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Prevention and treatment of drug-resistant Staphylococcus aureus

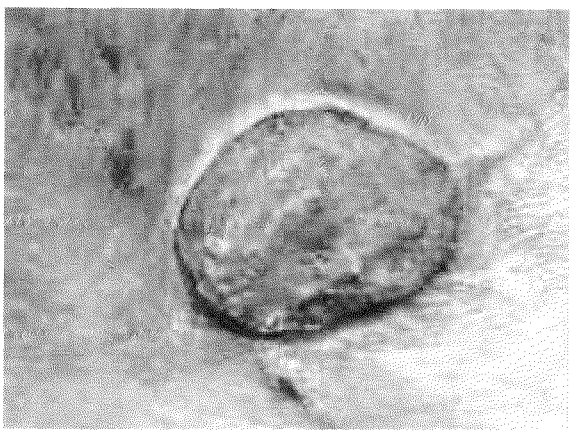
By Andrew Stafford and Dr Luke Bereznicki

Learning objectives

After reading this article, pharmacists should be able to:

- Recognise the clinical significance of the various strains of drug-resistant *Staphylococcus aureus*
- Describe the current evidence surrounding the use of prevention strategies
- Describe the current evidence for the antibiotic therapies available for the management of MRSA infection.

Competencies addressed: 3.1.2, 3.1.3, 3.2.2



MRSA (Methicillen Resistant Staphylococcus Aureus) It occured as a complication two years after cosmetic plastic surgery for a bust reduction.

1. Introduction

Despite significant efforts spanning more than 50 years, *Staphylococcus aureus* remains one of the most important bacterial pathogens globally.[1] It is likely that most pharmacists, wherever their area of practice, will be involved in the management of *S. aureus* infections in some way. The emergence of drug-resistant strains of *S. aureus* has complicated their management. Drug-resistant strains now account for a significant proportion of nosocomial (acquired in hospital) infections in Australia, especially in the eastern states,[2] and the incidence in the community is increasing.[3] In this article, we review the recent evidence relating to agents used in the control and treatment of infections caused by drug-resistant *S. aureus*, and the implications for pharmacists in their daily practice.

2. Nomenclature and prevalence

Historically, *S. aureus* has developed antimicrobial resistance rapidly; resistance to penicillin was noted only a year after its introduction in the 1940s, and was widespread by the 1950s.[4] Anti-staphylococcal penicillins (e.g. dicloxacillin, flucloxacillin) were introduced in 1959, and the first resistant strain emerged within two years. Resistance to antistaphylococcal penicillins was initially detected in laboratories using methicillin, hence the term 'methicillin-resistant *S. aureus*' (MRSA). There are many strains of MRSA, each with different virulence patterns and resistance profiles. Table 1 provides an overview of the characteristics of common strains of *S. aureus*. All strains of MRSA are resistant to β-lactams via a modification to a cell wall protein that prevents these antibiotics from binding.[1] In general, hospital-associated MRSA strains are resistant to a broader range of antibiotics than those found in the community. However, they are not necessarily more dangerous: several community-associated MRSA strains carry virulence factors that are associated with causing more severe disease than HA-MRSA.

Infections caused by *S. aureus* range from mild to moderate skin and soft tissue infections to more severe infections such as bacteraemia, endocarditis, pneumonia and necrotising fasciitis.[5] A recent meta-analysis evaluating the impact of *S. aureus* antibiotic resistance on patient outcomes demonstrated that infection with MRSA is associated with twice the mortality rate compared with methicillin-sensitive strains.[6] In Australia, there are an estimated 7,000 episodes of *S. aureus* bloodstream infections each year, of which about a quarter are caused by MRSA.[7] The majority of these are HA-MRSA infections, however the number of CA-MRSA infections is increasing.[3]

Approximately a quarter of the population is colonised with one or more strains of *S. aureus* at any one time.[8] Common sites of colonisation include the nose, throat, axilla and perineum. Colonisation does not always result in infection; however if an infection develops, it is likely that a colonising strain is responsible. Common alternative routes of infection

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Table 1: Basic nomenclature for strains of *Staphylococcus* aureus.[1,28] These definitions may vary between authors.

