage with topical mupirocin or fusidic acid. PFGE typing showed a single cMRSA strain to be present in all carriers. Most probably, the close contact and difficulty implementing hygiene were key factors in the high rate of transmission seen here.

Steam bath use

Furunculosis has previously been associated with Alaskan sauna use.[94] In a case-control study from rural Alaska in which an outbreak of furunculosis due to cMRSA was described, 88% of the cases and controls used saunas on a regular basis.[78] A major risk factor (relative risk 4.6) was being a client of a steam sauna that had environmental contamination with cMRSA, which was found by PFGE to be of one of two strains. The authors showed a scanning electron micrograph showing clusters of staphylococci embedded in a biofilm coating the wooden seats in the saunas.

NASAL CARRIAGE OF COMMUNITY MRSA

A number of studies have examined nasal carriage of cMRSA in community settings where cMRSA is common, including patients presenting to a Western Samoan hospital,[95] a rural outpatient clinic in New Mexico,[96] outpatients in Hawaii,[97] children attending emergency departments in Chicago[98] and the urban poor of San Francisco.[73] Carriage rates of 0.4% to 2.8% were reported among student volunteers in South Carolina,[99] but higher carriage rates of 6% in IVDUs from San Francisco[72] and 12% in household contacts of index cases with cMRSA infections have been noted.[77]

EMERGING DRUG RESISTANCE IN COMMUNITY MRSA

Resistance to non-β-lactam antimicrobials is clearly emerging in non-multiresistant MRSA strains. *In vitro* resistance in an Oceania strain isolate was readily induced to rifampicin, fusidic acid, ciprofloxacin and cotrimoxazole.[40] In Western Australia, resistance to mupirocin has emerged,[16] notably in areas where topical mupirocin was widely prescribed. On restriction of the prescription of mupirocin, resistance levels fell. Mupirocin resistance has also emerged in New Zealand (in both methicillin-susceptible and methicillin-resistant *S. aureus*), and again, this was ascribed to ready availability of this agent, including over-the-counter availability for a period.[100] Similarly, fusidic acid resistance in methicillin-susceptible *S. aureus* has been reported in the UK, which was attributed to the widespread use of this antibiotic in a topical preparation.[101,102] The ST80-MRSA-IV clone found throughout Europe is typically fusidic acid-resistant,[103] as is WA MRSA-1.[36,37]

A recent study from San Francisco found that 7% of isolates were resistant to ciprofloxacin, 10% were resistant to erythromycin, 3% were resistant to tetracyclines and 2% were resistant to all three drugs.[85] Recent work among children in Sydney has shown that resistance to erythromycin, fusidic acid, ciprofloxacin and tetracycline is emerging in multiple cMRSA lineages.[18] However, it is not yet known if this reflects the emergence of particular epidemic clones, or is a consequence of the widespread prescription of these agents.

Testing and reporting algorithms for non-β-lactam antimicrobials against non-multiresistant MRSA are not standardized. Often laboratories hide sensitivity results for non-β-lactams against MRSA in an effort to stop prescribers using these agents. However, it is important for clinicians to know which non-β-lactams can be used, particularly now that resistance to non-β-lactams is emerging among commonly seen strains. The SWAPS Staphylococcal Reference Facility in Sydney routinely tests tetracycline, erythromycin, gentamicin, ciprofloxacin, moxifloxacin, rifampicin, fusidic acid, mupirocin and cotrimoxazole, and reports sensitivity data for all of these agents except gentamicin.[104]

DNA FINGERPRINTING OF COMMUNITY MRSA STRAINS

Strain differentiation of cMRSA isolates is shedding considerable light on the epidemiology of these strains, especially from a global perspective. There is a vast literature pertaining to the application of different strain differentiation techniques to *S. aureus*, which is beyond the scope of this review. The traditional method of typing *S. aureus* is with phage typing,[105] and application of this method to cMRSA strains has shown that these strains are different from nosocomial strains.[2,38] Phage typing is labourious, and a considerable number of strains are

non-typable; for example, important clones like UK EMRSA-15[106] and the Queensland clone[104] are often non-reactive with basic set MRSA and experimental phages.

