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Community MRSA infection

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Introduction

THE bacterium *Staphylococcus aureus* is a successful and ubiquitous parasite of humans and other mammals. Large surveillance studies in diverse populations have shown that up to 30% of healthy individuals are colonised by *S aureus* at any point in time, either transiently or permanently.

Infection and disease do not occur in most people who are colonised with *S aureus*, because of the efficacy of innate and adaptive host immune defences. However, given the opportunity, *S aureus* will breach these defences and cause infection and disease.

Staphylococcal infections are common in community-based medical practice. Many infections caused by *S aureus* are minor and do not warrant antimicrobial therapy. However, *S aureus* is a frequent cause of severe disease, ranging from deep-seated bone infection to life-threatening septicaemia or toxic-shock syndrome.

A recent study estimated that there are up to 8000 cases of bloodstream infection caused by *S aureus* in Australia every year, of which

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10-20% are fatal. Other studies have shown that *S aureus* has overtaken viridans streptococci as the most common cause of infective endocarditis in all regions of the world, including Australia.

In addition to its ability to evade host immune defences, *S aureus* has a remarkable 'track record' for acquiring resistance to antimicrobial agents. Resistance to penicillin emerged soon after this antibiotic was first used for treating staphylococcal infection in 1941, and resistance to almost all other antimicrobials used to treat staphylococcal infection has been described, usually shortly after that agent was first used.

Until recently, all *S aureus* infections acquired in the general community could be assumed to be susceptible to anti-staphylococcal antibiotics such as flucloxacillin, dicloxacillin and cephalexin. However, in recent years new strains of antibiotic-resistant *S aureus*, known collectively as community methicillin-resistant *S aureus*, or cMRSA, have emerged worldwide.

S aureus has overtaken viridans streptococci as the most common cause of infective endocarditis in all regions of the world, including Australia.

These cMRSA strains have spread widely and rapidly and are an important cause of morbidity and mortality worldwide, including Australia. Of significant public health concern is the fact that some strains of cMRSA circulating in Australia have acquired potent virulence factors that make them more likely to cause invasive disease.

This review describes the epidemiology, clinical features, diagnosis and management of cMRSA infection.

Epidemiology

THE semi-synthetic antibiotic methicillin was developed in the 1950s to combat the growing problem of penicillin resistance in *S aureus*.

Just two years after its introduction, methicillin-resistant *S aureus* (MRSA) infection was first described in hospitalised patients and quickly became established in hospitals and health care facilities worldwide. For many years, MRSA was almost only found in hospitalised patients or in those in long-term care facilities such as nursing homes.

In the 1970s and 1980s, small clusters of MRSA infection appeared in some urban communities (eg, IV drug users) in the US. In the late 80s and early 90s, cases of MRSA infection in patients with no history of contact with health care started appearing in the Kimberley region of WA.

Shortly afterwards cases of so-called 'community MRSA' (cMRSA) infections were reported from the east coast of Australia and the NT. These infections were caused by strains of MRSA that were not multi-resistant (see definitions in table 1) and were genetically different to hospital MRSA strains.

In the late 1990s and the early 21st century, cMRSA also rapidly emerged in many other parts of the world (eg, the US, Europe) and cases of severe and fatal invasive infection in previously healthy children and adolescents were reported.

The Australian Group on Antimicrobial Resistance (AGAR) performs regular surveillance on *S aureus* isolated in laboratories across Australia. Recent surveillance has shown that the proportion of *S aureus* identified in these laboratories that are cMRSA is increasing across Australia (figures 1 and 2). In the most recent survey performed in 2004, 15% of all *S aureus* isolated from patients in outpatient settings was cMRSA.

Alarmingly, a recent study of skin and soft tissue infections presenting to 11 major emergency departments in the US showed that cMRSA was the most common cause.

There are some characteristic strains, or 'clones', of MRSA currently circulating in Australia. In the main these tend to be restricted to certain geographical areas or populations. However, over time they have spread within and between countries.

Risk factors

High rates of infection or colonisation with cMRSA have been described in several populations. In Australia, high rates of infection and carriage have been described in remote and rural communities and among expatriate Polynesians. Similar infection rates are found in other indigenous populations elsewhere (eg, in Alaskan Eskimos and Native Americans).

Outbreaks of cMRSA infection have been described in several settings. These include members of sporting teams (eg, rugby, American football), prisons, men who have sex with men, and day care centres.

These outbreaks have generally been attributed to the introduction of cMRSA into a situation of overcrowding and poor hygiene. Molecular epidemiology studies of organisms isolated from individuals involved in these outbreaks have shown they have been caused by single strains of MRSA that have probably been transmitted from person to person.

More recently it has become clear that cMRSA is no longer restricted to these subgroups and is in fact widespread in many communities in Australia and worldwide.

Diabetes mellitus and IV drug use are traditional risk factors for *S aureus* infection and colonisation. Outbreaks of cMRSA infection have been described in IV drug users, but there is no evidence to suggest that the group is more likely to be infected or colonised with cMRSA compared with the background population.

Figure 1: MRSA in WA, 1983-2005.

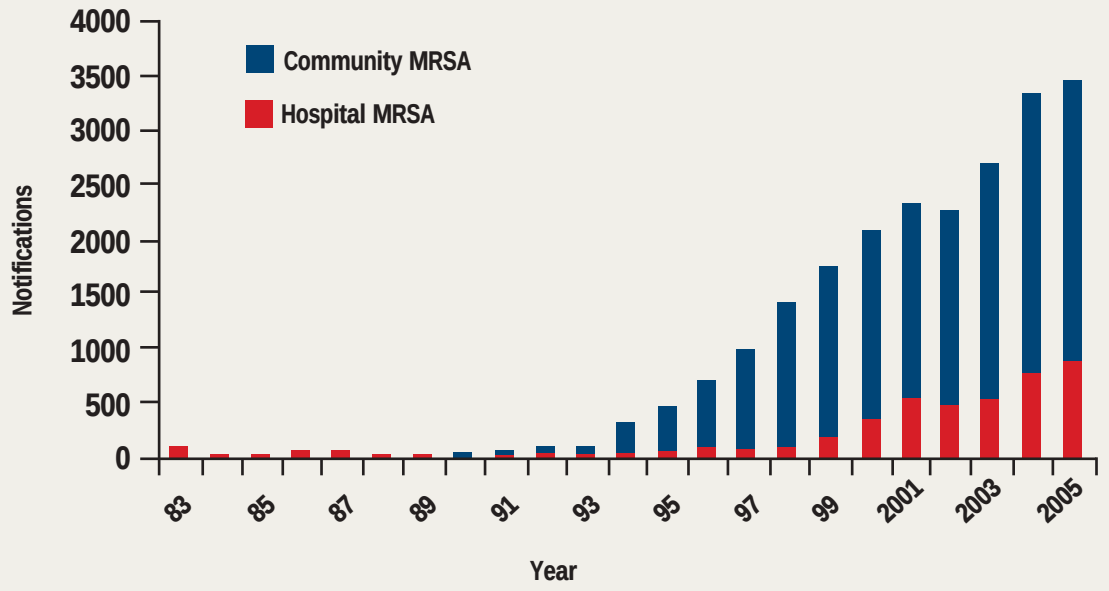


Figure 2: Community MRSA in Australia.

