Methicillin-resistant Staphylococcus aureus (MRSA) has become a ubiquitous bacterium in both the hospital and community setting. There are two major subclassifications of MRSA, community-acquired and healthcare-acquired, each with differing pathogenicity and management. MRSA is increasingly responsible for infections in otherwise healthy, active adults. Local outbreaks affect both professional and amateur athletes and there is increasing public awareness of the issue. Health-acquired MRSA has major cost and outcome implications for patients and hospitals. The increasing prevalence and severity of MRSA means that the orthopaedic community should have a basic knowledge of the bacterium, its presentation and options for treatment.

This paper examines the evolution of MRSA, analyses the spectrum of diseases produced by this bacterium and presents current prevention and treatment strategies for orthopaedic infections from MRSA.

Staphylococcus, a Gram-positive bacterium which grows in clusters of organisms, was classified into two primary species in 1884 by Rosenbach,1 Staph. aureus and Staph. albus. His classification was based on the morphological appearance of colonies and the ability to clot blood. Staph. aureus grows in deep yellow colonies on blood agar and is coagulase-positive while Staph. albus forms white colonies which lack the ability to clot blood. Penicillin disrupts the cross-linking of small peptide chains in peptidoglycans during the production of bacterial cell walls.2 As a result, pre-existing cells are unaffected, but newly-produced bacteria are unable to maintain their cell-wall rigidity and ultimately undergo lysis.

Within ten years of the widespread use of penicillin, Staph. aureus had developed resistance by producing penicillinase, an enzyme which cleaves the penicillin beta-lactam ring. To combat this resistance, a semisynthetic class of penicillins (e.g. methicillin) was introduced in the 1960s. Methicillin had an additional acyl-group on the beta-lactam ring which conferred a high degree of resistance to penicillinase and produced broader antibacterial activity against some Gram-negative bacteria.

Methicillin resistance developed in Staph. aureus at a slower pace than the initial resistance to penicillin, as shown in Table I.3 Expression of an alternative penicillin-binding protein, PBP2a, conferred resistance and rendered the entire antibiotic class ineffective. This is encoded on the meca gene, which is a component of a highly mobile genetic element known as the staphylococcal cassette chromosome (SCC).4 There are four main types of SCC which confer differing profiles of drug resistance. Type 1, 2 and 3 are typically found in healthcare-acquired MRSA and often encode resistance to other antibiotics. Type 4 is found in community-acquired MRSA and does not encode resistance to other antimicrobials.

Methicillin-resistant Staph. aureus: new subclassifications

Although initially a nosocomial pathogen, methicillin-resistant Staph. aureus (MRSA) has become increasingly prevalent in the community over the past two decades. As a result, it is now subclassified into community-acquired and healthcare-acquired MRSA with the latter including strains acquired in hospital or institutional settings. The distinction has important implications since each type differs in its pathogenic capacity, virulence, antibiotic resistance profile, and in the patient population affected.5 Table II gives the important differences between these two strains.

Community-acquired MRSA

This has been defined by the American Centre for Disease Control as resistant Staph. aureus isolated from an outpatient or inpatient within...
48 hours of admission. The evolution of this species is most likely to be the result of the transfer of mecA to strains of Staph. aureus in the community. The mecA locus harboured on SCC type 4 is now a recognised genetic characteristic of community-acquired MRSA. With the exception of methicillin, this particular SCC has little resistance to the other classes of antibiotic. It also carries the panton valentine leukocidin locus. This gene product causes lysis of neutrophils, enabling these bacteria to cause severe soft-tissue infection and necrotising pneumonia. Panton valentine leukocidin is expressed in nearly all strains of community-acquired MRSA, but is identified in only 2% of healthcare-acquired MRSA strains.

The carriage rate of community-acquired MRSA in the community as well as in the hospital setting varies widely in the literature. In a meta-analysis examining over 6000 patients, 1.3% of community members tested positive for community-acquired MRSA and 30% of MRSA isolates in hospitalised patients represented community-acquired MRSA, but is identified in only 2% of healthcare-acquired MRSA strains.