PFGE was, until recently, regarded as the best of the molecular methods, and in recent times application of 'Harmony' conditions has allowed considerable inter-laboratory reproducibility,[25] a major problem with any method that produces bands on gels. PFGE is still the best method to study the relatedness of small numbers of isolates, but MLST and SCC*mec* typing have emerged as the best ways, short of sequencing the entire genome, of determining global epidemiology.[12,26] These methods are reproducible between laboratories, and publication of such results allows immediate recognition of the clone, something not possible with any other typing method. Furthermore, the application of MLST/SCC*mec* typing allows a logical and universal nomenclature, expressed in the form ST-MRSA-SCC*mec*.[26]

The MLST work of Enright *et al.* has enhanced our understanding of the global epidemiology of MRSA.[26] In their seminal paper, 356 of 359 MRSA strains examined were found to constitute five clonal complexes; 11 of the well-described hospital epidemic clones belonged to these five clonal complexes. Thirty-five strains of community non-multiresistant MRSA were found to be more heterogeneous, belonging to 10 sequence types in seven clonal complexes.

More recently, Enright *et al.* constructed 'high-resolution evolutionary models' using data obtained from high-resolution multilocus typing.[67] This involved sequencing *S. aureus* surface protein (*sas*) genes, plus the seven housekeeping genes sequenced in MLST, and subjecting this to maximum parsimony analysis. Based on the isolates studied, they deduced from this model that *S. aureus* acquired SCC*mec* on at least 20 occasions, and that the SCC*mec* type IV associated with cMRSA was the methicillin resistance element more likely than all other types combined, to insert into *S. aureus*. It was hypothesized that SCC*mec* type IV originated from coagulase-negative staphylococci, and horizontal gene transfer resulted in it appearing in *S. aureus*.[107,108] Other researchers have examined a larger number of cMRSA clones with various typing methods, including MLST and SCC*mec* typing.[12] The US and Australian strains examined exhibited very rapid growth times, were usually non-multiresistant, had heterogenous resistance to methicillin and had diverse MLST sequence types with a different distribution to those studied by Enright *et al.*[26,67] Most had SCC*mec* type IVa, although a novel SCC*mec* was also seen.

As well as type IV, other types of SCC*mec* are also found in cMRSA. These include SCC*mec* V,[109] which has been found in cMRSA isolates from Adelaide[12] and Perth,[37] and a novel SCC*mec* that encodes a class B *mec* complex typical of a type IV SCC*mec* and a *ccrC* recombinase gene typical of a type V SCC*mec* in a cMRSA isolate from Brisbane.[12] Other arrangements of SCC*mec*, yet to be ascribed a name, have also been detected in *S. aureus* and coagulase-negative staphylococci.[107]

Whole genome sequencing has been performed on one strain of cMRSA, MW2 (USA400),[56] which was the isolate from one of the four fatal US paediatric cases described above.[15] This strain had the then novel allelic form of SCC*mec*, dubbed type IVa. It lacked resistance genes apart from those for methicillin resistance. Nineteen virulence genes were recognized, of which 17 were found in four of the seven genomic islands identified. The genes for PVL were found in a prophage inserted into the Sa2 genomic island. Additionally, 16 superantigen genes were identified, including staphylococcal enterotoxin H, which is a strong superantigen, although the TSST-1 gene was absent.

MLST/SCC*mec* types of common epidemic clones of MRSA are shown in Table 2, and the typical phenotypic and phage typing results of clones commonly seen in Australia are given in Table 3. The typical PFGE appearances of these clones are shown Fig. 1.