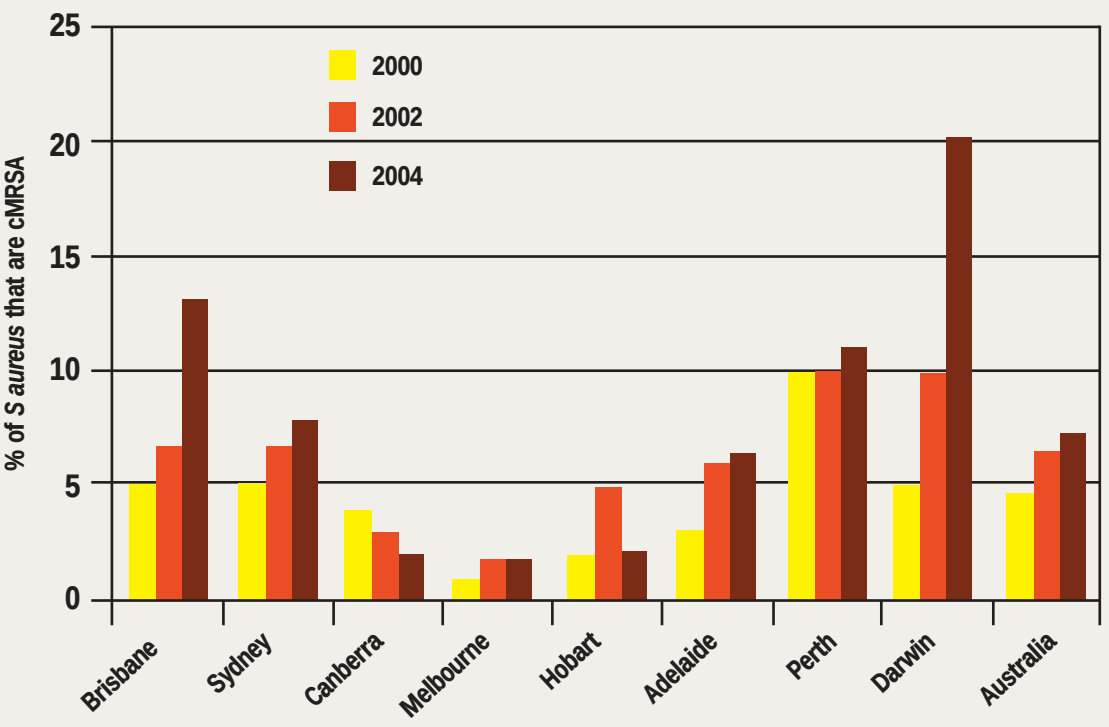


Table 1: Definitions

Methicillin-resistant *Staphylococcus aureus* (MRSA)
S aureus that is resistant to methicillin and all other beta-lactam antibiotics, ie, penicillins (eg, flucloxacillin, dicloxacillin), cephalosporins (eg, cephalexin), and carbapenems (imipenem and meropenem). Also known as oxacillin-resistant *S aureus* (ORSA).

Non-multiple-resistant MRSA (nmrMRSA)
An MRSA strain that is resistant to all beta-lactam agents but susceptible to two or more non-beta-lactam antibiotics used to treat staphylococcal infection (eg, clindamycin, cotrimoxazole, doxycycline, rifampicin, fusidic acid, ciprofloxacin).

Multiple-resistant MRSA (mrMRSA)
MRSA resistant to all beta-lactam agents and to three or more non-beta-lactam antibiotics, as above.

Community MRSA (cMRSA)
- *Community-acquired MRSA infection* — MRSA infection acquired in the general community in an individual with no history of recent contact with a hospital or long-term care facility (the definition of 'recent contact' varies).
- *Community-onset MRSA infection* — MRSA infection that is acquired in the general community in an individual when 'recent contact' with a hospital or long-term care facility cannot be excluded.

Epidemic MRSA (EMRSA)
An isolate of MRSA known to be readily transmissible from person to person. Examples of epidemic MRSA strains in Australia are the UK15 and UK16-MRSA strains and the common strains of hospital-acquired MRSA (Aus 2 and Aus 3 MRSA).

Non-epidemic MRSA (NMRSA)
An isolate of MRSA not thought to be readily transmitted from person to person.

'Golden staph'
The lay term for *S aureus*, often also used to denote MRSA in the media.

'Superbug'
A term used commonly in the media, variously to describe resistant microorganisms, virulent micro-organisms or organisms with both characteristics.

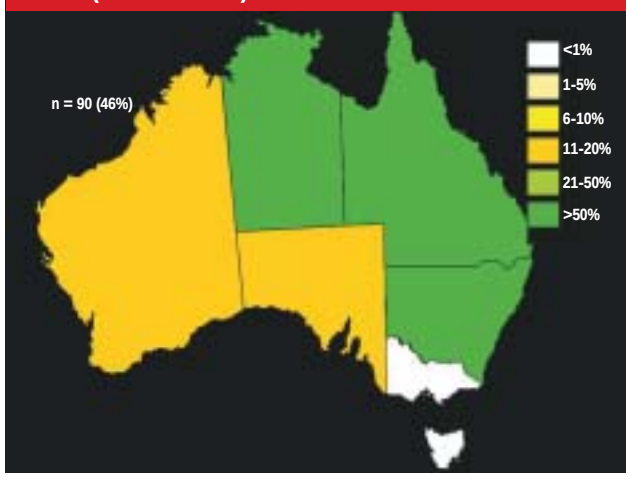
Resistance and virulence factors in cMRSA

The *mec* gene

RESISTANCE to methicillin in staphylococci is conferred by the presence of the *mec* gene in the staphylococcal chromosome. This gene encodes for an altered penicillin-binding protein 2a (PBP2a), which is a component of the bacterial cell wall.

Alteration in configuration of the protein means that beta-lactam antimicrobial agents (penicillins, cephalosporins and carbapenems) cannot bind to PBP2a, so the bacteria are not killed by these agents.

Figure 3: Prevalence of Panton-Valentine leukocidin in cMRSA isolates (% of all cMRSA).



