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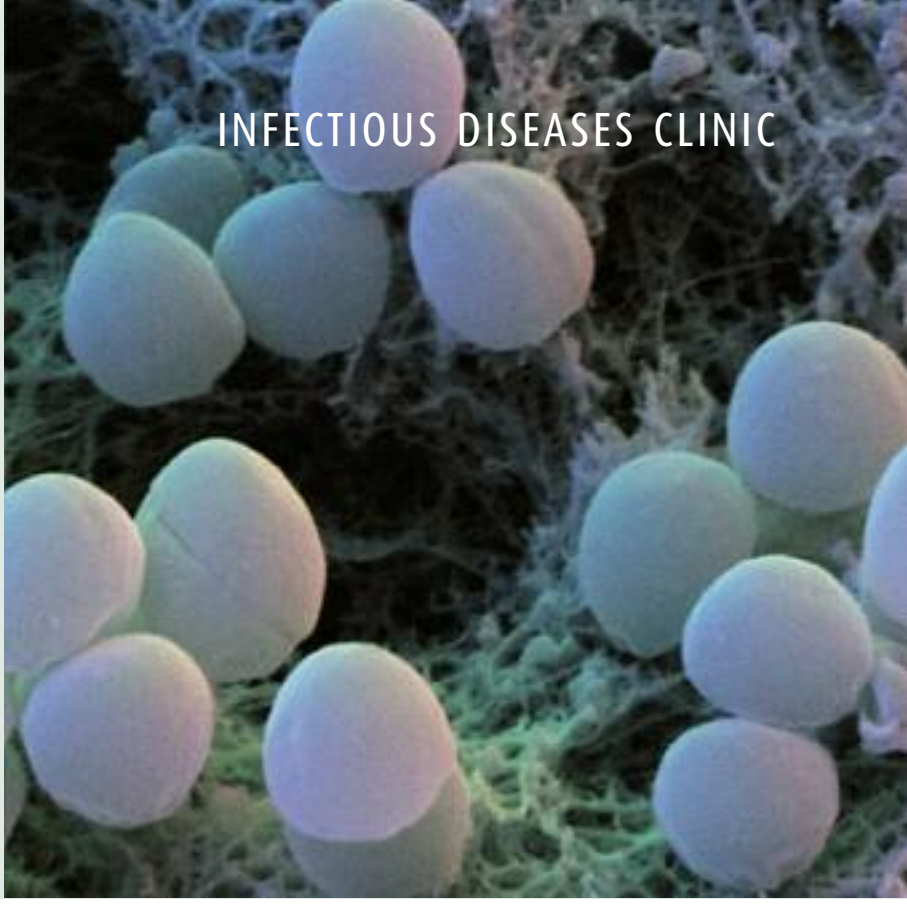
Managing MRSA infections in the community



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Staphylococcus aureus **infections seen in the community are now often due to methicillin-resistant strains. All suspected *S. aureus* lesions should be swabbed to determine whether methicillin-resistant strains are present and detect resistances to other non-beta-lactam antibiotics used in treatment.**

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Staphylococcus aureus has several salient features: it is associated with protean clinical manifestations ranging from colonisation to severe infections, it is spread person-to-person directly and via fomites, and it has the ability to acquire antibiotic resistance genes by horizontal gene transfer and mutation.[1] Epidemic waves of strains of *S. aureus* with resistance to key antibiotics have occurred since the 1940s:

- penicillin resistance in *S. aureus* in the mid-1940s
- waves of methicillin-resistant *S. aureus* (MRSA) in hospitals in the 1960s and the 1970s to the present
- MRSA in the community from the 1990s to the present.[1]

DEFINITION OF 'COMMUNITY' MRSA

The definition of 'community' was originally the reverse of nosocomial – that is, having the positive microbiological specimen taken within two to three days of hospital presentation. However, healthcare in the 21st century sees a blurring of the distinction between hospitals and the community, with the rise of the importance of nursing homes, day-surgery units, ambulatory care units and similar modes of healthcare delivery. Formerly nosocomial strains of MRSA have entered non-hospital settings, and community MRSA strains have entered healthcare environments, including hospitals. In addition, many people colonised or infected with community MRSA strains have risk factors usually associated with acquisition of hospital MRSA strains.