COMMON AUSTRALIAN COMMUNITY MRSA STRAINS

South-west Pacific (Oceania) clone

The South-west Pacific (Oceania) clone was the original non-multiresistant cMRSA seen in eastern Australia.[12,20,36,37,39] Given that it emerged in New Zealand[8,38] before it emerged in Australia, and was seen originally in persons with a strong connection to New Zealand,[11,14] it was most probably transported by human carriers across the Tasman Sea in the 1990s. Since then, the South-west Pacific (Oceania) clone has moved beyond the Polynesian group and is now also seen in rural Aboriginals.[104] It is strongly associated with boils and sometimes with bone and joint infections, but is rarely seen in blood cultures.[11,14,39] Typically, the Oceania clone is fully susceptible to non-β-lactam antimicrobials, but resistance does appear to be emerging slowly. In the 2000 AGAR survey, 8% of WSPP1 strains were resistant to erythromycin and 4% to ciprofloxacin. Resistance was higher among WSPP2 strains: 20% were resistant to erythromycin, 20% to mupirocin and 10% to trimethoprim.[110] These isolates possess the PVL gene.[12,43]

Queensland clone

The Queensland clone was first detected in Ipswich, Queensland, as a non-multiresistant MRSA causing infections in Caucasians.[42] Apart from causing boils, it was also implicated in bloodstream infection and necrotizing pneumonia. The 2000 and 2002 AGAR surveys found that it was a major clone, and the numbers increased between the two surveys.[36,37] Recently, the Queensland clone was detected in Aboriginals from rural New South Wales who were residing at a hostel in Sydney, and it was found to be the dominant clone causing boils in outback New South Wales.[104] Consequently, this clone has high epidemic potential. It is also positive for the PVL gene.[18,43,111]

WA MRSA clones

Recent work has shown that multiple unrelated clones constitute WA MRSA.[12,35–37,112] WA MRSA-1 is the most

Table 2 Examples of epidemic methicillin-resistant *S. aureus* (MRSA) clones[36,37,103,151–153]

MLST/SCC*mec* type	Common name	Alternative names
Non-multiresistant clones		
ST30-MRSA-IV	South-west Pacific	Western Samoan Phage Pattern-1/2; Oceania
ST93-MRSA-IV	Queensland	AGAR nmMRSA A; Brisbane pulsotype 'R'
ST1-MRSA-IV	WA MRSA-1, MW2, USA400	
ST129-MRSA-novel	WA MRSA-2	AGAR nmMRSA B
ST73-MRSA-IV	WA MRSA-3	AGAR nmMRSA C
ST8-MRSA-V	WA MRSA-4	AGAR nmMRSA E
ST8-MRSA-IV	WA MRSA-5	Original WA MRSA
ST8-MRSA-V		AGAR nmMRSA D
ST22-MRSA-IV	UK EMRSA-15	Barnim, German, Irish, Swedish
ST36-MRSA-II	USA200, UK EMRSA-16	Finnish
ST80-MRSA-IV	European	German, French, Scottish, Norwegian, Danish, Greek, Arabic
ST250-MRSA-I	Original MRSA, Archaic MRSA	Danish, German, Swiss, Uruguayan, British
ST5-MRSA-IV	USA800	Paediatric clone
ST72-MRSA-IV	USA700	Alaskan
Multiresistant clones		
ST239-MRSA-III	AUS-2/-3 MRSA, UK EMRSA-1, Hungarian, Brazilian	USA, Finnish, German, Greek, Irish, Dutch, Polish, Portuguese, Slovenia, Swedish, UK EMRSA-4/-11 Portuguese, Viennese
ST5-MRSA-I	UK EMRSA-3	Polish, Slovenian
ST5-MRSA-II	USA100, Japan/US	Finnish, Irish, UK, US VISA
ST8-MRSA-II	Irish-1	Irish, UK, USA
ST45-MRSA-IV	Berlin, USA600	Belgian, Finnish, German, Swedish
ST247-MRSA-I	Iberian,† UK EMRSA-5/-17	Belgian, Finnish, French, German, Portuguese, Slovenian, Spanish, Swedish, USA
ST8-MRSA-IV	USA300, Irish-2, EMRSA-2,-6, WA MRSA-12	Finnish, French, German, Irish, Dutch, UK, USA

