Preoperative Decolonization of Methicillin-resistant *Staphylococcus aureus*

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Screening should be considered for patients who are at high risk of being MRSA carriers and for those who are undergoing high-risk procedures such as prosthetic implantion.

Staphylococcus aureus penicillin resistance was first identified in 1944, and by the 1950s the first studies began to suggest a relationship between nasal carriage of *S aureus* and surgical site infections.[1] In fact, patients with *Staphylococcus* in their anterior nares are 2 to 9 times more likely to develop surgical site infections than non-carriers,[2,3] and for the first time in 1999, the Centers for Disease Control and Prevention (CDC) listed preoperative nasal carriage of *S aureus* as a risk factor for surgical site infection.[4] Even infections from elective procedures may be catastrophic, leading to further surgery, loss of the prosthesis, disability, and risk of mortality.[5] No general consensus exists concerning the optimal preoperative decolonization and/or prophylaxis of patients who are colonized with antibiotic resistance pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA).

The increasing rate of multi-drug resistant organisms is emerging as a public health crisis. In particular, MRSA increased from 2% of the total *S aureus* isolates reported to the CDC National Nosocomial Infections Surveillance System in 1975 to 57.1% in 2002. The trend continued with the number of reported MRSA infections up 13% from the previous 5-year period (1997-2001).[6]

A recent investigation conducted by the Association for Professionals in Infection and Epidemiology (APIC) showed that 46 out of every 1000 patients were either infected or colonized with MRSA. This rate is between 8 and 11 times greater than the previous MRSA estimates.[7] While MRSA infection rates in certain institutions and countries vary, the increasing acknowledgement of community-acquired MRSA and current antibiotic-prescribing trends make MRSA and potentially vancomycin-resistant *S aureus* a growing concern for the orthopedist.

Staphylococcus aureus is ubiquitous. It can easily be recovered from human skin and mucous membranes. Methicillin-resistant is a variant of *S aureus* that is resistant to all beta-lactam antibiotics (including penicillins and cephalosporins); by definition, MRSA must be resistant to methicillin, oxacillin, or nafcillin. The bacteria may also be resistant to aminoglycosides, erythromycin, quinolones and others. Studies involving dialysis patients, long-term care patients, and postoperative patients in the surgical intensive care unit report that patients colonized with MRSA were at increased risk for the development of *S aureus* infections when compared to methicillin-susceptible *S aureus* carriers.[8-10]

Advanced age, prolonged hospitalization, invasive procedures, and prior antibiotic therapy have all been listed as risk factors for the development of postoperative infection.[11] With the additional risk of MRSA colonization, surgical site infection becomes a dangerous and expensive possibility, especially for prosthetic implants that may require subsequent removal.

While *S aureus* located in the anterior nares has mostly been studied, colonization may occur in the axilla, a chronic wound or decubitus ulcer surface, perineum, around a gas-

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trostomy and tracheostomy site, or sputum. Most studies have shown that between 25% to 30% of the general population carry methicillin-susceptible *S aureus* in their anterior nares. The prevalence of MRSA colonization is not well documented[1] although a Welsh study reported MRSA colonization rates to be as high as 5.3% on orthopedic and surgical wards.[12]

SCREENING

Current guidelines recommend screening for *S aureus* colonization in only a limited patient population. Risk factors for community-based MRSA colonization that may warrant pre-surgical screening include: recent hospitalization within the past 24 months, current prolonged hospitalization, advanced age, outpatient visit within the past 12 months, nursing home admission within the past 12 months, antibiotic exposure within the past 12 months, severity of underlying disease, intravenous drug use, a history of invasive procedures, and close contact with a person who has any of the above risk factors.[13,14]

While current protocols for preoperative antibiotic prophylaxis, infection control policies, improved antisepsis, better surgical techniques, and postoperative wound care have improved surgical site infection outcomes, the continued overuse and misuse of antibiotics have kept postoperative infections an important issue for surgeons.

The focus of surgical site infections is on those patients with infections in the following situations: lengthy preoperative hospitalizations that may have an increased risk of acquiring resistant nosocomial organisms; trauma and elective surgeries affected by community-acquired resistant organisms; and active infections or colonization distant from the surgical site that have increased the incidence of surgical site infection.[15] In such instances, an appropriate decolonization regimen may be used to reduce or prevent the prevalence of surgical site infection.

DECOLONIZATION

The decolonization of MRSA in carriers has proven to be difficult. During the past 60 years, >40 different decolonization regimens have been tested (some are described in the Table), including the use of systemic antimicrobials, normal bacterial flora augmentation, antiseptic washes, and topical antimicrobials.[11,16-18] Because of their limited ability to penetrate the nasal epithelium, resistance of the organism, side effects of the medications, and the quickness of recolonization of the nares, oral antimicrobials have had limited success.