Table I. The time required for the prevalence rates of resistance to reach 25% in hospitals according to Chambers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year drug introduced</th>
<th>Years to report resistance</th>
<th>Years until 25% rate in hospitals</th>
<th>Years until 25% rate in community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1941</td>
<td>1 to 2</td>
<td>6</td>
<td>15 to 20</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1956</td>
<td>40</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>Methicillin</td>
<td>1961</td>
<td>&lt; 1</td>
<td>25 to 30</td>
<td>40 to 50 (projected)</td>
</tr>
</tbody>
</table>

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Table II. The differences in profiles of community-acquired (CA) and healthcare-acquired (HA)-MRSA

<table>
<thead>
<tr>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic profile</td>
<td>Multiple drug resistance present</td>
</tr>
<tr>
<td>Population affected</td>
<td>Recently hospitalised patients</td>
</tr>
<tr>
<td>More susceptible to beta-lactams, erythromycin, quinolones</td>
<td>Haemodialysis patients</td>
</tr>
<tr>
<td>Young, otherwise healthy people</td>
<td>HIV-infected patients</td>
</tr>
<tr>
<td>Outbreaks have occurred in athletes</td>
<td>Institutional patients (e.g. nursing homes, group homes)</td>
</tr>
<tr>
<td>Area of infection</td>
<td>Elderly</td>
</tr>
<tr>
<td>Skin, lungs</td>
<td>Varies</td>
</tr>
<tr>
<td>Genetic constitution</td>
<td>SCC 1 to 3</td>
</tr>
<tr>
<td>PVL gene, SCC†</td>
<td></td>
</tr>
<tr>
<td>* PVL, panton valentine leukocidin</td>
<td></td>
</tr>
<tr>
<td>† SCC, staphylococcal cassette chromosome</td>
<td></td>
</tr>
</tbody>
</table>

In Europe, community-acquired MRSA does not seem to cause as many soft-tissue infections as in the United States. While a large percentage of soft-tissue infections are caused by community-acquired MRSA in the United States, the community-acquired MRSA cutaneous infection rate in Europe only accounts for between 1% and 3% of presenting wounds. There is currently no consensus as to why there is this vast difference.

Hospital-acquired MRSA

This generally affects acutely and chronically-ill patients who require indwelling devices, such as catheters and central lines. Healthcare-acquired MRSA colonisation has implications regarding the overall health and prognosis of the patient. The nates have proven to be the most consistent site from which MRSA can be isolated and this may be due to the relative absence of local host defences. In addition, it has been reliably demonstrated that elimination of infections are increasingly common in athletes, especially in those engaged in team sports. Typically, athletes present with cutaneous abscesses on skin which is exposed during competition. The current recommendations for treatment of skin infections in sports include the aggressive evaluation of any suspected infection, incision and drainage of abscesses and culture of exudate. Nasal treatment with mupirocin is indicated for the entire team and staff once a documented community-acquired MRSA infection has occurred. Prevention strategies include aggressive monitoring of wounds, showering before the use of whirlpools, limiting sharing of equipment and frequent cleaning of equipment. The antibiotic treatment for community-acquired MRSA is different from that for healthcare-acquired MRSA (Table II).

In Europe, community-acquired MRSA infection often occurs in soft tissues. In a Centre for Disease Control review of 1647 community-acquired MRSA infections, 77% involved the skin and presented as abscesses or cellulitis. Only 6% of the cases were invasive infections.
MRSA from the nares reflects that from other areas of the body. A number of studies have established a correlation between the nasal carriage of Staph. aureus and infections in various settings. Nasal carriers of MRSA have an increased risk of developing MRSA bacteraemia, and in 80% of cases bacteraemic isolates from the same patient have identical genotypes.

Peri-operative colonisation with MRSA after admission to intensive care units significantly increases the risk of developing post-operative infection. One proposed mechanism for this is that intubation traumatises the colonised airway allowing MRSA access to the vascular system and that the air of the operating theatre is contaminated by nasal MRSA, which then seeds the wound. Mupirocin, an antibiotic produced from Pseudomonas fluorescens, has formed the cornerstone of the treatment of MRSA. It reversibly binds to bacterial isoleucyl-tRNA synthetase, an enzyme which promotes the conversion of isoleucine-tRNA to isoleucyl-tRNA, resulting in the inhibition of bacterial RNA and protein synthesis. Application of mupirocin ointment to the nares twice daily for five days has shown to eliminate MRSA in 91% of nasal carriers. At four weeks, 87% were still free from MRSA. Data regarding the effect of mupirocin on the post-operative infection rate were provided by Kluymans et al, who found that elimination of the carriage of MRSA in pre-surgical cardiothoracic patients decreased the post-operative surgical infection rate by 60%.