†The Iberian clone consists of several ST/SCC*mec* lineages: ST8-MRSA-IV/-II (multiresistant), ST8-MRSA-I/-III/-IV (non-multiresistant), ST250-MRSA-I (non-multiresistant), and ST247-MRSA-I (multiresistant).[151]
AGAR, Australian Group on Antimicrobial Resistance; EMRSA, epidemic MRSA; MLST, multilocus sequence typing; nmMRSA, non-multiresistant MRSA; SCC*mec*, staphylococcal cassette chromosome *mec*; ST, sequence type; WA, Western Australia.

Table 3 Distinguishing features of common epidemic clones of methicillin-resistant *S. aureus* (MRSA) in Australia[20,25,35–37,42]

Clone	Typical resistance pattern	Urease	PVL
Multiresistant clones			
AUS-2	Tet, Ery, Tmp, Gen, Cip	Pos	Neg
AUS-3	Tet, Ery, Tmp, Gen, Cip, $HgCl_2$, PMA	Pos	Neg
Irish 2	Ery, Tmp, Cip	Neg	Neg
Non-multiresistant clones			
UK EMRSA-15	Ery, Cip	Neg	Neg
UK EMRSA-16	Ery, Cip	Pos	Neg
Oceania	Nil, Ery	Pos	Pos
Queensland	Nil, Ery	Pos	Pos
WA MRSA 1	Ery, Fus	Pos	Neg

Cip, ciprofloxacin; EMRSA, epidemic MRSA; Ery, erythromycin; Fus, fusidic acid; Gen, gentamicin; $HgCl_2$, mercuric chloride; Neg, negative; PMA, phenyl mercuric acetate; Pos, positive; PVL, Panton-Valentine leukocidin; Tet, tetracycline; Tmp, trimethoprim.

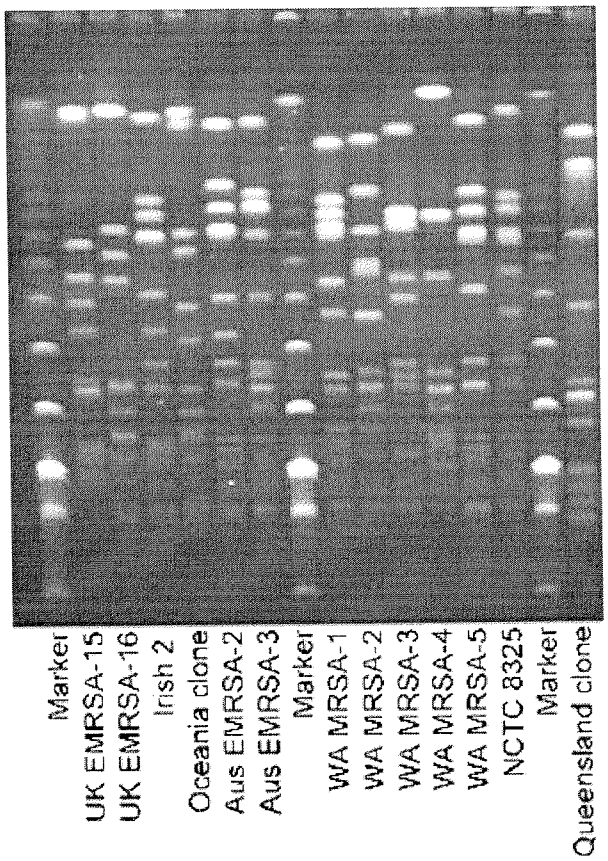

Figure 1 Pulsed-field gel electrophoresis (PFGE) patterns of common Australian MRSA clones.

common cMRSA seen in Western Australia.[36,37] It is also seen in Northern Territory, South Australia and Queensland, but rarely in other states. WA MRSA-2 constitutes one-third of cMRSA from Western Australia, but is rarely seen outside of this state. WA MRSA-3 and WA MRSA-4 are less common isolates seen in Western Australia.