The *mec* gene is found as part of a larger genetic element known as staphylococcal cassette chromosome *mec* (SCC*mec*). This element is capable of mobilisation, and is therefore potentially transmissible from organism to organism, although this does not appear to be a particularly frequent event in nature.

Other genes that confer resistance to other antimicrobial agents can be found in the SCC*mec* element or, alternatively, they may be inserted into other parts of the chromosome, or acquired independently on plasmids.

Panton-Valentine leukocidin

Panton-Valentine leukocidin (PVl) is an exotoxin that causes lysis of white blood cells and other cell lines, and is thought to be an important virulence determinant in *S aureus*. The genes coding for PVl are also found as part of a potentially mobile genetic element on the *S aureus* chromosome.

PVl was first described in the 19th century by researchers studying the effect of *S aureus* on tissues. This toxin is not commonly present in community-acquired *S aureus* isolates. However, its presence has been closely associated with invasive cMRSA infection, including cutaneous abscesses and necrotising pneumonia.

Certain strains of cMRSA commonly found in Australia (particularly on the east coast) frequently express PVl toxin (figure 3).

Clinical features of MRSA infection

Skin and soft tissue infection

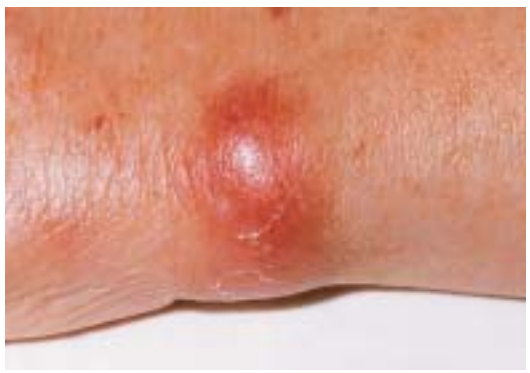
SUPERFICIAL infection of the skin and supporting structures is the most common presentation of community MRSA infection.

Common types of cutaneous staphylococcal infection include impetigo, folliculitis, carbuncles, furuncles, cellulitis and botryomycosis (a chronic granulomatous form of *S aureus* infection that results in nodule or ulcer formation, often in immunosuppressed hosts).

Symptoms and signs of cMRSA skin or soft tissue infection are the same as those caused by methicillin-susceptible *S aureus*, although cMRSA strains that produce PVl are more likely to result in pus-forming infections (eg, carbuncles, furuncles and abscesses).

Invasive infection

All forms of invasive staphylococcal infection can be caused by cMRSA. This includes deep-seated abscesses, pyomyositis, pneumonia, septic arthritis and osteomyelitis, visceral abscesses (eg, kidney, liver, lung or brain), bacteraemia and infective endocarditis.



Subcutaneous abscess caused by cMRSA. Incision and drainage resulted in cure without antimicrobial therapy.

Image reproduced courtesy of the department of medical illustrations, Royal Perth Hospital, WA.

Two uncommon but very fulminant presentations of invasive cMRSA infection are necrotising pneumonia and necrotising fasciitis. These have been reported in previously well individuals and usually present with signs and symptoms of severe infection, including severe pain at the site of infection, hypotension, tachycardia and cyanosis.

As these infections are usually associated with PVl-producing cMRSA strains and are rarely reported with methicillin-susceptible *S aureus*, it is suspected that PVl may be responsible for the extensive and rapidly progressive tissue necrosis that is a feature of both of these infections.

Staphylococcal toxic shock syndrome

This rare condition can occur either as a result of infection or colonisation with a strain of *S aureus* that produces toxic shock syndrome toxin 1 or another enterotoxin in an individual with no pre-existent immunity to these toxins. Several cases of toxic-shock syndrome have been described in association with cMRSA infection.

Diagnosis

Because of the rapid emergence of cMRSA in almost all regions of Australia, it can no longer be assumed that a pus-forming skin or soft tissue infection is caused by an organism that is sensitive to beta-lactam antibiotics such as flucloxacillin, dicloxacillin, amoxicillin-clavulanic acid or cephalexin.

Therefore, it is important that GPs are aware of the epidemiology and prevalence of cMRSA infection in their region.

To support decisions regarding choice of antimicrobial therapy for suspected staphylococcal infection, it is critically important that appropriate specimens be collected and submitted to the microbiology laboratory at the time of initial assessment.

If possible, tissue, fluid or pus from the lesion should be collected and submitted for microscopy and culture and susceptibility testing. If available, these are preferable to swabs, as any bacteria in the specimen will survive for longer in tissue or fluid than on the end of a swab, particularly if transport to the laboratory is delayed.

Treatment of cMRSA infection

General measures

TREATMENT of cMRSA infection does not differ significantly from that of other staphylococcal infections. The basic principles of treatment are:

- Drain pus and debride infected tissue.
- If there are signs and symptoms of systemic infection or extensive local infection, prescribe systemic antimicrobial therapy.
- Review the patient regularly to ensure clinical response.

The importance of draining pus and debriding infected tissue cannot be overstated in staphylococcal infection, particularly that caused by cMRSA. Most antimicrobial agents penetrate poorly or not at all into the centre of abscesses, and dead or devitalised tissue is not perfused.

Therefore, surgical management is primary in pus-forming infection; antimicrobial therapy plays an adjunctive role only. In fact, in many cases of mild-moderate cMRSA infection, antimicrobial therapy is not required if the infection is minor and has been dealt with surgically.

Figure 4: Isolate of cMRSA that is susceptible to clindamycin (DA2) and erythromycin (E15).

Figure 5: Isolate of cMRSA that is susceptible to clindamycin (DA2) but resistant to erythromycin (E15). Inducible resistance to clindamycin is demonstrated by the flattening of the zone of inhibition proximate to the erythromycin disc.

Antimicrobial therapy

Unfortunately there are minimal published data on the clinical efficacy of any antimicrobial agent for the treatment of cMRSA infection. At the time of writing, there are no published randomised controlled trials comparing one antimicrobial (or combination of antimicrobials) to another for this infection.

Accordingly, the following recommendations regarding antimicrobial therapy are based on data from laboratory studies, animal models, non-controlled clinical trials, or have been extrapolated from clinical trials conducted in hospital-acquired MRSA infection.

Antimicrobial agents commonly used to treat patients with mild-moderate cMRSA infections are listed below and summarised in table 2.

Lincosamides (clindamycin, lincomycin)

The lincosamides have some structural similarities to the macrolides, although they are chemically unrelated. Clindamycin is a synthetic derivative of lincomycin and is the more frequently prescribed agent in this class in Australia.

Lincosamides bind to the 50S subunit of the bacterial ribosome, inhibiting protein synthesis. They have bacteriostatic activity against *S aureus*. Clindamycin is active against most strains of cMRSA, has excellent bioavailability after oral dosing, and is widely distributed in most body fluids and tissues (including bone and abscesses).