Rifampin (Rifadin; Sanofi Aventis, Bridgewater, New Jersey) suppresses RNA synthesis in susceptible bacteria.[19] While this mechanism of action is shared with other antibiotics, many studies have shown that rifampin is the most active agent for *S aureus* eradication.[20] This can be partially explained by the fact that the nose is the most important site for carriage and rifampin has better nasal penetration than most other antibiotics.[21] However, antimicrobial resistance may occur during and even after treatment with rifampin alone in a significant amount of patients; therefore, using other antibiotics (oral or topical) in combinations may decrease the probability of resistance.

Tetracyclines inhibit protein synthesis and are bacteriostatic. This class of antibiotics has good activity against MRSA, desirable pharmacokinetic properties, easy dosing schedules and few side effects.[22] Studies have shown that no statistically significant difference exists in the eradication of MRSA carriage between rifampin monotherapy and combinations of rifampin with other antimicrobial agents, including tetracyclines.[20] However, using combination therapy with a tetracycline may decrease the likelihood of developing resistance to rifampin.

Trimethoprim/sulfamethoxazole (Septra; GlaxoSmithKline, Philadelphia, Pennsylvania and Bactrim; Roche, Nutley, New Jersey) has excellent bactericidal activity against susceptible MRSA.[23] Both trimethoprim and sulfamethoxazole interfere with bacterial folic acid synthesis. Previous data suggest that trimethoprim/sulfamethoxazole may decrease the number of MRSA-colonized patients, but may not permanently eradicate the MRSA carrier state.[24] Trimethoprim/sulfamethoxazole typically is reserved for susceptible staphylococcal infections, including community-acquired MRSA.

Ciprofloxacin (Cipro; Bayer Pharmaceuticals, Wayne, New Jersey) is bactericidal and its mode of action depends on blocking bacterial DNA replication. It has been used in the past because it is able to achieve high concentrations in the sweat and may persist in the axilla and nostril for several weeks.[25] Most isolates of methicillin-susceptible *S aureus* are susceptible to ciprofloxacin, however its use has fallen out of favor because of the selection of MRSA, which is almost entirely resistant to the fluoroquinolones.[26]

Local agents as treatment options seem to be the most promising because of their ease in application, ability to deliver high drug amounts to the affected area, and effectiveness over long periods of time.[1,2,27,28] Of these topical intranasal applications, mupirocin ointment (Bactroban Nasal, GlaxoSmithKline) has proven to be the most effective.[29]

Mupirocin has a unique mechanism of action in which it blocks protein synthesis in bacteria. Because this mechanism of action is not shared with any other antibiotic, mupirocin has few problems of antibiotic cross-resistance. Mupirocin demonstrated the ability to eliminate 97% of *S aureus* nasal carriage in health care workers within 24 hours of application.[30]

A prospective, randomized, placebo-controlled clinical tri-

al reported in the *New England Journal of Medicine* in 2002 showed that the use of intranasal mupirocin in patients who had *S aureus* in their anterior nares did not significantly reduce the rate of surgical site infection from *Staphylococcus* but significantly decreased the rate of other nosocomial *S aureus* infections.[31] Conversely, a meta-analysis from 2005 concluded that preoperative intranasal mupirocin appears to decrease the incidence of surgical site infection when used as prophylaxis in nongeneral surgery, including orthopedic surgery.[32]

Table

Selected Preoperative Methicillin-Resistant *Staphylococcus aureus* Decolonization Regimens

Drug	Regimen[a]	Common Side Effects	Notes
Chlorhexidine (2%)	Daily topical wash for 3-7 days[b]	Skin irritation	Available over-the-counter
Doxycycline	100 mg twice a day for 7 days[b]	Photosensitivity, gastrointestinal distress	• Avoid in children aged <8 years • Caution in hepatic impairment
Mupirocin	1 cm applied to nares 2-3 times per day for 5-7 days[b]	Burning, pruritus, dry skin, eythema	Avoid long term use
Povidone-iodine (5%)	Topically 4 times per day for 5 days	Skin irritation	Available over-the-counter
Rifampin	300 mg twice per day for 7 days[b]	Reddish-orange discoloration of urine, stools, sweat, saliva, or tears	• Adjust dose for renal impairment • Avoid in hepatic impairment • Numerous drug interactions

[a]*Regimen should be complete prior to surgical procedure.*
[b]*Combination therapy for complete eradication up to 3 months.*

The current recommended regimen includes the application of 2% mupirocin calcium ointment to the anterior nares 2 to 3 times a day for 5 days. A follow-up nasal swab culture performed ⩾1 weeks after decolonization therapy is useful since nasal colonization will not be successfully eradicated in all patients. Those with wounds, ulcers, or tracheostomy sites colonized by MRSA are not as likely to respond to this 5-day topical intranasal therapy.[33]

Another potential therapeutic agent is retapamulin (Altabax; GlaxoSmithKline), a new, novel pleuromutilin antibacterial developed for topical use. However, retapamulin lacks data confirming its application in the decolonization of MRSA.