MRSA surgical infections are clinically and financially more costly than non-MRSA infections. An analysis by Engeman et al of 479 patients with deep surgical-site infection from Staph. aureus showed that MRSA patients had a longer hospital stay and a higher hospitalisation charge than those with methicillin-sensitive Staph. aureus (MSSA). In addition, methicillin resistance was independently associated with increased mortality. Roche et al reported that the length of stay in hospital was almost trebled in a series of 318 patients with MRSA undergoing orthopaedic procedures.

Previous MRSA infection at any site is a high risk factor for both persistent colonisation and further MRSA infections. Huang and Platt identified 209 adult patients diagnosed with either colonisation or infection with MRSA over a period of six months. Over a follow-up of 18 months, 30% of colonised patients developed infection from MRSA, with bone and joint infections having the highest rates of recurrence. Patients with underlying chronic skin conditions such as atopic dermatitis and those on haemodialysis had significantly higher colonisation rates with Staph. aureus and MRSA.

**MRSA and orthopaedic surgery.** The increasing number of elderly and trauma patients who require orthopaedic surgery has resulted in an increase in the rates of MRSA infection. The overall infection rate following internal fixation is approximately 5%, with open fractures being disproportionately affected. MRSA produces a biofilm and it is that which predisposes it to cause infections in implants. The bacteria adhere to the implant, become sessile, reduce their metabolic rate, and secrete a glycocalyx layer which protects them from antibiotics, phagocytosis and opsonisation. Biofilm-associated bacteria are up to 100 times more resistant to antibiotics, including vancomycin as demonstrated by marked increases in the minimum inhibitory concentration. MRSA has a large number of surface proteins which facilitate adhesion to foreign bodies. Within a colony, cell-to-cell interactions are mediated by polysaccharide adhesion molecules which confer a quorum-sensing ability, inhibiting further bacterial reproduction once an ideal colony number has been reached. These biofilm-covered colonies then act as a reservoir for MRSA increasing difficulty in eradication, hence the rationale for removing orthopaedic hardware in cases of chronic infection with MRSA.

**MRSA and antibiotics.** The selection of peri-operative antibiotics has been the subject of several investigations. Kalmeijer et al examined 272 patients admitted for elective orthopaedic procedures. They were characterised by age, gender, date of surgery, date of discharge, length of hospitalisation, operating time and the diagnosis of diabetes. The findings in nasal swabs and swabs taken from surgeons were recorded. The MRSA carriage rate was 27%, with an overall infection rate of 6.6%. The only variable predictive of post-operative infection was nasal colonisation with MRSA. In a similar study by the same group, patients requiring internal fixation or metal prostheses received prophylaxis with nasal mupirocin for four days. There was a significant reduction in surgical-site infection rates of MRSA in the treatment group. Wilcox et al also found a decrease in orthopaedic surgical-site infections in patients treated with pre-operative mupirocin.

In 2004, Merrer et al examined the MRSA carriage rate in patients admitted with fractures of the femoral neck. Those admitted from home had an MRSA colonisation rate of 2%, while those admitted from an assisted-care facility had a higher rate at 16%. The authors recommended the use of pre-operative intravenous vancomycin and mupirocin in patients admitted from chronic-care facilities. Sanderson also proposed that a combination of vancomycin and mupirocin should be used in patients with a history of MRSA colonisation or infection, as well as in those who were current carriers. Formal recommendations for the pre-operative use of vancomycin include patients who have a life-threatening allergy to cephalosporins and in residents of institutions in which there is a high rate of MRSA infection. The prophylactic intravenous dose of vancomycin of 15 mg/kg must be given 60 minutes before the skin incision in order to obtain detectable levels in the skin.