Although clindamycin causes diarrhoea in 3-10% of patients, *Clostridium difficile*-associated diarrhoea and colitis is less common, occurring in less than 1% of patients.

Although clinical trial data are lacking, clindamycin is considered by most experts to be an appropriate first-line agent for treating mild-moderate cMRSA infection. However, as erythromycin-resistant strains of cMRSA often exhibit inducible resistance to clindamycin (figures 4 and 5), clindamycin should not be used for infections caused by erythromycin-resistant cMRSA.

Cotrimoxazole (trimethoprim-sulphamethoxazole)

This synergistic combination inhibits bacterial folate synthesis at two different enzymatic stages. In Australia, most cMRSA isolates are susceptible to cotrimoxazole, and clinical experience suggests this agent is effective therapy in mild-moderate cMRSA infection.

However, several adverse events are associated with cotrimoxazole. Nausea, diarrhoea and rash are the most common, but more serious reactions such as Stevens-Johnson syndrome, neutropenia, thrombocytopenia and nephro- and hepatotoxicity may also occur. Serious reactions are more likely to occur in the elderly.

Tetracyclines (tetracycline, doxycycline, minocycline)

Tetracyclines act to inhibit mRNA translation at the bacterial ribosomal level. They are bacteriostatic against *S aureus*, and most cMRSA isolates are susceptible to these agents.

Doxycycline and minocycline are well absorbed orally, have good tissue penetration, and have better anti-staphylococcal activity than tetracycline. However, there are few published data for the treatment of cMRSA with these agents.

One recently published US retrospective case series of 24 patients with MRSA infections reviewed the outcomes of patients treated with oral minocycline or doxycycline 100mg twice daily. Most patients (79%) had complicated skin or soft tissue infection caused by cMRSA.

The overall clinical success rate was 83%, and three of the four clinical failures were in patients with osteomyelitis or septic arthritis. There was one discontinuation due to nausea from minocycline after five days, and another due to vomiting from doxycycline after 10 days.

These data suggest that doxycycline and minocycline may be reasonable oral options for the treatment of mild-moderate cMRSA infection.

Macrolides and azalides (erythromycin, clarithromycin, roxithromycin, azithromycin)

Like the lincosamides, these agents inhibit bacterial protein synthesis by binding to the 50S subunit of the bacterial ribosome. They are bacteriostatic against *S aureus*. They are generally inactive against multiresistant MRSA isolates but are active against 65-75% of cMRSA in Australia.

Resistance to erythromycin often confers resistance to the newer macrolides and azalides, as well as reducing activity of other classes of antimicrobials, including the lincosamides and streptogramins.

Erythromycin and clarithromycin are powerful inhibitors of cytochrome P450 (CYP450) liver enzymes (particularly the 3A4 and 1A2 isoenzymes), and can therefore increase the plasma drug levels of various agents, such as warfarin, theophylline and cisapride, leading to serious adverse drug reactions.

The newer agents roxithromycin and azithromycin are less potent CYP450 enzyme inhibitors and are less susceptible to serious interactions.

Rifamycins

Rifampicin inhibits chain initiation of bacterial RNA polymerase and inhibits the transcription of DNA to RNA. It is bactericidal against *S aureus*, including virtually all strains of cMRSA.

Rifampicin has good oral bioavailability, with extensive penetration into tissue (including bone and lung), body fluids and abscesses. However, it is not PBS approved for the treatment of staphylococcal infection, is expensive and is difficult to obtain outside public hospitals.

Because of the rapid emergence of resistance when used as monotherapy, rifampicin must always be administered in combination with another antimicrobial. It is usually combined with fusidic acid, a tetracycline or a quinolone.

Rifampicin is a powerful CYP3A4 enzyme inducer and will reduce the concentration and efficacy of many drugs, including the oral contraceptive pill, cyclosporin and prednisolone.

Patients receiving rifampicin should be counselled regarding the reddish-orange staining of bodily fluids such as urine and tears. The wearing of soft contact lenses should be avoided while using rifampicin, because these can become stained.

Rare adverse events include immune-mediated influenza-like symptoms, haematological abnormalities, hepatitis and interstitial nephritis.

Fusidic acid (sodium fusidate)

Fusidic acid inhibits bacterial protein synthesis by interfering with an elongation factor that promotes translocation on the bacterial ribosome.

About 95% of cMRSA strains are susceptible to fusidic acid; however, recent increases in resistance have been linked to community use of a topical preparation of fusidic acid.

Like rifampicin, it must be combined with another active agent to prevent the rapid emergence of resistance. Fusidic acid is mainly used for oral outpatient treatment of mild-moderate cMRSA infection, in combination with rifampicin, a tetracycline or a fluoroquinolone.

Fusidic acid is well absorbed orally and has extensive tissue penetration. GI upset is common, and hyperbilirubinaemia may occur in up to 50% of patients.

Fluoroquinolones (ciprofloxacin, moxifloxacin)

Fluoroquinolones act by inhibiting the supercoiling of bacterial DNA, and are bactericidal against *S aureus*. Ciprofloxacin prevents DNA replication by inhibiting DNA gyrase, and moxifloxacin acts by inhibiting both DNA gyrase and topoisomerase IV.

Most cMRSA isolated in Australia are susceptible to these agents, although resistance in cMRSA is common in regions where fluoroquinolone use is widespread (eg, North America).

Ciprofloxacin is occasionally used to treat cMRSA infection. However, as staphylococci commonly develop resistance to ciprofloxacin given as monotherapy, it should only be used in combination with another active agent (eg, fusidic acid or rifampicin).

Moxifloxacin has excellent oral bioavailability and was designed for increased potency against Gram-positive organisms such as *S aureus*. However, it does not have useful activity against ciprofloxacin-resistant strains of staphylococci, and most experts recommend it should also be combined with another active agent when treating cMRSA infection.

Fluoroquinolones bind to drugs containing multivalent cations, such as antacids, sucralfate, calcium, zinc, magnesium and iron, resulting in a significant decrease in oral absorption. Concomitant administration should be avoided, and fluoroquinolones separated by at least two hours from these multivalent cations.

The most common adverse effects of these agents include nausea, diarrhoea and dizziness. Rare adverse events include tendonitis and hepatotoxicity. Moxifloxacin should not be given to patients receiving agents that prolong the QTc interval (including quinidine, amiodarone and sotalol), as the QTc may be further lengthened, which can cause ventricular arrythmias, including Torsades de pointes.

Oxazolidinones

Linezolid is the only currently available member of this class of antimicrobials. It has extensive activity against Gram-positive bacteria, including MRSA. However, the development of resistance during therapy has been described.