Name	Abbreviation	Comments
Methicillin-sensitive *S. aureus*	MSSA	Generally resistant to β-lactamase labile penicillins, but sensitive to methicillin derivatives and most cephalosporins
Methicillin-resistant *S. aureus*	MRSA	Resistant to all currently available β-lactam antibiotics, including penicillins and cephalosporins
Hospital- associated methicillin-resistant *S. aureus*	HA-MRSA	Australian HA-MRSA isolates are typically 'multiresistant' – resistant to three or more non-β-lactam antibiotic classes, except for vancomycin
Community-associated methicillin-resistant *S. aureus*	CA-MRSA	CA-MRSA isolates are generally sensitive to a wider selection of antibiotics than HA-MRSA, hence may also be referred to as non-multiresistant MRSA (nm-MRSA)
Non-multiresistant oxacillin-resistant *S. aureus*	NORSA	A strain of CA-MRSA with a characteristic resistance profile (resistant to β-lactams but sensitive to clindamycin and trimethoprim-sulphamethoxazole). Associated with high rates of necrotising pneumonia and aggressive soft tissue infection
Vancomycin-intermediate *S. aureus* and vancomycin-resistant *S. aureus*	VISA and VRSA	Reduced susceptibility (VISA) or resistant to (VRSA) vancomycin. May be also be referred to as GISA (glycopeptide-intermediate *S. aureus*) if resistant to teicoplanin

include skin-skin and skin-fomite contact.[6] In hospitals, the most important factor influencing MRSA transmission appears to be poor hand hygiene.[2]

3. Prevention and control

As MRSA infections are difficult to treat, prevention and control strategies are of prime importance in their management. In the hospital environment, numerous guidelines have been developed to minimise the spread of MRSA infections, predominantly through targeting healthcare workers.[9] There is very little evidence regarding MRSA prevention outside the hospital environment. A 2008 Cochrane review of studies involving MRSA infection control strategies for nursing home residents did not identify any trials of such interventions.[10] Currently, there is no uniform MRSA control strategy in Australian hospitals, and the success of MRSA control has varied substantially with different strategies.[11] Two core components of many of these control strategies are hand hygiene and bacterial decolonisation.

a. Hand hygiene

Hand hygiene refers to either hand-washing with soap and water or the use of alcohol-based gels or foams that do not require the use of water, and gloves. It is considered the most important measure for preventing health care-associated infections such as HA-MRSA, as poor hand hygiene compliance and technique is strongly implicated in HA-MRSA transmission.[2,12]

Many interventions, and combinations of interventions, have been trialled to improve compliance with hand hygiene. These include written educational materials, workshops, continuous feedback on performance, poster campaigns and increasing the availability of antiseptic solutions. There is limited evidence regarding the most effective intervention/s to improve compliance with hand hygiene. A recent Cochrane review of studies conducted before 2007 found that most trials were small scale, poorly controlled and lacking long-term follow-up data.[13] An Australian study published last year reported on the effect of a state-wide multi-faceted hand-hygiene program in Victorian hospitals. The program, which included lectures, workshops and promotional materials, improved staff hand-hygiene compliance significantly from 20% to 53% after 12 months.[14] Importantly, the number of clinical isolates of MRSA and patients with MRSA bacteraemia were significantly reduced because of this intervention.

There are limited data with respect to the choice of cleaning agent; plain soap, antiseptic soap and antiseptic hand rub (either alcohol or alcohol/chlorhexidine) have all been successfully used.[13] Compared to hand-washing with soap and water, using alcohol-based hand rub solutions is easier to perform and takes less time, and is therefore preferred in many settings. There is some evidence that antiseptic hand rubs are more effective than soap. The introduction of a bedside alcohol-based hand disinfectant into a Swiss teaching hospital resulted in a significant improvement (from 48% to 66%) in hand hygiene compliance and decreased the rates of nosocomial infection and transmission of MRSA.[15]

b. Decolonisation

No general consensus exists concerning the use of bacterial decolonisation for patients who are colonised with antibiotic resistance pathogens, including MRSA. Prior asymptomatic nasal carriage is not always identifiable in the setting of MRSA infections.[16,17] Most studies have been conducted in the hospital setting, hence less is known about the optimal role of decolonisation in the community. Providing antibiotic prophylaxis to family members is not currently recommended, and administering decolonising regimens to whole families has not been studied.[17]

A systematic review of six trials published prior to 2003 concluded that the available evidence was inadequate to recommend the use of topical or systemic agents to eliminate MRSA in colonised patients. Subsequent to this review, there is now evidence that decolonisation of hospitalised patients may reduce the incidence of MRSA infection. A study of the utilisation of intranasal mupirocin and chlorhexidine baths in MRSA-colonised patients in three hospitals in the United States demonstrated a significant reduction in the incidence of MRSA infection.[18]

The optimal regimen and duration of therapy for eradicating MRSA colonisation is uncertain. Both topical and systemic therapies, either alone or in combination, have been used.