Newly-approved antibiotics for use in Europe and the United States against MRSA include intravenous daptomycin. This cyclic lipopeptide has concentration-dependent bactericidal activity. It has broad-spectrum activity against...
Gram-positive organisms, including MRSA. The efficacy of this drug in treating MRSA soft-tissue infections and MRSA osteomyelitis has been demonstrated. However, there is little data regarding the use of daptomycin in the setting of orthopaedic surgical infections, and no randomised controlled trials have been published. Linezolid, an oral oxazolidinone antibiotic which interferes with bacterial ribosomes, has excellent bio-activity and is bacteriostatic against MRSA. Favorable outcomes have been documented with the use of linezolid in treating MRSA orthopaedic infections, although no randomised controlled trials have been performed. Older antibiotics including trimethoprim-sulphamethoxazole, tetracyclines, rifampicin and clindamycin may have activity against certain strains of MRSA. Quinolones, while sometimes seeming to be an option based on sensitivity testing in MRSA, are of limited value in the orthopaedic setting since resistance develops rapidly. Combination therapy with more than one agent (e.g. quinolone + doxycycline + rifampicin) may be considered in unusual cases in which more efficacious therapy is not an option. The removal of hardware is essential to the clearance of MRSA infection.

Because of differences in the resistance of MRSA strains in the United States and the United Kingdom, there are variations in the protocol for antibiotic treatment. In the United Kingdom, tetracyclines may be used in adults with soft-tissue infections unless there is a high risk of the development of endocarditis or bacteraemia. In addition, clindamycin should be strongly considered in MRSA soft-tissue infections in which the bacteria are sensitive to erythromycin. In treating osteomyelitis, glycopeptides can be used in combination or alone, with strong consideration for clindamycin when erythromycin-sensitive variants are present.

**Alternative antibiotic delivery mechanisms.** In order to combat local infection, new methods of antibiotic delivery have been developed. Antibiotic-impregnated cement provides local delivery of the antibiotic without systemic complications. This allows elution of the antibiotic through a cost-effective medium. Bucholz et al began to study this application in Hamburg. Their results gave a success rate of 77% in one-stage revision of infected total hip replacements. The revision surgery used antibiotic-laden cement without systemic antibiotics. Marks, Nelson and Lautenschlager published the first elution studies demonstrating that oxacillin, cefazolin and gentamicin were released in biologically active forms from the cement. In addition, they demonstrated that Palacos cement (Zimmer, Warsaw, Indiana) eluted larger amounts of antibiotics for longer periods of time than Simplex cement (Stryker, Kalamazoo, Michigan) due to the increased pore size.

Several characteristics are required in an antibiotic for effective incorporation into cement as follows: water solubility, heat stability, favourable elution properties, antimicrobial activity against common pathogens and the maintenance of the mechanical integrity of the cement. A number of studies have examined the effect of the common antibiotic-cement combinations. Vancomycin elution can be significantly augmented with the addition of tobramycin to the cement. Masri, Duncan and Beauchamp demonstrated the elution characteristics using the prosthesis of antibiotic-loaded acrylic cement system with a variety of vancomycin and tobramycin antibiotic concentrations. When 3.6 g of tobramycin was used, the minimum inhibitory concentration was consistently above that for sensitive organisms. The recommended combination of 3.6 g of tobramycin and 1 g of vancomycin with 40 g of cement gave the best elution characteristics. Antibiotics elute from Palacos bone cement in higher concentrations for longer periods than from Simplex P and Sulfix cements (Zimmer). The effect of the antibiotics is very localised, with minimal systemic levels detected. For example, 3.6 g of tobramycin in 30 g of cement will produce serum levels lower than 3 ml/l. There has only been one documented case of renal failure attributed to a low-dose gentamicin Palacos spacer. Additional studies have shown that certain preparations can have deleterious effects on the cement mantle. Lyophilised vancomycin greatly reduces the number of cycles to failure of Simplex cement. In addition, liquid antibiotics should not be added to the cement.

Antibiotic-laden cement should be prepared according to its use. Low-dose antibiotic cement (1 g to 2 g of antibiotic/40 g of cement) should be used for prophylactic purposes. Higher doses (> 2 g/40 g) are used for therapeutic applications such as in beads and spacers. The addition of over 4.5 g of antibiotic per 40 g of cement weakens the bone cement and should not be used for the fixation of prostheses.

Clinical studies have demonstrated the advantages of using antibiotic-laden cement. In one study Chiu et al randomised 340 primary total knee replacements into two groups. One group received 2 g of cefuroxime in 40 g of Simplex cement while the other had Simplex alone. At a mean follow-up of 49 months there was a significant difference in the deep infection rate (0% vs 3.1%, p = 0.02). Furthermore, a retrospective review of over 10 000 hip replacements by Espehau et al showed that the use of systemic antibiotics in combination with antibiotic-laden cement gave the highest medium-term survival.