Linezolid is expensive and is not available on the PBS at present. Its use is reserved for hospitalised patients who are intolerant of first-line therapies for moderate to severe cMRSA infection, or when these have failed.

Pristinamycin

Pristinamycin is an oral streptogramin antimicrobial that inhibits protein synthesis. It is not registered in Australia and is only available through the special access scheme (SAS) for unregistered products.

Pristinamycin has been used as an oral alternative in MRSA infection when other agents cannot be used for reasons of resistance, allergy or intolerance.

Topical antimicrobial agents (eg, mupirocin, fusidic acid, clindamycin)

In most cases of mild superficial staphylococcal infection (eg, bullous impetigo, folliculitis and mild wound infections), debridement of infected tissue and/or regular cleaning of the area is effective treatment, and antimicrobial therapy is not required.

Topical antimicrobial agents with anti-staphylococcal activity (eg, mupirocin, chloramphenicol, fusidic acid and clindamycin) are sometimes used for treating mild superficial staphylococcal cMRSA infection. These agents are all active against most cMRSA strains.

While short-term use of these agents may be appropriate in selected patients, their extensive or prolonged use is strongly discouraged by most experts, given the significant risk of resistance emerging while on therapy.

Resistance to mupirocin is widespread in hospitals where this agent has been used inappropriately for preventing or treating infection; this in turn limits options for perioperative staphylococcal decolonisation, which has been shown to reduce the risk of surgical site and invasive *S aureus* infection in many settings.

Use of topical fusidic acid or clindamycin is particularly concerning, as these agents are frequently used for treating moderate-severe cMRSA infection, and resistance to these agents is already present in cMRSA (see above).

Outpatient intravenous antimicrobial therapy for moderate-severe cMRSA infection

Outpatient IV antimicrobial therapy (OPAT) delivered as part of a "Hospital in the Home" program is now widely available in most urban regions of Australia. These OPAT programs allow patients who are medically stable to complete their course of IV antimicrobials in their place of residence.

At our institution, nursing staff visit patients on a daily basis to administer IV antimicrobials supplied by the hospital pharmacy department. Specialised medical staff led by an infectious diseases physician provide medical governance for patients on the program.

Patients with moderate-severe cMRSA infection (eg, cellulitis, bacteraemia, endocarditis, deep-seated abscesses, and bone and joint infections) are frequently managed on our OPAT program.

The most common agents used in OPAT for cMRSA infection are the glycopeptides (vancomycin and teicoplanin), which have bactericidal activity against most cMRSA strains. These are administered either by continuous infusion through an electric or elastomeric device over a 24-hour period, or, in the case of teicoplanin, as a daily bolus injection.

Plasma drug levels of vancomycin (and occasionally teicoplanin) are taken primarily to determine that an effective dose is being given.

Future treatment options

Much of recent antimicrobial development has been directed towards treating resistant Gram-positive organisms, including MRSA. Unfortunately, most new agents in the 'pipeline' are only available in IV form.

This includes the recently registered tigecycline (a glycylcycline derivative of minocycline). Daptomycin (a cyclic lipopeptide), and several derivatives of vancomycin or teicoplanin (oritavancin, telavancin and dalbavancin) are not yet registered in Australia.

There is a new generation cephalosporin (ceftobiprole) in phase-III trials with good activity against MRSA, which may soon be available in oral as well as IV formulation. Another promising agent in development is iclaprim (a selective dihydrofolate inhibitor related to trimethoprim), which also shows promising activity against MRSA.

Empirical treatment of suspected *S aureus* infection in the era of cMRSA

GPs are frequently required to initiate therapy for infections suspected to be due to *S aureus* without having microbiology results to confirm the diagnosis or to demonstrate susceptibility to the chosen agent.

Current Australian recommendations for the empirical treatment of mild-moderate skin and soft tissue infection suggest using an antistaphylococcal beta-lactam (eg, di- or flucloxacillin) as first-line therapy.

Cephalexin is recommended for patients with non-immediate-type penicillin hypersensitivity, and clindamycin for patients with immediate-type penicillin hypersensitivity.

Some patients with cMRSA infection who receive an antistaphylococcal beta-lactam antibiotic as empirical therapy appear to respond clinically.

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Table 2. Antimicrobial agents for cMRSA infection

Drugs highlighted in bold are considered usual first-line therapy by ourselves and other experts. However, it should be noted that there are no controlled clinical trials comparing use of any of these agents to each other (alone or in combination) in treating cMRSA infection.
Susceptibility results should act as a guide to appropriate antimicrobial prescribing. However, therapy should be revised if clinical response is not as would be expected despite in-vitro susceptibility to that agent.

Class	Antimicrobial	Dose	Comments
Macrolides	Erythromycin	500mg q 6h	Take with food, GI upset frequent Drug interactions (CYP450 inhibitor)
	Clarithromycin	500mg q 12h	Drug interactions (CYP450 inhibitor)
	Roxithromycin	300mg q 24h	Longer half-life, fewer drug interactions
Azalides	Azithromycin	500mg q 24h	Long intracellular half-life, fewer drug interactions
Lincosamides	**Clindamycin**	**300-450mg q 8h**	**First-line therapy for nmrMRSA. Watch for diarrhoea**
Cotrimoxazole	**Trimethoprim + sulphamethoxazole**	**160/800mg q 12h**	**Take with food. Increased toxicity in the elderly (rashes, haematological)**
Tetracyclines	**Doxycycline**	**100mg q 12h**	**Take with food, and remain upright for 15 minutes post dose. Nausea is common. Tooth discolouration in children and infants exposed during pregnancy. Minimise sun exposure**
	Minocycline	100mg q 12h	Take with food. Vertigo is common. Can cause benign intracranial hypertension, and tooth discolouration in children and infants exposed during pregnancy. Minimise sun exposure
Rifamycins	**Rifampicin**	**300mg q 12h**	**Use as part of combination therapy only. Colours secretions red/orange. Significant drug interactions (usually reduces efficacy of interacting drugs). Not readily available outside of hospitals**
Fusidic acid	**Fusidic acid**	**500mg q 12h**	**Use as part of combination therapy only. Can cause hepatitis**
Fluoroquinolones	Ciprofloxacin	500mg q 12h	Not recommended as monotherapy of staphylococcal infection
	Moxifloxacin	400mg q 24h	Better staphylococcal activity and once-daily dosing. Fewer drug interactions than ciprofloxacin
Streptogramins	Pristinamycin	500mg-1g q 8h	Obtain through SAS scheme (not registered in Australia). Commonly causes GI upset and rash
Oxazolidinones	Linezolid	600mg q 12h	Neuropathies in longer-term treatment. Weak MAOI. Expensive.

