

## Fortnightly Review

### Diagnosis and management of methicillin resistant *Staphylococcus aureus* infection

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#### Methicillin resistance in *Staphylococcus aureus*

*Staphylococcus aureus* is renowned for countering almost any antibiotic challenge. Its history since the advent of penicillin is one of increasing resistance to antibiotics. Methicillin was the first semisynthetic penicillin resistant to penicillinase to be derived from the penicillin nucleus and was a major advance in the treatment of staphylococcal infections. Because of its toxicity and ineffectiveness if given orally it was gradually superseded by newer penicillinase resistant penicillins such as flucloxacillin. However, methicillin is still used for susceptibility testing of staphylococci in the laboratory and so methicillin resistance is an indicator of flucloxacillin resistance. Staphylococcal resistance to methicillin is not due to the destruction of the antibiotic by a bacterial enzyme such as  $\beta$ -lactamase but is related to decreased affinity of the organism's penicillin binding proteins for methicillin and also the synthesis of an extra penicillin binding protein with very low affinity for  $\beta$ -lactam antibiotics.

Methicillin resistance in staphylococci was reported in 1961, soon after the introduction of methicillin, and naturally occurring strains may have been around before the advent of methicillin.<sup>1-3</sup> There was a gradual increase in methicillin resistance in England throughout the 1960s, but during the 1970s attention was focused on the Gram negative bacteria, with some complacency about Gram positive bacteria.

Various epidemic strains of methicillin resistant *S aureus* (EMRSA) appeared in the 1980s.<sup>4</sup> The first of these, EMRSA-1, bore many resemblances to a strain that caused large outbreaks in hospitals in eastern Australia in the late 1970s.<sup>5</sup> It probably first appeared in England in 1980-1 and went on to cause major endemic and epidemic problems. These were centred in hospitals in the North East Thames region of London, but also spread widely to hospitals in other parts of London and outside London.<sup>6-8</sup> Since then

#### Box 1—Methicillin resistance in *Staphylococcus aureus*

- Methicillin resistance indicates flucloxacillin resistance
- There are many different strains of MRSA
- MRSA strains are usually resistant to many other antimicrobials
- Methicillin resistance is not a marker for virulence or spread
- Some MRSA have epidemic potential
- MRSA may possess all the *Staphylococcus aureus* virulence factors
- MRSA may cause severe infections or merely colonisation

#### Summary points

- Control of methicillin resistant *Staphylococcus aureus* (MRSA) is difficult and costly
- Management of infections has two aspects: management of the individual patient and management of an endemic or epidemic problem with MRSA in a hospital
- Control of epidemics relies essentially on good hygienic practices and hospital policies to restrict the use of antibiotics
- The costs of ignoring an outbreak are higher than those associated with its control, particularly when the costs of potential legal action are taken into account

many other epidemic strains have been identified. For instance, a new strain, termed EMRSA-16, was recognised in an outbreak in the orthopaedic and geriatric wards of a hospital in Northamptonshire in 1991. This went on to become established in two district general hospitals and a London teaching hospital in 1992, and isolates were received from 13 other hospitals in England and Wales.<sup>9</sup>

These later strains may have evolved from the earlier ones, but they are distinctly different. In particular, many of the resistance determinants in the newer strains are chromosomal rather than plasmid-borne, which may stabilise them. It is now clear that genetic information may be transferred by a fairly promiscuous process between ubiquitous, relatively non-pathogenic organisms and pathogenic organisms sharing overlapping habitats (for example, coagulase negative staphylococci, *S aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Enterococcus faecalis*).<sup>10-12</sup> This development has worrying implications. Add the selective pressures of topical and systemic antibiotics, compromised patients, invasive procedures, and the hospital environment and it is easy to imagine how outbreaks with multiresistant strains of *S aureus* may arise and persist.

#### Virulence and epidemic potential

Arguments rage about the virulence and epidemic potential of strains of methicillin resistant *S aureus*. These bacteria are largely hospital pathogens and it is often argued that they behave as opportunistic pathogens. However, they are a heterogeneous group of organisms and as such do not all behave in the same way (box 1). It is clear that methicillin resistance itself

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is not a marker of epidemic potential or virulence, but it is still unclear which factors are linked to these aspects of behaviour. Virulence factors in these staphylococci tend to be those of the more common methicillin sensitive *S aureus* (MSSA). In general, the resistant staphylococci are as capable as the sensitive staphylococci at producing the impressive array of factors implicated in virulence and pathogenicity such as coagulase, DNase, haemolysins, protein A, and other extracellular toxins.