More recently, three groups with MRSA infection have been considered:

- community onset or associated without traditional MRSA risk factors (positive specimen taken outside of hospital or less than 48 hours after hospital admission)
- community onset (positive specimen taken outside of hospital or less than 48 hours after admission) and associated with traditional MRSA risk factors
- hospital (healthcare)-associated (positive specimen taken 48 hours or longer after admission).[2]

MRSA RISK FACTORS[5]

Healthcare-associated MRSA
Contact with a hospitalised person
Hospitalisation
Indwelling devices
Intubation
Recent antibiotic use
Renal insufficiency
Surgery

Community-onset MRSA
Children, young adults
Contact sports
Day-care centres
Low socioeconomic status
Indigenous people
Institutionalised
Intravenous drug use
Men who have sex with men
Military recruits
Patient reports of having had a 'spider bite'*
Prison inmates
Recent antibiotic use
Use of steam baths

*The pain of community MRSA infection is often intense and patients often state a spider has bitten them; however, questioning reveals that no spider was actually seen.

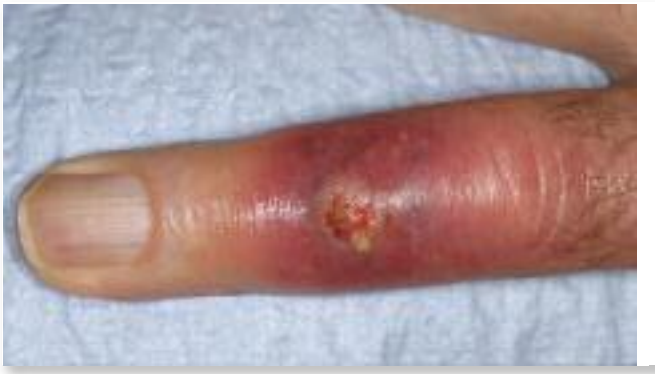

Figure 1. Abscess caused by MRSA infection.

EPIDEMIOLOGY OF COMMUNITY MRSA

Following the emergence of MRSA in the early 1960s, strains were found mostly in association with hospitalised patients.[3] This continued until the early 1980s, when the first descriptions were made of novel strains associated with community patients in Detroit, USA, who were intravenous drug users.[4] These strains were different genetically from hospital MRSA strains and also less resistant to non-beta-lactam antibiotics than hospital strains. This remained a local phenomenon until multiple simultaneous epidemics were described in the USA, Canada, Western Australia, the Northern Territory, New Zealand, Papua New Guinea, Turkey and eastern Australia due to different local strains of community MRSA.[5] The common features were that the strains were: seen in patients with little or no contact with hospitals, less resistant to non-beta-lactams (and were most often susceptible to all or all but one non-beta-lactam), and prominently associated with skin and soft tissue infections, especially boils. In addition, the patients infected with MRSA were more often indigenous and/or from lower socioeconomic groups.

Community MRSA has now been found in most countries where surveillance occurs. Probably the most notorious strain is the so-called USA300 clone, which has caused a pandemic in the USA such that most staphylococcal infections in patients presenting to US emergency departments are now caused by this strain.[1]

Australian community MRSA epidemiology

In Australia, community MRSA was first seen in Perth in the early 1990s; strains were non-multiresistant, and patients were often from remote areas of Western Australia.[6] Shortly after this, an outbreak in New Zealand of a different strain (the 'South West Pacific' strain) was described,[7] and this strain was then seen in eastern Australian cities.[8] The turn of the millennium saw the emergence of 'Queensland' MRSA,[9] which spread in the next decade to become the most common community MRSA in Australia.

Hospital outbreaks of community MRSA

Given the size of community MRSA pandemics, entry of these strains into hospitals and then cross-infection to other patients has been surprisingly uncommon. It was reported in the initial Detroit cases,[10] and in one hospital outbreak in Perth,[11] but it has now become an important issue in the USA with the rise of the USA300 clone.[12]

MRSA risk factors

Isolation of community MRSA from a patient is more likely if certain 'community-onset MRSA risk factors' are present, as depicted in the box on this page. However, with the rise in the incidence of community MRSA, patients who do not have these risk factors now often isolate MRSA, and the only way to tell is to take swabs of all staphylococcal lesions. Failure to recognise that a patient's lesions are due to MRSA can delay the institution of appropriate anti-MRSA antibiotics, if required.