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This can occur either because the infection would have responded without antimicrobial therapy (eg, an abscess that has been adequately drained), or because the infection was caused by a strain of cMRSA with heterogenous methicillin resistance (ie, some of the organisms in the infection are actually methicillin-susceptible).

However, other patients with moderate-severe infection are potentially at significant risk of morbidity or mortality should they receive inappropriate empirical therapy for cMRSA infection.

Awareness of the local epidemiology of cMRSA is important in determining which antimicrobial should be used as empirical therapy for *S aureus* infection. Information regarding the incidence and prevalence of cMRSA and advice regarding appropriate empirical and definitive therapy should be available from a clinical microbiologist in your region.

In regions or populations where cMRSA is known to be prevalent, consider initiating antimicrobial therapy that is active against both methicillin-susceptible and methicillin-resistant *S aureus*, such as clindamycin, cotrimoxazole or doxycycline.

The choice of agent will be determined by patient factors and prescriber preference: at present there are no comparative data to suggest which particular agent(s) should be used as first-line therapy, although this data may become available in the future.

Duration of therapy

Unfortunately, very few clinical studies have directly addressed the issue of duration of therapy for most infections caused by *S aureus*. Therefore any recommendations are based largely on expert opinion and/or data from non-randomised non-controlled studies.

At present, there is no evidence that cMRSA infections are more 'resistant' to appropriate antimicrobial therapy, or require longer duration of therapy to achieve cure. Therefore duration of therapy for most mild-moderate cMRSA infections is the same as that for infection caused by methicillin-susceptible *S aureus*.

For example, large carbuncles caused by cMRSA should be treated for a minimum of five days in addition to adequate drainage, and mild-moderate cellulitis should be treated for a minimum of 7-10 days.

In all cases the patient should be reviewed regularly, and the total duration of treatment determined by clinical response. If the patient deteriorates despite apparently appropriate therapy, they should be considered for IV antimicrobial therapy in addition to surgical intervention, if indicated.

All patients with bacteraemia (bloodstream infection) due to *S aureus* (including cMRSA) should undergo careful clinical examination and imaging (including echocardiography) to elucidate the cause of the bacteraemia and to exclude endocarditis and metastatic infection.

Because of the significant risk of subclinical endocarditis and metastatic infection being present at the time of diagnosis, all patients with bacteraemia due to cMRSA require a minimum of 14 days of IV antimicrobial therapy. If the above complications are present, prolonged IV therapy (2-6 weeks) is commonly required, often followed by prolonged oral therapy.

Infection-control implications of cMRSA

LITTLE is known about the transmissibility of cMRSA strains in the community setting. However, several outbreaks of cMRSA infection have been described in hospitals (where the index patient came from the community). This suggests that transmission of cMRSA can occur from person-to-person via the hands of health care workers or other means.

As with any patient interaction, standard precautions should be employed routinely when assessing and treating a patient suspected or known to be colonised or infected with cMRSA.

Handwashing has been repeatedly shown to be highly efficacious in limiting the transmission of multi-resistant organisms in hospital settings. Antiseptic handrubs (eg, alcohol with or without chlorhexidine) are similarly effective in preventing transmission of MRSA in the hospital environment.

Figure 6: Possible origin of community MRSA.

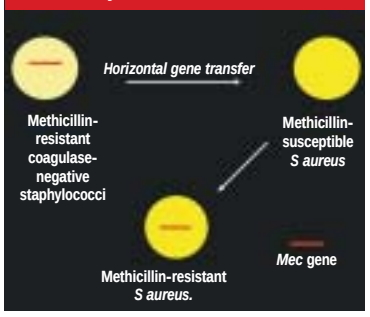
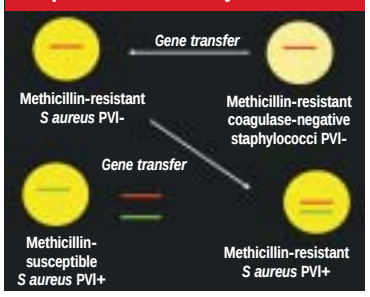


Figure 7: Possible origin of PVl-positive community MRSA.



Patients with colonisation or infection caused by known epidemic strains of MRSA are frequently placed on 'additional precautions' in hospitals (ie, gown and gloves for staff, single room isolation). Most experts suggest that such contact precautions are not routinely required in lower-risk settings such as outpatient clinics or GP surgeries.

Where did community MRSA come from?

The answer to this question is currently unknown. However, most experts agree that most cMRSA strains have a very different genetic makeup and epidemiology to hospital MRSA, and are very unlikely to be hospital MRSA strains that have escaped into the community.

It has also been assumed (although not conclusively demonstrated) that overuse of beta-lactam antimicrobials may be behind the recent increase in prevalence of cMRSA. Excessive use of these agents would be selective for methicillin-resistant staphylococci, but this does not fully explain why cMRSA appeared when it did.

It is believed that the SCC*mec* genetic element is capable of excising itself from one organism (eg, a methicillin-resistant strain of coagulase-negative staphylococci) and inserting itself into a methicillin-susceptible *S aureus*. If this occurred, the methicillin-susceptible *S aureus* will become resistant to methicillin and other beta-lactam antibiotics (ie, it will be an MRSA).

It has been suggested (although not proven) that this can occur via bacteriophage transfer of DNA (a virus that is capable of transporting DNA from one bacterium to another).

Similarly, as the genes for PVl are also found on a potentially mobile element (in this case a prophage), independent transmission of this virulence factor from *S aureus* to another strain of *S aureus* is possible.

Figures 6 and 7 demonstrate how an isolate of methicillin-susceptible *S aureus* might acquire the SCC*mec* and PVl genes.

Tips for diagnosis and management of community MRSA infection

- Know your local epidemiology (your microbiologist will be able to assist).
- If there is pus present, let it out: antibiotics are only adjunctive therapy for boils and abscesses, and are often not required.
- Send specimens for microscopy, culture and susceptibility testing when available.
- Chase results and be prepared to revise antimicrobial therapy accordingly.

Authors' case studies

Recurrent staphylococcal infection in several household members

MS M brings her son Max, four, to see you. He has been experiencing repeated attacks of "boils" in the past few weeks and has been prescribed cephalexin and Augmentin syrup on two visits to another doctor in the practice in the two weeks before this visit, without success. He is otherwise well and immunisations are up to date.

Ms M's sexual partner, Mr P, has recently been treated for an abscess on his thigh, which was shown to be caused by MRSA. She does not live in the same house with him.

On examination, Max is well and active but has several vesicular lesions on his upper chest and arms. Some of the lesions contain pus, whereas others are flaccid blisters that rupture easily, forming a crust.