Methicillin resistant *S aureus* may cause severe and life threatening infections. Studies have case matched patients with infections due to methicillin sensitive and methicillin resistant bacteria and found no significant differences in the two groups, and in Dublin methicillin resistant *S aureus* bacteraemias had a high case fatality rate.<sup>13</sup> In an American outbreak 30% of all bacteraemias in a three year period were caused by methicillin resistant *S aureus*, which was a direct cause of death in 44% of these patients.<sup>14</sup> This study also reported a high rate of infection, 260 of 286 affected patients being infected and not simply colonised. Other places in England and abroad have had similar experiences. In the Royal London Hospital's EMRSA-1 outbreak severe infections (septicaemia, endocarditis, meningitis) were notable in the early days, before full containment measures were instituted.<sup>6</sup> In this outbreak there were also two instances where EMRSA-1 was responsible for a toxic shock-like illness; this was probably associated with enterotoxin production as toxic shock syndrome toxin-1 was not isolated from these strains.<sup>15</sup>

The transmission and acquisition of methicillin resistant *S aureus* is a multifactorial process depending not only on organism factors but also on host factors such as abnormal or damaged skin, length of hospital stay, previous antibiotic treatment, and probably the use of topical antimicrobial agents. There also seems to be genetic predisposition to carriage of *S aureus*, or lack of it. Not surprisingly, the hospital areas mainly affected are the intensive care, burns, dermatology, and surgical units.

### Diagnosis

It is not possible to diagnose methicillin resistant *S aureus* infection from the patient's clinical condition as there is no characteristic clinical picture that differentiates this from other staphylococcal infections. Diagnosis of infection or colonisation will depend on the submission of appropriate specimens to the microbiology laboratory. When infection is suspected these should be from the site or sites of infection, whereas screening for colonisation (box 2) should include samples from the nose, throat, wounds, other skin lesions, insertion sites of intravascular lines, tracheostomies, catheter urine samples, perineum, and sputum. The usual strictures apply: samples should always be fresh; actual pus is better than a wound swab; and swabs in transport medium are better than dry swabs. Normal sampling methods to detect colonisation are relatively insensitive, so several sets of clear specimens are required before a patient can be declared free of

#### Box 2—Sampling sites to detect colonisation

- Nose
- Throat
- Perineum
- Sites of abnormal or damaged skin
- Wounds
- Insertion sites of intravascular lines
- Catheter urine samples
- Sputum if expectorating

#### Box 3—Procedure for colonised or infected patients

- Discharge patients with instructions for clearing MRSA colonisation if their condition allows
- If discharge is not possible, admit them to an isolation room or ward
- Submit further cultures to assess extent of colonisation and dispersal
- Assess whether MRSA strain has previously exhibited epidemic potential
- Mark the patient's records for future recognition
- Treat infection with the appropriate antimicrobial agents
- Treat colonisation with antiseptics and topical agents
- Assess the vulnerability of the other patients on the ward
- Consider screening other patients and staff in areas where the patient has been, to detect other affected people or the source
- Reinforce hygienic precautions and infection control measures, including restrictions on the use of antibiotics
- Decide whether the ward should be closed to admissions and thoroughly cleaned

methicillin resistant *S aureus*. During a screening operation, sensitivity of detection can be improved by placing the swabs directly into a salt enrichment broth on the ward. However, this delays the result by a further day compared with a direct plate culture on blood or nutrient agar.

The detection of methicillin resistance poses problems for the microbiologist as its expression is affected by many physical and chemical factors, such as light, temperature, osmolality, and pH.<sup>16-19</sup> This may result in a population seeming methicillin sensitive unless culture conditions are manipulated to bring out methicillin resistance. This is commonly done either by incubating the strain at 30°C or by adding extra salt to the medium. Further difficulties arise in typing the staphylococcus, as many strains are untypable by the standard phages.

### Managing patients with MRSA

#### ISOLATION

Containment measures should be instituted when evidence of methicillin resistant *S aureus* has been obtained from a patient as it is not possible to determine the behaviour of the particular strain from laboratory information. The patient should be admitted to an isolation room or unit. The need for scrupulous attention to hand washing by staff must be reinforced, as most staphylococci are spread by the hands. Transmission through the air may occur and is most likely with heavily colonised people, termed "dispersers" or "cloud babies." Skin conditions such as eczema predispose to widespread dispersal of staphylococci on skin scales through the air. It is virtually impossible to clear methicillin resistant *S aureus* from such people, which has serious consequences if the affected person is a health care worker. Sideroom isolation may fail where air dispersal is a factor or where hand hygiene of staff is unsatisfactory. In these circumstances isolation in a dedicated isolation ward with staff well versed in infection control procedures may be necessary (boxes 3 and 4).