WA MRSA-5 is the original cMRSA described from Western Australia. It is the only WA MRSA clone that possesses the PVL gene. Most WA MRSA clones have SCC*mec* IV, but some have the recently described SCC*mec* V.[12,37]

UK EMRSA-15

UK EMRSA-15 is the notorious British export, which was first detected in the Midlands and south of England, and then spread throughout Britain to become the most common MRSA clone seen in specimens in that country.[113] It is also the most common MRSA isolate seen in bloodstream infections in the UK,[114] and infection with this strain causes considerable morbidity and mortality. UK EMRSA-15 appears to have a predilection for the very elderly, especially if they reside in nursing homes. It appeared in Perth in 1996,[115] and in the rest of Australia shortly afterwards.[36,37] Recent data shows the prevalence of EMRSA-15 to be rising in New South Wales, and 25% of MRSA bacteraemias in some large hospitals in this state are due to EMRSA-15.[104]

EMRSA-15 is readily recognized in the laboratory. Nearly 100% of strains are resistant to ciprofloxacin and 60% to 70% are resistant to erythromycin, but they are usually susceptible to all other non-β-lactams.[106] Unlike most other MRSA strains, EMRSA-15 isolates are urease-negative and lipase-positive.[112]

EMRSA-15 possesses SCC*mec* type IVa,[26] and therefore is genetically a cMRSA. Could it have originally been a community strain that entered the healthcare setting before it was detected? Other community strains have entered the hospital setting to cause nosocomial infections,[116] including those involved in the original cMRSA outbreaks.[30]

Other clones

Two clones from the UK and Ireland have been seen periodically in Western Australia but not elsewhere (i.e. UK EMRSA-16 and Irish 2).[37] AUS-2 and AUS-3 MRSA are identical by MLST and SCC*mec* typing, but are distinguishable on an extended antibiogram/resistogram, phage typing and PFGE.[37] The original multiresistant MRSA seen in Sydney and Melbourne hospitals has evolved into AUS-2 and AUS-3 MRSA clones, which comprise the majority of endemic nosocomial multiresistant MRSA seen in Australia. AUS-2 MRSA is mainly seen in Brisbane, Sydney and Melbourne, while AUS-3 MRSA is mainly seen in Adelaide but also in Melbourne and Darwin.

AUS MRSA was probably exported to the UK,[117] and is known there as UK EMRSA-1. It initially caused epidemics there but is now uncommon.

RECOGNITION OF METHICILLIN RESISTANCE IN COMMUNITY MRSA

Detection of community strains of MRSA poses special problems. Whereas nosocomial MRSA strains are multiresistant, providing a clue if they test methicillin-susceptible, this clue is absent with non-multiresistant strains.[118] Community strains have heterogenous methicillin resistance.[39] In addition, MICs to methicillin and oxacillin are lower than for typical nosocomial multiresistant strains, and in some cases they can be at or lower than standard breakpoints.[118,119]

Methicillin is a better substrate than oxacillin for the detection of methicillin resistance in these strains,[118,119] but unfortunately production of methicillin has ceased, forcing laboratories to use the inferior substrate. There is good evidence that cefoxitin is superior to oxacillin for detecting methicillin resistance,[120] including in non-multiresistant strains,[121] and the NCCLS have recently included cefoxitin as one of the recommended substrates to detect methicillin resistance.[122] Borderline oxacillin-resistant *S. aureus* ('BORSA') strains have MICs hovering around the NCCLS breakpoints.[123] These strains are not uncommon, and can readily be detected by virtue of the fact they lack the *mec*A gene and penicillin-binding protein 2a (PBP 2a).[123]