Table 2: Antibiotics used in managing CA-MRSA infection.[22,23,29]

Agent	Typical adult dosages	Comments
Clindamycin	• 300-600mg every 6-8 hours	• Potentially suppresses production of MRSA virulence factors • Available as oral and IV preparations
Fusidic acid/sodium fusidate	• 500mg every 12 hours (sodium fusidate) • 750mg every 12 hours (fusidic acid)	• Usually combined with another agent, e.g. rifampicin as resistance develops rapidly • 500mg of sodium fusidate is equivalent to approximately 750mg fusidic acid • Available as oral and parenteral preparations
Glycopeptides (vancomycin or teicoplanin)	• 1g every 12 hours (vancomycin) • 800mg every 12-24 hours (teicoplanin)	• Despite limited studies into the value of monitoring levels, these are generally performed (as trough levels) • Teicoplanin can be administered by once-daily IM injection; useful for outpatient therapy • Not orally absorbed, administered parenterally for systemic infections
Moxifloxacin	• 400mg once-daily	• More active against *S. aureus* than ciprofloxacin • Usually combined with another agent, e.g. rifampicin to minimise development of resistance • Available as oral and IV preparations
Rifampicin	• 600mg daily	• Not used as monotherapy as resistance develops rapidly • Potent inducer of CYP3A4 isoenzymes; associated with numerous drug interactions • Available as oral and IV preparations
Sulphamethoxazole+ trimethoprim	• 1,600+320mg (two double strength tablets) twice-daily	• Older patients more likely to experience serious adverse effects than younger patients (e.g. skin reactions, blood dyscrasias) • Available as oral and IV preparations
Tetracyclines (doxycycline or minocycline)	• 100mg twice-daily	• Not widely used to treat CA-MRSA due to resistance being relatively common • Available only as oral preparations

Agents used topically include mupirocin (for eradication of nasal colonisation) and chlorhexidine baths. Most regimens using mupirocin involve its application to the anterior nares two to three times daily for five to seven days. This agent has no structural similarities to systemic antibiotics, however mupirocin resistance has been reported (24% of MRSA isolates in one study).[17] Chlorhexidine body-washing can reduce MRSA skin colonisation, however studies have found that eradication has only been successful when used in combination with intra-nasal mupirocin, with or without systemic antibiotics.[19]

There is some limited evidence that tea tree oil (the essential oil of *Melaleuca alternifolia*) has clinically useful antimicrobial activity against MRSA and may therefore be indicated in MRSA decolonisation.[20,21] Trials to date, however, have involved very small sample sizes. A larger placebo-controlled trial is currently investigating the efficacy of tea tree oil in preventing MRSA colonisation and infections in hospital intensive care units in Ireland.[21]

Despite limited evidence, oral antibiotics with activity against the colonising isolate may be used in conjunction with topical therapy. Agents that have been used include rifampicin, doxycycline, fusidic acid, minocycline and sulphamethoxazole-trimethoprim. To date, the studies into systemic therapy that have been undertaken have involved very small sample sizes, and hence such therapy is not routinely recommended.[17]

4. Treatment

Antibiotics are not always required in the management of microbiologically-proven MRSA infections. Localised infections such as small furuncles and abscesses often respond to surgical incision and drainage alone.[22] Larger or more serious MRSA infections will require antibiotic therapy. There is limited evidence to guide practitioners in the management of MRSA infection, however recommended treatments adhere to the 'antibiotic creed':[22,23]

- **M**icrobiology guides therapy wherever possible
- **I**ndications should be evidence-based
- **N**arrowest spectrum required
- **D**osage appropriate to the site and type of infection
- **M**inimise duration of therapy
- **E**nsure monotherapy in most situations.