Chlorhexidine (Hibiclens; GC America, Alsip, Illinois) strongly adsorbs to bacterial membranes, causing leakage of small molecules and precipitation of cytoplasmic proteins. Chlorhexidine is thus bactericidal on contact and has the advantage of producing a residual antibacterial effect.[34] In fact, the decreasing prevalence of nasal carriage of MRSA that has been observed from patients in the intensive care unit[35] may be attributed to treatment with mupirocin nasal ointment and chlorhexidine baths.

Povidone-iodine (Betadine; Purdue Pharma, Stamford, Connecticut) acts by destroying microbial protein and DNA. The mechanism of action of iodine is diverse, which may explain why bacterial resistance has not been apparent. Results suggest that povidone-iodine may be a possible alternative to mupirocin for the elimination of nasal carriage of *S aureus* and may have a role in the prevention of colonization and infection caused by MRSA, including mupirocin-resistant strains.[32]

Bacitracin (Baciguent; Johnson & Johnson, New Brunswick, New Jersey) interferes with the bacterial cell wall synthesis.[36] In one investigation, bacitracin ointment was ineffective in eliminating *S aureus* from the anterior nares and had a post-treatment carrier rate equal to the control rate.[37] Because of its lack of efficacy, bacitracin should no longer be considered for MRSA decolonization.

The decolonization of MRSA from those orthopedic patients with decubitus ulcers or other chronic wounds is more difficult, and the actual benefit of eradication of the carrier state is controversial. Low and even high-level mupirocin-resistant strains of MRSA have been associated with decolonization protocols exceeding a 10-day course.[38-40] Furthermore, intranasal application of mupirocin has limited effectiveness in eradicating colonization even with prolonged regimens in patients who carry the organism at multiple body sites.[17]

Because decolonization has virtually always been used in combination with other control measures, its efficacy has been difficult to determine. Furthermore, even with existing infection control standards, the outcomes are debated. However, a recent open-label, randomized controlled trial reported in *Clinical Infectious Diseases* showed treatment with topical mupirocin, chlorhexidine gluconate washes, oral rifampin, and doxycycline for 7 days was safe and effective in eradicating MRSA colonization in hospitalized patients

THE BOTTOM LINE

- No general consensus exists concerning the optimal preoperative decolonization.
- Patients with *Staphylococcus* in their anterior nares are 2 to 9 times more likely to develop surgical site infection than noncarriers.
- Decolonization protocols may be beneficial and cost-effective in certain patient populations such as patients who are immunocompromised, have had a recent admission to a hospital or nursing home, had antibiotic exposure within the past 12 months, have a history of invasive procedures, and/or had close contact with a person who has any of the above risk factors.

for at least 3 months.[41] This is the first study demonstrating a decolonization regimen that has long-term eradication of MRSA.

COST

In addition to ensuring product efficacy, clinicians should consider the overarching financial impact of MRSA infections and decolonization/treatment options. The cost-effectiveness of using intranasal mupirocin has been evaluated in multiple studies.

A study in 1996 estimated that >$16,000 would be saved per surgical site infection prevented when intranasal mupirocin ointment was used prior to surgery.[42] Other studies not involving surgical patients value the savings to Medicare of $784,000 to $1.117 million per 1000 hemodialysis patients annually if mupirocin prophylaxis were implemented.[43] The estimated savings per patient screened or treated in conjunction with nonemergent surgery requiring postoperative hospitalization[44] was $102 and $88 respectively.

RECOMMENDATIONS

Although the goal of decolonization is the elimination of the MRSA carrier state to decrease the morbidity associated with subsequent *S aureus* infections and potential antibiotic toxicities, its value in the general orthopedic patient remains contested. The answer is more obvious if the patient is immunosuppressed and colonized or has had a history of repeated infections caused by the MRSA strain with which they are colonized.

Considerable benefit exists with the use of mupirocin in reducing nasal colonization and subsequent systemic infections with *S aureus*. Instead of committing each patient to the decolonization protocol, the orthopedist should assess each unique situation based on clinical and laboratory evidence to avoid the expense of the decolonization protocol as well as the excess use of mupirocin and the ensuing development of resistance.

While debate exists in the literature regarding the benefits of routine decolonization protocols in preventing surgical site infection and postoperative nosocomial infections, screening should be considered for patients who are at high risk of being MRSA carriers and for those who are undergoing high-risk procedures such as prosthetic implantation.[10]

Currently, many orthopedic procedures are unscheduled and the time required for the incubation of cultures before decolonization with mupirocin is started makes such a protocol impractical. The development of rapid diagnostics to more rapidly identify *S aureus* is needed before the surgeon will see maximum benefits with mupirocin prophylaxis or a decolonization regimen. However, the patient who is undergoing an elective surgery and has at least one risk factor for colonization should be considered for mupirocin therapy alone or in combination with an effective oral antimicrobial.

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