Where it is unclear if an isolate is methicillin-resistant or not, a test detecting the gene or its product must be performed. Detection of the *mec*A gene by PCR[124] or DNA hybridization[125] is well described, and these are regarded as the 'gold standard' tests. Detection of the product, PBP 2a, by latex agglutination correlates well with *mec*A PCR, and is a satisfactory substitute.[126,127] However, non-multiresistant MRSA strains can give a slow reaction, and the full three minutes reaction time must be allowed to elapse before calling the test negative.[128] One study found that the reaction time needed to be extended to 15 min to achieve 100% sensitivity.[129] As well, some strains are only latex-positive after induction with oxacillin (e.g. taking growth from around an oxacillin disc) or salt, and BORSA strains can give a false-positive result.[128] If the PBP 2a result is indeterminate, *mec*A PCR should be performed.

TREATMENT OF INFECTIONS WITH COMMUNITY MRSA

Antimicrobial therapy

While non-multiresistant MRSA strains are susceptible to the majority of non-β-lactam antimicrobials, there are few data on the accuracy of testing non-β-lactams against non-multiresistant MRSA as virtually all studies have focused on detection of methicillin resistance. One group found a problem with detection of resistance to cotrimoxazole,[40] which is one of the commonly used agents against these strains. Fusidic acid resistance can be heterogenous,[130] which may cause a problem in detecting resistance to this agent.

There are virtually no *in vitro* or *in vivo* data on the efficacy of individual non-β-lactam antimicrobials against non-multiresistant MRSA strains. One can probably extrapolate the limited data about the performance of non-β-lactams against MSSA to MRSA strains susceptible to the drug in question, but mostly this has not been tested.[131] Recently, a single-point pharmacodynamic analysis was performed to provide a theoretical answer.[132] In this model, gentamicin was predicted to have significant activity against non-multiresistant MRSA strains, suggesting that it might be possible to use gentamicin for a short period to cover the possibility that a patient may have infection with non-multiresistant MRSA. It was shown that while flucloxacillin alone was inactive against non-multiresistant MRSA in a time-kill assay, the addition of gentamicin resulted in bactericidal activity.[132] The single-point pharmacodynamic model predicted that treatment with ciprofloxacin would fail, with the emergence of resistant mutants,[131] which is well-described clinically.[133] Fourth-generation fluoroquinolones were predicted to be successful against MSSA and non-multiresistant MRSA without the emergence of resistant mutants, and moxifloxacin was predicted to be superior to gatifloxacin.[131] The new glycopeptide oritavancin was also predicted to perform well against MSSA, non-multiresistant MRSA and multiresistant MRSA.[131]

Drugs exhibiting time-dependent killing that were predicted in this model to be therapeutically successful against non-multiresistant MRSA were fusidic acid, clindamycin, teicoplanin, vancomycin and linezolid.[40,131] Erythromycin, doxycycline, flucloxacillin and quinupristin/dalfopristin were predicted to fail. It could be argued that tissue uptake by macrolides and tetracyclines is so good that perhaps pharmacokinetic/pharmacodynamic parameter modelling cannot be applied to these classes of drugs.[134,135] As initial reports of the use of quinupristin/dalfopristin have described therapeutic success against MRSA, including difficult-to-treat cases,[136,137] the model may not be applicable to streptogramins.

It has recently been suggested that drugs that shut down ribosomal translation of proteins in *S. aureus*, such as clindamycin or linezolid, might decrease production of toxins such as PVL and therefore these drugs might be specifically indicated in the treatment of serious cMRSA infections.[138] However, this hypothesis remains to be tested in animals and in humans.