You notice that Ms M also has some pustular lesions on her forearms and on both upper thighs.

A swab of Max's and Ms M's skin lesions cultured non-multiple resistant MRSA (see box above).

After discussion with a clinical microbiologist, staphylococcal decolonisation was planned for the family. Initially all active lesions were treated with drainage and simple cleaning with soap and water.

After pustular lesions were no longer present on any family member, topical staphylococcal decolonisation was started on Max, Ms M and Mr P, using 2% mupirocin nasal ointment tds, 1% triclosan bodywash as a replacement to soap when bathing, and 20% cetrimide shampoo every third day — all for 10 days.

In addition, Ms M and Mr P were advised to wash their and Max's bedclothes in hot water twice weekly for two weeks.

When reviewed two weeks after completing decolonisation therapy, Max and Ms M were lesion free. Nasal swabs from Ms M, Max and Mr P were negative for *S aureus* carriage, suggesting successful decolonisation.

Microscopy			
Many white cells seen			
Many Gram-positive cocci seen			
Culture			
Heavy growth of methicillin-resistant *Staphylococcus aureus* (MRSA)			
Susceptibilities			
Di/flucloxacillin	R	Cotrimoxazole	S
Cephalexin	R	Doxycycline	S
Erythromycin	S	Fusidic acid	S
Clindamycin	S	Rifampicin	S

R = resistant, S = susceptible

Comment

Most GPs will be familiar with patients presenting with recurrent staphylococcal infection, or cases of cutaneous *S aureus* infection occurring in several members of a household simultaneously.

Certain strains of *S aureus* are considered more capable of colonising, being transmitted and causing pyogenic skin infection, including multiple carbuncles, bullous impetigo ("school sores") or even severe invasive disease.

Strains of cMRSA that produce PVl are a well-known cause of abscesses.

Staphylococcal decolonisation is commonly attempted in this setting. A range of different decolonisation regimens is used, mainly because there are very minimal clinical data to support a particular regimen in terms of what to use and for how long.

The regimen mentioned is used as first-line therapy by the authors for patients with recurrent staphylococcal infection at our institution, with a success rate of about 70%. However, strict adherence to the regimen is required, and incomplete therapy frequently results in relapse.

If active lesions cannot be entirely eradicated before starting decolonisation, the addition of oral antimicrobial therapy (eg, clindamycin 300mg tds) can be added to the topical decolonisation therapy.

Two different formulations of mupirocin ointment are available in Australia. Mupirocin 2% ointment (Bactroban ointment) contains mupirocin calcium 20mg/g plus polyethylene glycol, whereas mupirocin 2% nasal ointment (Bactroban Nasal Ointment) has the same amount of mupirocin but is carried in a different vehicle (white soft paraffin containing a glycerin ester).

The nasal ointment is considerably more expensive than the other formulation. However, it has been specifically formulated for use in the anterior nares and is the only formulation used in clinical studies of staphylococcal decolonisation.

Unless all household members who are colonised or infected with the 'pyogenic strain' of *S aureus* are treated simultaneously, it is likely decolonisation will not be successful and the cutaneous infections will continue to recur.

If decolonisation is unsuccessful or the disease is particularly severe, referral to an infectious disease physician or clinical microbiologist is suggested. A history of diabetes mellitus and unreported IV drug use should be sought, as these conditions are frequently associated with recurrent staphylococcal infection.

Rarely, an underlying immune deficiency is found to be the cause for the recurrent infection (usually in children).

Further reading

Available on request from julian.mcallan@reedbusiness.com.au

Online resources

For Australian doctors

Two good sites for antimicrobials and antimicrobial resistance:

- Australian Society for Antimicrobials: www.asainc.net.au
- Australian Group on Antimicrobial Resistance: www.antimicrobial-resistance.com

For patients

Two reasonably good sites (based in the US) for patients are:

- Alliance for the Prudent Use of Antibiotics: www.tufts.edu/med/apua/mrsa/mrsa.html
- Centers for Disease Control and Prevention: *Community-associated methicillin-resistant* Staphylococcus aureus *(CA-MRSA)*: www.cdc.gov/ncidod/dhqp/ar_mrsa_ca.html

GP's contribution

DR MATILDA METLEDGE
Sydney, NSW

Case study

MR B, 75, has long-term type 2 diabetes and morbid obesity. His diabetes is poorly controlled, largely due to non-compliance.

He has a persistent lower-leg ulcer that has been present for months despite regular debridement and dressings both at home and in the surgery.

Often his ulcer oozes serous fluid, and swabs of this consistently grow cMRSA. He has at various times been treated with topical Bactroban, with limited success.

Questions for the authors

Is chronic colonisation cMRSA likely to be a major cause of non-healing?

No. In the absence of local and or systemic signs of inflammation, it is likely that MRSA is simply colonising the ulcer.

Is the use of topical agents such as Bactroban justified in cases like this?

Mupirocin and other topical antimicrobial agents should not be used in patients with chronic ulcers, as there is no evidence that they result in faster healing times, and their use will promote the development of antimicrobial resistance.

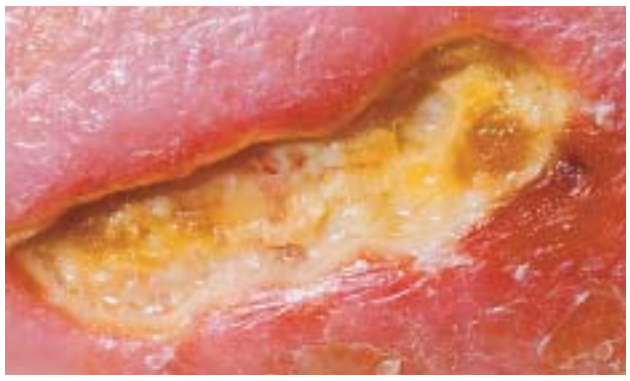
If there are local and or systemic signs of inflammation, systemic antimicrobial therapy guided by susceptibility results should be used.

As most dressings are done by nursing staff, should they be monitored for carriage of cMRSA? If so how often?

All health care staff should employ standard precautions when attending patients who have (or may have) cMRSA infection. This includes the wearing of gloves when dressing wounds, and hand hygiene after every patient contact.

When patients are known to carry an 'epidemic' strain of MRSA, additional precautions are often instituted in hospitals, but these are generally not recommended in the community setting.

Health care staff with suspected staphylococcal infection should have samples collected for culture and, if found to be positive for cMRSA, should be treated accordingly.



Non-healing surgical wound colonised with non-multiple-resistant methicillin-resistant *S aureus*.