#### TREATMENTS

The treatment of patients affected with methicillin resistant *S aureus* falls into two categories: treatment of colonisation and treatment of infection. The ablation of widespread colonisation (boxes 5 and 6) presents a problem as none of the currently available antiseptics

(hexachlorophane, triclosan, chlorhexidine, povidone-iodine) is fully effective, although they are used in hair and body washing for want of something better. The treatment of limited carriage, particularly nasal carriage, has been revolutionised by mupirocin,<sup>20</sup> but reports of reduced susceptibility to this agent should alert us to the danger of excessive or inappropriate use.<sup>21</sup> In some instances carriage may not be ablated by topical agents or by systemic treatment of infection, and recourse to rifampicin may be necessary, possibly in combination with ciprofloxacin.

Strains of *S aureus* vary in their degree of methicillin resistance and in their pattern of resistance to other antimicrobial agents. Most are resistant to penicillin and susceptible to fusidic acid, rifampicin, teicoplanin, and vancomycin, but the rest of their antibiogram varies widely. EMRSA-1 is characteristically resistant to penicillin, tetracycline, erythromycin, methicillin, and clindamycin; variably resistant to gentamicin and chloramphenicol; usually sensitive to neomycin, fusidic acid, ciprofloxacin, and rifampicin in patients not receiving these drugs; and consistently sensitive only to vancomycin and teicoplanin.

#### Box 4—Prevention of spread of MRSA

- Isolation of affected patient; removal and treatment of affected staff
- Thorough hand washing before and after contact with affected patients or their immediate environment
- Gloves for handling contaminated dressings or linen
- Masks for procedures which generate staphylococcal aerosols (chest physiotherapy, sputum suction, etc)
- Gowns or plastic aprons for close contact with patients or their immediate environment
- Disposal of waste and linen according to policy for "infected" materials and linen
- Terminal room disinfection with a phenolic disinfectant, with special attention to horizontal surfaces and areas that collect dust
- Defined procedures for patient's visits to specialist departments, surgery, ambulance transportation, transfer to another hospital, etc: MRSA patients should normally be dealt with at the end of the working session
- Limit use of agency staff in affected areas

There are formidable problems in the treatment of methicillin resistant *S aureus* infections (box 7), given the scarcity of available agents. The mainstay of treatment is vancomycin, although experience with a newer glycopeptide, teicoplanin, is growing.<sup>22,23</sup> Teicoplanin may replace vancomycin as it is easier to administer and has a longer half life. It may be less toxic than vancomycin, although reports of vancomycin toxicity have been exaggerated and probably relate to the earlier, dirtier product, the "Mississippi mud" of the 1950s.

Vancomycin is cheaper but requires careful monitoring and slow infusion. Tolerance may occur, requiring combination therapy, for example with rifampicin. Rifampicin is an excellent antistaphylo-

#### Box 5—Treatment of colonisation

- Skin and hair: antiseptic detergent for washing to decrease the staphylococcal load
- Nose and sites of limited carriage: mupirocin. Chlorhexidine based creams are less effective but may be required if MRSA is resistant to mupirocin
- Antibiotics such as rifampicin and ciprofloxacin may occasionally be required to eradicate colonisation

#### Box 6—Clearance of MRSA

- Sample nose, perineum, skin lesions, and other previously positive sites weekly
- The patient is deemed clear of MRSA if results of three complete sets of screening tests are negative
- Relapses may occur if the patient receives antibiotics later

coccal agent, but resistance arises readily if it is used alone.<sup>24-26</sup> There are also concerns that its widespread use may jeopardise its value in the treatment of tuberculosis. Some of the newer quinolones such as ciprofloxacin have antistaphylococcal activity, but resistance also arises and treatment failure despite continued susceptibility of the organism to ciprofloxacin has been reported.<sup>27,28</sup> These agents may have a role in the treatment of non-life threatening infections.