As shown in Table 1, community-associated and hospital-associated MRSA strains may show substantial differences in their antibiotic sensitivities. Sensitivity testing is therefore of paramount importance when treating these infections. CA-MRSA may be successfully managed with agents such as clindamycin, rifampicin, tetracyclines, or trimethoprim-sulphamethoxazole. Table 3 summarises agents that are often used in treating CA-MRSA infection once sensitivity has been identified. HA-MRSA, however, will typically be resistant to the majority of these agents, leaving only glycopeptides (until recently) for such infections.[23] In recent years, several new antibiotics which are active against MRSA have become available, and may be employed as alternatives to glycopeptides in MRSA infections.

a. Glycopeptides

There are two glycopeptide antibiotics currently available in Australia, vancomycin and teicoplanin. Both are active against MRSA, although vancomycin is less expensive and there is more clinical experience with it. Vancomycin has been successfully used for MRSA infections for more than 40 years, and it remains the treatment of choice for HA-MRSA infections.[23] Recent evidence, however, has cast doubt on the suitability of this agent as the preferred antibiotic for treatment of serious systemic MRSA infections.

Despite high rates of vancomycin-resistant *Enterococci*, vancomycin resistance in *S. aureus* remains uncommon. Strains with reduced *in-vitro* susceptibility (VISA) have been described since the late 1990s, although complete resistance (VRSA) is rare.[24] It is becoming evident that overcoming

Table 3: Selected new agents used in managing MRSA infections.[22,30,31] All are administered parenterally except for linezolid which may also be given orally.

Name	Class and mode of action	Comments
Currently available in Australia		
Linezolid (Zyvox)	Oxazolidinone, inhibits protein synthesis	• Weak inhibitor of monoamine oxidase A; increases risk of serotonin toxicity when used with other serotonergic agents • Adverse effects include thrombocytopenia, optic neuropathy and lactic acidosis
Quinupristin-dalfopristin (*Synercid*)	Combination of two streptogrammins, synergistically inhibit protein synthesis	• Use is limited by adverse effects such as arthralgia, myalgia and thrombophlebitis • Potent inhibitor of CYP3A4 isoenzymes; associated with numerous drug interactions
Tigecycline (*Tygacil*)	Glycylcycline (tetracycline derivative); inhibits protein synthesis	• Less likely to cause drug interactions than linezolid or quinupristin-dalfopristin • Derived from minocycline; may have adverse effects similar to other tetracyclines
Daptomycin (*Cubicin*)	Cyclic lipopeptide, disrupts bacterial cell membrane ion channels	• May interact with statins (increases risk of myopathy); cease statin during therapy with daptomycin • Not suitable for MRSA pneumonia as inactivated by pulmonary surfactant
Yet to be approved or marketed in Australia		
Ceftobiprole	Cephalosporin with high affinity for MRSA PBPs; interferes with cell wall synthesis	• Currently marketed in Canada and approved for use in Switzerland • Preliminary studies have demonstrated safety, tolerability and efficacy profiles similar to alternatives
Lipoglycopeptides (dalbavancin, telavancin and oritavancin)	Semi-synthetic derivatives of glycopeptides; inhibit cell wall synthesis	• Dalbavancin probably closest to being marketed; this agent has a very long half life, allowing once per week dosing • Data on telavancin and oritavancin very limited at this stage

the issue of reduced susceptibility to vancomycin requires more than simply increasing vancomycin doses. Although VISA strains remain susceptible to higher concentrations of vancomycin *in-vitro*, therapeutic failures have been reported in the literature with increasing frequency.[24,25] This has lead to guidelines by the Infectious Diseases Society of America to maintain much higher vancomycin troughs than previously recommended when treating severe MRSA infections such as hospital-acquired pneumonia.[4] Recent preliminary data, however, suggests that these higher doses may not yield therapeutic benefits and may be associated with adverse effects.[4] There have therefore been several investigations into the efficacy of alternative agents to vancomycin to treat MRSA infections.

b. Alternative agents

Apart from vancomycin and teicoplanin, four agents that have activity against HA-MRSA are presently available in Australia. These are linezolid, quinupristin+dalfopristin, tigecycline and daptomycin. Several other agents with application in managing these infections are likely to be marketed within the next few years. These include ceftobiprole, and the lipoglycopeptides dalbavancin, telavancin and oritavancin.[22] A brief overview of a selection of these new agents is shown in Table 3.