INFECTIONS CAUSED BY COMMUNITY MRSA

Community MRSA causes a similar clinical spectrum to methicillin-susceptible *S. aureus*, which ranges from asymptomatic carriage to overwhelming septicaemia and death. Typical *S. aureus* infections include skin and soft tissue infections (boils, carbuncles and purulent cellulitis; Figure 1), various surgical site

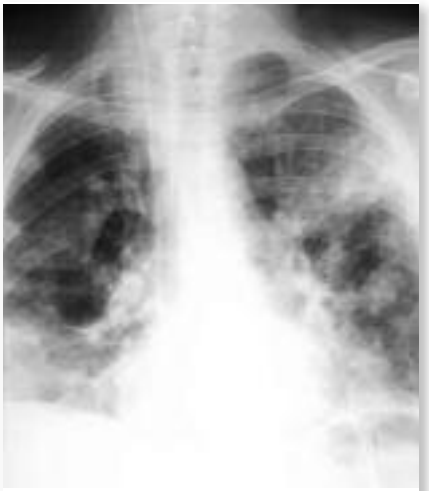

Figure 2. Lung lesions in a patient infected with MRSA.

infections (including superficial, deep and implant infections, bacteraemia and endocarditis), deep abscesses, pneumonia (Figure 2), osteomyelitis, septic arthritis and rare manifestations such as meningitis and other CNS infections.

Genes coding for an exotoxin called Panton-Valentine leukocidin are found in most community MRSA strains; strains with these genes are associated with boils[13] and necrotising pneumonia.[14]

EMERGENCE OF FURTHER DRUG RESISTANCE IN COMMUNITY MRSA

When first detected, community MRSA strains are usually susceptible to all or all but one of the non-beta-lactams.[15] Resistance to rifampicin, fusidic acid, trimethoprim-sulfamethoxazole and ciprofloxacin is readily induced *in vitro*.[16] Mupirocin resistance emerged in Western Australia in areas where this agent was used freely, but has become less common with restriction of prescribing of this drug.[17] In the UK, use of topical fusidic acid induced substantial resistance.[18] More recently in Sydney, resistance to erythromycin, fusidic acid, ciprofloxacin and tetracyclines has been increasingly seen in multiple lineages of MRSA.[19]

DIAGNOSTICS

Pivotal to diagnosis of MRSA is to take microbiological specimens, firstly, to determine if the patient's infection is caused by MRSA (Figure 3) and, secondly, to allow susceptibility testing to non-beta-lactams. Susceptibility to key drugs used in treatment, such as macrolide/lincosamide antibiotics, is becoming increasingly less predictable.

Wound swabs

It is important to take swabs of the purulent lesions. Moistening the swabs with sterile saline prior to taking the swabs increases the bacterial yield. Debris should be removed from lesions prior to swabbing to reduce the chance of isolating commensal organisms.

Staphylococcal carriage swabs

Swabbing contacts, especially family members, may detect clinically silent carriers, although 20 to 30% of people at any given time harbour *S. aureus* in the anterior nares and the strain isolated from a contact may not be the same as that in the patient. Additionally, contacts of a particular patient who have positive swabs may feel responsible for infecting the index case. Thus, the value of the extra information gained from swabbing for carriage should be considered, particularly if the finding will not impact on treatment of the index case or of possibly colonised contacts, and given that it can cause psychosocial issues for those who are positive.

Detection of *S. aureus* carriage is traditionally performed with swabs of the anterior nares. It is important that the swabs are moistened prior to insertion 2 to 3 cm into the anterior nares and that the lateral and medial sides of each nostril are sampled. A single swab has a sensitivity of 50 to 80% for detection of *S. aureus*, and so a negative swab does not rule out carriage.

In the detection of nasal (and/or throat) carriage, it is important to instruct the laboratory to look for both methicillin-sensitive *S. aureus* (MSSA) and MRSA, as sometimes the samples are treated as MRSA screening swabs and the presence of MSSA is not sought.

Figure 3. MRSA cultured on horse blood agar.

Other specimens

If incision and drainage are performed, the best specimen to send to the laboratory is the pus itself. Blood cultures should be taken (two sets to increase sensitivity and decrease problems of sorting out contaminants) if there is the possibility of systemic sepsis. Note that the absence of fever can occur in patients with positive blood cultures and occasionally these samples can be the only specimens to yield the pathogen.

Deep-seated infections warrant the obtaining of diagnostic specimens, usually by needle biopsy. However, if radiological or surgical drainage is performed, the microbiological specimens must be submitted, firstly, to recognise unusual pathogens and, secondly, to allow detection of antibiotic resistance, both of which are more common today.