#### Box 7—Treatment of infection

- Severe or life threatening infection: vancomycin or teicoplanin. Combination therapy may be required—for example, with rifampicin
- Non-life threatening infection: appropriate treatment according to the antibiotic susceptibility of the strain of *S aureus*

#### Management of endemic or epidemic MRSA

Control rests on good hygienic practices and hospital policies to restrict the use of antibiotics. Hospital surveillance and an awareness of other local units and hospitals similarly affected are crucial. There needs to be prompt recognition of cases and impending outbreaks. The necessary containment measures will vary according to the epidemic potential of the methicillin resistant *S aureus*, but this is not usually known in advance. Experience with some strains of methicillin resistant *S aureus*, including EMRSA-1, shows that isolation or cohort wards may be necessary.<sup>6</sup> Surveillance of high risk admissions, screening of wards with affected patients, the tagging of affected patients' records, and the restriction of staff and patient movement within and between hospitals are also important aspects of control and are detailed in the revised guidelines for the control of epidemic methicillin resistant *S aureus*.<sup>29</sup> In some instances such as an endemic problem in a less critical area of the hospital, eradication of the methicillin resistant strain may prove impossible, requiring an acceptance of living with it. Control here may mean limiting spread outside that area.

#### The future

As yet little is known about the factors that make a particular strain of methicillin resistant *S aureus* virulent or capable of spread. The rapid identification of epidemic strains and the factors responsible for spread and colonisation would permit a more targeted approach and save on containment measures. Other areas warranting further research include the development of new topical and systemic agents, more rapid and sensitive methods of detecting colonisation, and improved typing methods.

An outbreak of methicillin resistant *S aureus* is costly business (box 8). It is generally agreed that the costs of ignoring EMRSA are higher than those associated with its control, particularly when the costs of potential legal action are taken into account. The average cost of treating a bacteraemia with methicillin

### Box 8—Costs of an MRSA outbreak

- Cost to patients: pain and discomfort, loss of time and earnings, inconvenience, excess morbidity, and mortality
- Cost to the hospital: delayed discharge and attendant costs, drugs and antiseptics, containment measures, infection control procedures, litigation, contracts imperilled, exclusion of affected staff

resistant *S aureus* is about seven times that of treating a bacteraemia with methicillin sensitive *S aureus*.<sup>30</sup> Containment measures use increasingly scarce resources. A 1987 study in the North East Thames region put the recurrent annual financial cost then of containing outbreaks at around £250 000 in the worst affected hospitals. In addition, there were capital costs associated with the establishment of an isolation ward. Another cost that must not be neglected is that of litigation by infected patients, a growing hazard of outbreaks in hospitals. Hospitals then need to show that well documented and effective control measures are in place. Furthermore, infection control now features as one of the main quality indicators in contracts between purchaser and provider agencies.

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## Grand Rounds: Hammersmith Hospital

### Tuberculous pericarditis with rapid progression to constriction

#### Prompt diagnosis and treatment are needed

Pericarditis is the main diagnosis in 1 in 1000 patients admitted to hospital, and 4% of cases are caused by tuberculosis.<sup>1</sup> Tuberculosis is responsible for up to 7% of cases of pericardial tamponade and a similar percentage of cases of tamponade in which the patient requires pericardiectomy because pericardial constriction develops.<sup>2</sup> We report a case of tuberculous pericarditis in which pericardial constriction developed rapidly despite anti-tuberculous drugs.

#### Case history

A 28 year old Sri Lankan man was transferred to our hospital for investigation and treatment. He had been admitted to another hospital three days previously with a four week history of malaise, loss of appetite, weight loss (5 kg), reduced exercise tolerance, and rigors. He had recently arrived in England from Sri Lanka and had no significant medical history. He was heterosexual. On examination he had a temperature of 39°C, his pulse was 100 beats/min with a palpable paradox, and his blood pressure was 120/70 mm Hg with 20 mm Hg of paradox. The jugular venous pressure was raised by 7 cm and Kussmaul's sign was

present. A third heart sound was heard together with bibasal crepitations. He had hepatosplenomegaly but no ascites or peripheral oedema.

His haemoglobin concentration was 123 g/l, white blood cell count  $12.4 \times 10^9/l$ , platelet count  $370 \times 10^9/l$ , and the erythrocyte sedimentation rate 48 mm in the first hour. His biochemical profile was normal but his C reactive protein concentration was 200 mg/l. Three early morning urine samples yielded no growth. An electrocardiogram showed a sinus tachycardia, with a rate of 119 beats/minute, with T wave inversion in the inferolateral leads. Chest radiography showed cardiomegaly (fig 1). He had good biventricular function, normal valvular structure and function, but a large pericardial effusion (fig 2). Pericardiocentesis yielded 1.5 litres of uniformly blood stained fluid. The fluid contained an exudate with a protein concentration of 540 g/l, glucose concentration of 1.9 mmol/l (serum glucose 5 mmol/l), and numerous lymphocytes. A Mantoux test was performed and gave positive results at a dilution of 1 in 10 000. Computed tomography showed evidence of para-aortic and paracolic lymphadenopathy. On the basis of fever, lymphadenopathy, and the large pericardial effusion he was started on



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