Once the antibiotics have eluted from the cement, the cement surface becomes available for formation of the biofilm. One alternative to this problem is the use of biodegradable protein-derived materials such as gelatin, albumin, and antibiotic-laden type-1 collagen sponges. Preliminary data suggest that there is therapeutic elution for only 48 hours with these devices. The use of calcium sulphate is another alternative; however, it releases 58% of its antibiotic within the first 24 hours and can lead to the formation of a seroma during its absorption. The use of morsellised bone graft is also an option since it can effectively absorb both vancomycin and tobramycin and continues to elute these substances for over three weeks.
Treatment of MRSA implant infections. The goal in the management of MRSA infections is successful eradication of the infection and an optimal outcome for the patient. This is usually accomplished by surgical debridement and treatment with antibiotics. When dealing with joint replacement, the traditional approach is a two-stage exchange of the implant with concurrent antibiotic therapy. For those patients unable or unwilling to undergo further surgery, lifelong suppressive antibiotic therapy is another option in which the infection is suppressed below the level of overt clinical symptoms. This approach does not eliminate the infection itself.

In the setting of an infected fracture, the treatment goals are healing of the fracture, optimal rehabilitation and the prevention of chronic osteomyelitis. The implants may have to remain in place while antibiotics suppress infection, until the fracture has healed. At that point, the implanted hardware is generally removed to allow systemic antibiotics to eradicate the infection effectively.

Infection control effectiveness. Simple measures have been very effective in decreasing the spread of MRSA. Finland and Denmark, have prevalence of MRSA of 1%, one of the lowest among developed nations. This low rate may be due to a strict national policy for screening patients to detect colonisation, the use of strict barrier precautions, and cohort nursing. Johnston et al. studied the effect of the segregation of patients. In their study, the first ward consisted of general orthopaedic patients and those at low risk for MRSA colonisation. The control ward had general orthopaedic patients and general surgery patients and no specific segregation policy was used. There was a significant difference in the incidence of new MRSA cases between the segregated and mixed wards. Bianet al. demonstrated similar results of such segregation policies. Until 1998, all of the elective orthopaedic procedures in their institution were performed in a freestanding orthopaedic hospital. All surgical procedures were then centralised into a regional medical centre with a concordant increase in the number of orthopaedic infections. A policy was then instituted in which patients undergoing elective orthopaedic procedures were housed in a separate ward which excluded trauma patients and those who had been admitted from outside care facilities. Over two years, there was a significant difference in the infection rate in those undergoing elective joint replacement when segregated from patients at high risk for MRSA carriage. Others have reported in the incidence of MRSA in orthopaedic and trauma patients following the introduction of a hospital-based policy to deal with MRSA.

Conclusions

Community- and healthcare-acquired MRSA are different organisms. Each affects different patient populations, produces distinct infections and requires unique treatment. There is strong evidence that MRSA colonisation correlates with a higher rate of MRSA infection. Colonisation elimination strategies are effective and may lower post-operative infections when coupled with targeted peri-operative antibiotic prophylaxis. In addition, evidence supports the separation of patients who are potential carriers from those who are at a lower risk of carriage as an effective strategy of the prevention of infection. Antibiotic-laden cement may be used in both the prophylaxis against infection as well as in its treatment. Additional studies are needed to determine the best strategies for the prevention of infection and the treatment of MRSA in sports medicine and in orthopaedic settings.

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References

9. Lindenmayer JM, Schoenfeld S, O’Grady R, Carney JK. Methicillin-resistant Staphylococcus aureus in a high school wrestling team and the surrounding community.
Nasal carriage of Staphylococcus aureus is a major risk factor for surgical site infections. Chemotherapeutic strategies targeting Staphylococcus aureus biofilm formation and antimicrobial susceptibility are currently under investigation. A randomized, placebo-controlled study has shown that mupirocin nasal ointment can reduce the incidence of methicillin-resistant Staphylococcus aureus (MRSA) orthopaedic surgical site infections.

Infections associated with orthopedic implants, such as total hip replacement, have been a concern. The use of perioperative mupirocin to prevent methicillin-resistant Staphylococcus aureus (MRSA) patient exposure by infection control measures has been studied. Cefuroxime-impregnated cement in primary total knee arthroplasty: a prospective, randomized study of three hundred and forty knees has shown promising results. Use of antibiotic-impregnated cement in total joint arthroplasty has been investigated.
