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Resistant Organisms in Infected Total Knee Arthroplasty: Occurrence, Prevention, and Treatment Regimens

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Abstract

Infection of a primary joint arthroplasty can be a life-changing event for a patient. When the infecting organism demonstrates antibiotic resistance, treatment can be prolonged, and the chances for a successful outcome may be decreased. Antibiotic resistance has been an evolutionary process since the introduction of pharmacologic treatment and until recently has been more problematic with nosocomial types of infections. Methicillin-resistant Staphylococcus aureus skin infections within the community among school or sports teams has been a recent cause for concern. Hospitals have implemented screening and/or isolation procedures to reduce the risk of spreading these resistant organisms and identify patients colonized with resistant organisms. These measures have been successful in patients undergoing total joint arthroplasty. It is important for the orthopaedic surgeon to be knowledgeable about the emergence of resistant bacteria, preoperative and intraoperative screening guidelines, and postoperative considerations to prevent resistant organism infections in total joint arthroplasty patients.

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Periprosthetic joint infection is a rare yet challenging complication of total joint arthroplasty.[1] The treatment of this condition imparts an immense economic and social burden.[2-4] This complication may occur at a rate of 1.5% to 2.5% after primary hip or knee arthroplasty and is associated with marked morbidity and mortality.[5-7] The treatment strategy for periprosthetic joint infection currently relies on the delivery of local and systemic antibiotics directed against the infecting organism. The type and the antibiotic sensitivity of the infecting organism are known to influence the outcome for the treatment of periprosthetic joint infection.[4-6] Periprosthetic infections caused by organisms resistant to antibiotics have a less optimal outcome than those caused by antibiotic-sensitive organisms.[4]

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Most periprosthetic joint infections are caused by gram-positive organisms, with *Staphylococcus aureus* and *Staphylococcus epidermidis* infections occurring most often.[2,8] *S aureus* has gained notoriety for its resistance to antibiotics in nosocomial as well as community-acquired infection over the past years. This finding has led the medical community to target patients who are colonized with resistant organisms and initiate policies to decrease the spread of these organisms.

A study of antimicrobial susceptibility of *S aureus* isolated from superficial skin and wound infections over a 2-year period from 2005 to 2007 revealed that 57.8% of these cases were methicillin resistant, with little difference in numbers between community- and hospital-acquired infections.[9] It has been shown that younger patients tend to have clindamycin resistance, whereas the elderly population has higher rates of ciprofloxacin resistance. This finding is attributable to the use of these antibiotics in these age groups. Only trimethoprim/sulfamethoxazole, gentamicin, and linezolid exhibited susceptibility rates greater than 95%.[9]

The incidence of nosocomial infections caused by methicillin-resistant *S aureus* (MRSA) has been on the rise since the first strains were reported in 1960 in London.[10] In US hospitals, the percentage of MRSA-associated nosocomial infections rose from 2.4% in 1975 to 29% in 1991, and the incidence of methicillin-resistant coagulase-negative staphylococci infections increased from 20% in 1980 to 60% in 1989.[11-13] The liberal use of wide-spectrum antibiotics; an increase in the use of hemodynamic and other invasive monitoring devices, which violate natural barriers to bacterial invasion and act as conduits; and the rise in the number of surviving immunocompromised patients are some of the important contributors to the rise in the incidence of methicillin-resistant pathogens.[14,15] The resistance of *S aureus* to methicillin has been attributed to a plasmid transfer and the presence of the *mecA* gene in the *Staphylococcus* organism. The genetic profiling of these bacteria has been helpful in determining their origins of resistance.[16]

There have been a significant number of reported outbreaks of MRSA acquired in the community. These organisms have been reported in prison populations as well as sports teams and usually manifest as skin infections.[17] Other organisms continue to adapt and show resistance, even though MRSA has received the most publicity over the past few years. The rise in the incidence of infections with vancomycin-resistant enterococcus (VRE) is another example of this worrisome trend.[18]

The emergence of the resistant organisms in the community and hospitals has unfortunately translated to a higher incidence of periprosthetic joint infection caused by resistant organisms, at least at some institutions.[4,19-23] The main pathogens causing periprosthetic joint infection currently are methicillin-resistant strains. The increase in the number of infections caused by methicillin-resistant organisms could potentially compromise the success of current treatment of this condition.