TREATMENT

The four key aspects of treatment of MRSA are to:

- drain pus
- possibly prescribe antibiotics
- educate patients in hygiene measures
- consider eradication of carriage state.

TREATMENT OF SPECIFIC COMMUNITY MRSA INFECTIONS[20-22]

Skin and soft tissue infections

- 'Drain and refrain'*
- Prescribe antibiotics if the lesion is greater than 5 cm in diameter or if the patient has systemic sepsis or is immunocompromised
  - oral: clindamycin, trimethoprim-sulfamethoxazole, doxycycline
  - intravenous: vancomycin
- Educate patient on hygiene measures
- If infection is recurrent or other contacts have infections consider MRSA eradication

Bacteraemia

- Uncomplicated (patient has positive blood cultures, no implant, negative blood cultures after two to four days' antibiotic treatment, defervescence within 72 hours of starting antibiotics, no evidence of metastatic foci of infection)
  - intravenous: vancomycin for two weeks
- Complicated (patient has endocarditis, persistently positive blood cultures after two to four days' antibiotic treatment, defervescence more than 72 hours after starting antibiotics, metastatic foci of infection)
  - intravenous: vancomycin for four to six weeks
  - endocarditis: consider valve replacement
  - metastatic foci: drain if possible
  - infected prosthesis: replace

Pneumonia

- Vancomycin, linezolid or clindamycin (if susceptible) for seven to 21 days depending on severity and response
- Drain empyema

* See details in the section on 'Surgery'. Drain refers to incision and drainage, and refrain refers to refraining from prescribing antibiotics.

Treatment of specific community MRSA infections

The box on this page summarises the recommended treatment of specific community MRSA infections.[20-22] Treatment of osteomyelitis, septic arthritis, infected orthopaedic implants, CNS infections and other complicated and rare community MRSA infections is beyond the scope of this paper. The reader is referred to other sources for information on these infections,[20-22] and consultation with an infectious diseases physician and/or microbiologist and appropriate surgeon is recommended.

Surgery

Drainage of abscesses and boils remains the mainstay of treatment and is probably more important in the era of substantial antibiotic resistance when empirical antibiotics may not cover the pathogen, and exposure to broad-spectrum antibiotics selects out drug-resistant bacteria. Thus, clinicians are advised to 'drain and refrain' – that is, if the patient is not immunocompromised and is not systemically septic, and the abscess is smaller than 5 cm in diameter and amenable to drainage, incision and drainage without antibiotics are recommended.[20-22]

Antibiotic selection

For more information on antibiotic selection or community MRSA, the reader is referred to the treatment guidelines below:

- *Therapeutic Guidelines Antibiotic, version 14* (available in hard copy, electronic form for smart phones and via Clinical Information Access Project [CIAP])[20]
- Infectious Diseases Society of America's clinical practice guidelines for MRSA, published in *Clinical Infectious Diseases*[21]
- *Sanford Guide to Antimicrobial Therapy 2011*.[22]

Empirical choice

The selection of empirical antibiotics is becoming challenging with the increasing incidence of methicillin resistance in community *S. aureus* strains causing infections. In locales where MRSA is uncommon, and the patient is systemically well and has no evidence of a deep-seated infection, the usual oral anti-staphylococcal treatment with beta-lactams (flu[di]cloxacillin or cephalexin/cephazolin) could be empirically prescribed unless there is a contraindication. However, if community MRSA is common in the geographical region – for example, present in more than 20% of *S. aureus* isolates – or if the patient has septicaemia and/or evidence of a deep-seated infection, parenteral anti-MRSA treatment should be prescribed.

Traditional oral treatment of MRSA has been with rifampicin and fusidic acid, because when MRSA strains first emerged they were resistant to all other oral antibiotics. Both these antibiotics have good oral bioavailability but they have significant issues with side effects, particularly gastrointestinal intolerance.[20] Additionally, supplying rifampicin is difficult, as it is not subsidised by the PBS for staphylococcal infections. Rifampicin induces hepatic cytochrome enzymes and thus interferes with drugs such as the contraceptive pill, warfarin and anticonvulsants.