I. Linezolid

Linezolid (*Zyvox*) is approved in Australia for treating suspected or proven infections due to multiresistant Gram positive organisms such as MRSA. The evidence-based literature suggests that linezolid may be superior to vancomycin for the treatment of MRSA skin and soft tissue infections and nosocomial pneumonia.[26] In a trial comparing linezolid with vancomycin for patients with MRSA skin infections, patients treated with linezolid exhibited a significantly higher microbiological cure rate compared to the vancomycin group.[26] Retrospective analysis of two studies involving patients with nosocomial MRSA pneumonia found a higher overall survival rate for those treated with linezolid compared to vancomycin.[22] A prospective trial comparing linezolid to vancomycin in the management of nosocomial MRSA pneumonia is currently being undertaken, which should clarify the role of linezolid in managing these infections (nosocomial pneumonia with suspected or proven methicillin-resistant *Staphylococcus aureus* (ZEPHYR). Refer to: www.ClinicalTrials.gov, identifier NCT00084266).

II. Quinupristin+dalfopristin

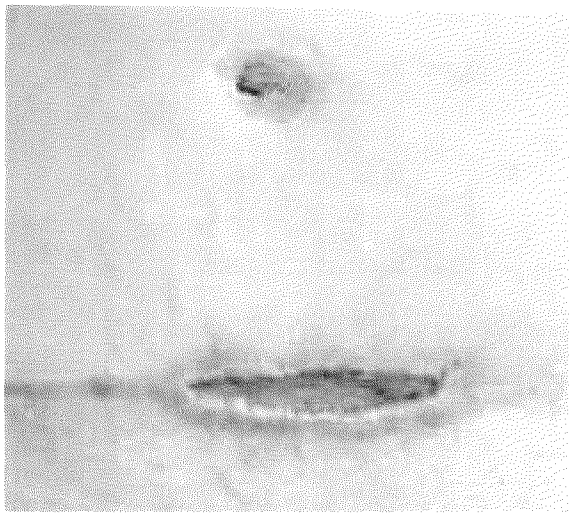
Like linezolid, quinupristin+dalfopristin (*Synercid*) is approved for use in Australia in managing MRSA infections. Comparative studies of this product and vancomycin have found that quinupristin+dalfopristin is probably comparable in efficacy to vancomycin, however substantially higher cost, increased risk of side effects and multiple drug interactions limit its use in the treatment of serious MRSA infections.[27]

III. Tigecycline

Tigecycline (*Tygacil*) has been studied in treating intra-abdominal and skin infections, including those caused by MRSA. In a study comparing tigecycline to the combination of vancomycin and aztreonam in treating skin and skin-structure infections, both regimens achieved comparable rates of MRSA eradication.[27] As severely ill patients have been excluded from trials evaluating tigecycline, the role of this agent is currently limited to patients with less severe MRSA infections, as an alternative to vancomycin.

IV. Daptomycin

Daptomycin (*Cubicin*) was discovered in the late 1970s, but unacceptably high rates of myalgia and elevated creatine kinase levels in early trials led to its development being abandoned. Following the widespread dissemination of MRSA, clinical trials resumed, and daptomycin is now



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marketed for MRSA endocarditis, bacteraemia and skin and soft tissue infections.[27] In a study of patients with *S. aureus* bacteraemia, daptomycin was compared to current standard therapy (including vancomycin for MRSA infections).[27] Daptomycin was found to be equivalent to standard therapy, although patients who received daptomycin displayed a significantly higher incidence of creatine kinase elevation. This drug should not be used to treat MRSA pneumonia as it penetrates lung tissue poorly and binds to pulmonary surfactant.[27]

5. Conclusion

Drug-resistant strains of *Staphylococcus aureus* are important pathogens, both in hospitalised patients and those in the community. Pharmacists are therefore ideally placed to improve the management of these infections, from promoting hand hygiene programs to antibiotic selection and monitoring. The availability of new agents with activity against drug-resistant strains of *S. aureus* may somewhat alleviate growing concerns over the diminishing efficacy of vancomycin, however the appropriate and judicious use of these agents will be paramount to ensure therapeutic success in the future.

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