Surgery

Surgery is an important part of the treatment of staphylococcal infections. In particular, surgical debridement to remove pus and necrotic debris, liberal irrigation, and sometimes packing of wounds and re-operation are integral to successful treatment.[139] One study noted that all the patients with cMRSA infections improved after surgical drainage of abscesses, and no patient with cMRSA received antibiotics to which the organisms tested suscetpible.[14]

Immune therapy

The potential for the use of antibodies against PVL for treating cMRSA infection was suggested by *in vitro* work.[140,141] Intravenous immunoglobulin neutralized the effects of staphylococcal superantigens TSST-1, enterotoxins A, B, C_1, C_2, C_3, and E, and exfoliative toxin, on T-cell stimulation.[141] Commercial intravenous immunoglobulin preparations were found to have detectable levels of anti-PVL antibody by enzyme immunosorbent assay.[140] These preparations were shown to neutralize pore formation and the cytopathic effect of recombinant PVL and *S. aureus* culture supernatants on polymorphonuclear neutrophils.[140]

A case-control study in toxic-shock syndrome due to *Streptococcus pyogenes* found that patients treated with immunoglobulin had a 67% 30-day survival rate, as compared with 34% in controls ($P = 0.02$).[142] No such study in *S. aureus* toxic shock syndrome has been conducted, let alone one in cMRSA infection. Although the authors of the anti-PVL antibody study suggested using this treatment for severe cMRSA infection,[140] until further information is available, its routine use cannot be recommended. However, it could be considered for life-threatening cMRSA infections.

HOSPITAL OUTBREAKS WITH COMMUNITY MRSA STRAINS

Although infrequently reported, cMRSA strains have caused outbreaks within hospitals. The initial reports of cMRSA in Detroit described the outbreak initially in

intravenous drug users, but subsequently there were cross-infections with strains with similar antibiograms and phage typing patterns.[30] Although WA MRSA strains have been commonly seen in Perth, only one hospital outbreak has occurred, which was controlled by strict infection control procedures.[116]

A nosocomial outbreak with the cMRSA strain MW2 (USA400) has recently been reported in Minnesota.[143] Eight women developed skin and soft tissue infections (including four cases of mastitis), after giving birth in an obstetric unit. The route of transmission was not determined. Surveillance cultures of healthcare workers, the hospital environment, and other neonates were negative for MRSA. The outbreak was stopped with the implementation of infection control procedures.

Similarly, an outbreak of cMRSA in neonates and mothers in a French obstetric unit has also been reported.[144] Inspection of the PFGE patterns showed that case isolates were indistinguishable from the PFGE patterns of the ST80-MRSA-IV strain known to be a dominant cMRSA in Europe. Despite institution of increased hygiene measures and removal of the index case, the outbreak persisted for 9 weeks. Institution of environmental hygiene measures were required to halt this outbreak.

PREVENTION OF THE SPREAD OF COMMUNITY MRSA

Interventions to control cMRSA have been described in a Danish study.[145] The outbreak occurred in Northern Jutland and involved 46 people in 26 households. All individuals colonized or infected harboured an ST80-MRSA-IV, PVL-positive clone. Patients were decolonized by showering with 4% chlorhexidine, and applying topical nasal chlorhexidine or mupirocin ointment. They were also instructed to wash towels and clothes at a water temperature >90°C. Of the 16 individuals who complied, 15 were able to be decolonized. Unfortunately, despite successful eradication, the epidemic clone was repeatedly re-introduced by visitors from the Middle East.

CONCLUSIONS

cMRSA epidemics are well underway in many areas of the world. These strains have a predilection for causing boils, probably because most harbour the PVL gene, and most are non-multiresistant. Although most, but not all, strains possess type IVa SCC*mec*, typing (including MLST) has shown that multiple diverse clones exist. Children and persons of low socioeconomic status are most likely to acquire these strains, but epidemics are now being seen in new groups, including sports people, prison inmates and homosexual men. Methicillin-resistant strains may be expected to replace methicillin-susceptible ones over the next few years, but it remains to be seen whether they will also develop multiresistance.

In patients with infections potentially due to *S. aureus*, it is important to swab all lesions, to use a sensitive and specific method for detecting methicillin resistance, and to test and report a full range of sensitivities to non-β-lactam antimicrobial agents.

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