Community MRSA strains are usually at present not multidrug resistant, allowing the use of other non-beta-lactam antibiotics that are better tolerated and available via the PBS. Oral agents that are recommended for community MRSA infection include clindamycin (for use in adults), trimethoprim-sulfamethoxazole, and doxycycline (if the patient is over 8 years of age). These three drugs all have excellent bioavailability by the oral route. Both clindamycin and trimethoprim-sulfamethoxazole have significant adverse effects.[20] The intravenous route of administration (for clindamycin or trimethoprim-sulfamethoxazole) is only required if oral absorption is unreliable – for

example, if the patient has septicaemia or septic shock, or if malabsorption states, etc., are present.

Note that coverage of beta-haemolytic streptococci is suboptimal with trimethoprim-sulfamethoxazole, doxycycline and rifampicin/fusidic acid. If one of these agents is used, a beta-lactam should be added if streptococci might also be present in a dual infection.

Linezolid is a new drug that is efficacious against MRSA and is available in oral and intravenous formulations. However, it is not readily available outside of hospitals and is too toxic and expensive for routine use.

Intravenous agents for severe local disease and/or systemic sepsis include vancomycin, clindamycin or lincomycin (note that lincomycin is cheaper, as its available on the PBS, and has a different dosage than the intravenous formulation of clindamycin), linezolid and daptomycin. Vancomycin is the usual agent chosen due to familiarity, relatively low toxicity and low cost.

Definitive choice

The definitive choice of antibiotics is guided by susceptibility testing results. As this is becoming less predictable, it is more important to take diagnostic specimens from all patients with staphylococcal infections. Generally, the recommendations for empirical therapy would be followed and the antibiotic changed only if there is treatment failure and/or detection of resistance to the empirical antibiotics.

If the MRSA isolate tests erythromycin resistant but clindamycin susceptible, it is likely to have inducible macrolide, lincosamide and streptogramin B (MLSB) resistance. This means that erythromycin (generally with poor results in skin and soft tissue infections irrespective of resistance) will fail but clindamycin probably will work. However, occasionally, mutants can be selected by clindamycin, resulting in therapeutic failure.[23]

KEY POINTS

- Always swab suspected staphylococcal lesions, as they are now often due to methicillin-resistant *Staphylococcus aureus* (MRSA).
- Surgery is an important aspect of MRSA treatment.
- Drain and refrain (from antibiotics) if the patient is previously well, lesions are less than 5 cm in diameter and drainable and the patient does not have systemic sepsis.
- For lesions that are 5 cm or larger and/or if the patient has systemic sepsis, empirical antibiotics should be used.
- Empirical antibiotic choice depends on the likelihood of the infection being caused by MRSA versus methicillin-sensitive *S. aureus*.
- Definitive antibiotic choice depends on culture and susceptibility results – this requires taking swabs and other specimens.
- Educate the patient with MRSA infection in hygiene measures.
- If a patient has a history of recurrent boils and/or involvement of family contacts, implement staphylococcal eradication management.

If infection is localised to the skin and soft tissues and the patient does not exhibit sepsis, treatment with clindamycin could be continued if the isolate tests erythromycin resistant and clindamycin susceptible; however, if there is sepsis and/or deep infection this approach is too risky and an alternative drug should be chosen.

Anti-ribosome antibiotics

Antibiotics active against ribosomes, such as clindamycin and linezolid, might decrease exotoxin production and have been postulated to have a special role in treatment of community MRSA infections.[14, 21] This is unproven clinically.

Hygiene measures

All patients with purulent *S. aureus* lesions will disseminate staphylococcal cells widely into the immediate environment. To prevent others being inoculated, it is important to advise patients to do the following:

- cover draining wounds with dressings
- have regular showers and wash hands with soap or alcoholic hand gel, especially after manipulating wound or dressings
- not share towels, linen, razors or other personal items.

Eradication of carriage state

It is important to elicit a history of recurrence of boils, and of recurrent boils in family members in considering eradication of the carriage stage. This will be the subject of a future article in *Medicine Today*.

CONCLUSION

Staphylococcal infections in the community are increasingly being caused by MRSA. Suspected staphylococcal lesions should be swabbed to determine whether the *S. aureus* strain is methicillin-resistant, and also to detect resistances to other key drugs currently useful in treatment. The most common MRSA infection is boils, and a 'drain and refrain' approach works well for this infection. Empirical and definitive antibiotic treatment increasingly needs to be aimed at MRSA. It is important to recognise recurrent skin sepsis in patients and their families to interrupt the cycle of transmission. MT

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