Routine surveillance for MRSA colonisation in health care workers is not performed in most settings, but is performed when staff start employment in hospitals with a low prevalence of epidemic MRSA (eg, in WA), to detect and eradicate epidemic MRSA carriage, or when there is an outbreak of epidemic MRSA.

General questions for the authors

Is isolation of children warranted with cMRSA-positive impetigo or boils if the child attends a day care centre?

Outbreaks of cMRSA infection and colonisation have been described in children (and staff) in day care. Therefore it would be prudent for parents of children with cutaneous cMRSA infection not to send their children to day care unless the infection is being treated and is improving, or unless lesions can be covered with a non-removable dressing.

However, the same advice applies for any cutaneous infection caused by transmissible organisms (eg, methicillin-susceptible *S aureus*, group A streptococcus, scabies).

Should decolonisation be attempted in all patients with cMRSA-positive infections in the general practice setting and, if so, with what regimen?

Decolonisation therapy is not recommended for all patients with cMRSA infection. It should be considered in those with recurrent cMRSA infection, or for household contacts of these patients who have asymptomatic cMRSA colonisation.

There is no one single regimen that has been demonstrated to be superior to another in this setting, but most experts would agree that intensive treatment with topical antibacterials (including nasal mupirocin and antibacterial bodywashes), enhanced household hygiene (eg, handwashing, hot washing of bed linen), with or without oral antimicrobial therapy for all infected or colonised household members (eg, the regimen used in the first Authors' case study) is often effective.

How to Treat Quiz

Community MRSA infection — 23 February 2007

INSTRUCTIONS

Complete this quiz to earn 2 CPD points and/or 1 PDP point by marking the correct answer(s) with an X on this form. Fill in your contact details and return to us by fax or free post.

FAX BACK	FREE POST	ONLINE
Photocopy form and fax to (02) 9422 2844	How to Treat quiz Reply Paid 60416 Chatswood DC NSW 2067	www.australiandoctor.com.au/cpd/ for immediate feedback

1. Which TWO statements about infection with *Stapylococcus aureus* are correct?
- ❑ a) *S aureus* is the most common cause of infectious endocarditis in Australia
- ❑ b) *S aureus* septicaemia has a mortality rate of >80%
- ❑ c) All infections caused by *S aureus* should be treated with antimicrobial therapy
- ❑ d) Colonisation with *S aureus* occurs in up to 30% of healthy people

2. Which TWO statements about cMRSA are correct?
- ❑ a) In Australia cMRSA accounts for about 30% of the *S aureus* isolates in the community
- ❑ b) Outbreaks of cMRSA occur in situations associated with poor hygiene and crowding
- ❑ c) It is believed that cMRSA has evolved from hospital MRSA strains brought out into the community
- ❑ d) cMRSA can be spread from patient to patient via the hands of health care workers

3. Rebecca, 22, is a student who lives with her boyfriend. She presents with her third episode of painful boils in her left axilla in three months. The first two episodes responded slowly to dicloxacillin, but recurred about 10 days later on each occasion. She is not systemically unwell, takes no regular medications and is not pregnant. She has no past history of recurrent infections. Which TWO actions are most appropriate in managing Rebecca?
- ❑ a) Prescribe cephalexin instead of dicloxacillin
- ❑ b) Drain any pus from the boils
- ❑ c) Refer Rebecca to hospital
- ❑ d) Send a sample of pus for pathology testing

4. You think Rebecca's infection may be caused by cMRSA. Which TWO antibiotics would be an appropriate choice for empirical treatment?
- ❑ a) Amoxycillin-clavulanic acid
- ❑ b) Doxycycline
- ❑ c) Rifampicin
- ❑ d) Clindamycin

5. You discuss staphylococcal decolonisation with Rebecca. This process may involve the use of which TWO preparations?
- ❑ a) Topical clindamycin for the next eight weeks
- ❑ b) Low-dose doxycycline for three months
- ❑ c) 1% triclosan body wash
- ❑ d) Nasal 2% mupirocin ointment

6. Which THREE other measures would you advise for Rebecca?
- ❑ a) Screening for diabetes
- ❑ b) Referral to an immunologist for investigation of possible immunodeficiency
- ❑ c) Washing all bedclothes in hot water twice a week for two weeks
- ❑ d) Testing her partner for *S aureus* colonisation as well

7. Which TWO statements about antibiotics used to treat cMRSA are correct?
- ❑ a) Clindamycin is a good choice of antibiotic for infections with erythromycin-resistant cMRSA
- ❑ b) Cotrimoxazole works by inhibiting bacterial folate synthesis
- ❑ c) Rifampicin, fusidic acid and ciprofloxacin should not be used as monotherapy in treating cMRSA
- ❑ d) Rifampicin is available on the PBS for treatment of *S aureus* infection

8. Which ONE antibiotic is bactericidal for cMRSA?
- ❑ a) Tetracycline
- ❑ b) Roxithromycin
- ❑ c) Clindamycin
- ❑ d) Ciprofloxacin

9. Tony, 35, has a painful abscess on his upper leg, with some surrounding cellulitis. You are working in an area with a relatively high incidence of cMRSA infections and after draining his abscess feel it is necessary to start Tony on antibiotic therapy. He is concerned about possible side effects. Which TWO statements about specific antibiotic side effects are correct?
- ❑ a) Cotrimoxazole can cause neutropenia and thrombocytopenia
- ❑ b) Clindamycin use results in diarrhoea in about 30% of patients
- ❑ c) Ciprofloxacin can cause rupture of the Achilles tendon
- ❑ d) Fusidic acid causes reddish-orange staining of bodily fluids

10. Which TWO statements about cMRSA infections are correct?
- ❑ a) cMRSA infections require a longer duration of antibiotic therapy than infections with methicillin-susceptible *S aureus*
- ❑ b) Patients with bacteraemia due to cMRSA need at least one week of IV antibiotics
- ❑ c) Echocardiography is an important investigation in patients with cMRSA bacteraemia
- ❑ d) Necrotising fasciitis is a form of fulminant infection with cMRSA

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Australian Doctor Education.

HOW TO TREAT Editor: **Dr Marcela Cox**
Co-ordinator: **Julian McAllan**
Quiz: **Dr Marcela Cox**

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer. Your CPD activity will be updated on your RACGP records every January, April, July and October.

NEXT WEEK Squamous cell carcinoma is the second most common skin cancer behind basal cell carcinoma. Increase your chances of picking them up by picking up next week's How to Treat on SCC and its precursors. The author is **Dr Suresh Chandra**, consultant dermatologist specialising in Mohs' micrographic surgery and cosmetic dermatology. He is in private practice in Bentleigh, Victoria; VMO, Monash Medical Centre, Clayton, Victoria; and director, Victorian Mohs Micrographic Surgery and Skin Cancer Centre, Bentleigh.