The Rise of Resistant Organisms

The cause of the rise in the incidence and the spread of periprosthetic joint infection caused by methicillin-resistant organisms is being questioned. The number of individuals colonized with methicillin-resistant organisms in hospitals and also in the general population has been steadily increasing.[7,13,24] A recent study found that more than 50% of isolates of *Staphylococcus* in the United States are now resistant to methicillin.[9] *S epidermidis* is now the single most common cause (50% to 75%) of intravenous catheter-related infections in the United States, regardless of the nature of the catheter.[25] Colonized patients are the chief source of MRSA in hospitals.[15,24] The colonized patients and personnel serve as endogenous reservoirs for the transfer of these pathogens to other individuals who may be colonized and/or develop overt infections. A recent study found that between 10% and 40% of individuals tested at outpatient offices or on admission to the hospital have nasal carriage of MRSA.[13] Nasal carriage of resistant organisms is known to be a major risk factor for surgical-site infections based on published guidelines of the Centers for Disease Control and Prevention.[15,24]

There are other potential contributors to the rise in the incidence of resistant organisms. Although difficult to prove, the liberal use of antibiotics in the community in general, and in orthopaedic practice in particular, is one such factor that has led to the emergence of resistant organisms. The liberal use of antibiotics accounts for the change in antibiotic resistance of pathogens; effective action should be taken to reverse this trend or halt its progression.[26]

There are many measures that the medical community can implement to prevent the spread of resistant organisms and infections caused by these pathogens.[17,23] Simple measures such as regular hand washing, the use of disposable gloves, isolation of infected or colonized patients, and administration of appropriate perioperative prophylactic antibiotics are some examples of such strategies. Decolonization strategies are also being actively investigated. Trimethoprim/sulfamethoxazole and mupirocin nasal ointment have been used with variable success.[21,25,27,28] In addition, the medical community needs to restrict the use of antibiotics, in particular broad-spectrum antibiotics such as ciprofloxacin, ceftazidime, and imipenem that are known to increase the prevalence of MRSA.[13]

Despite these preventive measures, the incidence of resistant organisms in periprosthetic joint infection may escalate exponentially as the number of knee arthroplasties performed each year increases. Periprosthetic infections in general and those caused by methicillin-resistant organisms will continue to pose serious epidemiologic, therapeutic, and economic challenges and may soon be the focus of attention in many US hospitals.[9]

Preventive Screening Measures

The use of nasal swabs is a well-known method to screen patients for organisms. In recent years, various investigators have reported the positive influence of preoperative screening in decreasing periprosthetic joint infection caused by resistant organisms.[25] In the study reported by Wilcox and associates,[25] patients were screened for MRSA with nasal swabs; if positive for MRSA, mupirocin was administered nasally for 5 days, and the patient bathed or showered with 2% triclosan the night before surgery. That study reported a decrease in MRSA surgical-site infection from 23 per 1,000 cases over a 6-month period during which the screening was not used to 3.3 and 4 per 1,000 cases for the next two consecutive 6-month intervals, respectively. Sankar and associates[21] reported on the use of MRSA swab cultures of the nares, axilla, and groin in total hip and knee arthroplasty patient populations. If any swab was positive, the patients were treated until repeat cultures were negative. Patients with positive screening tests were not allowed in the orthopaedic ward during this time interval. The comparison group used in their study was 395 patients (210 total knee arthroplasties [TKAs] and 185 total hip arthroplasties) over the previous year before institution of the swab screening. They found that there were no MRSA infections during the screening period, compared with four infections before screening. There was also a significantly shorter length of stay after the screening process was instituted. These screening procedures appear to have positive results and, after further evaluation, may need to be implemented in both tertiary and community hospitals.

Various hospitals have now implemented isolation procedures for patients who are found to be positive for MRSA based on rectal, groin, superficial wound, or nasal swabs. In many instances, these patients are kept in the same ward or adjacent rooms on a hospital floor. There is little evidence to date that these protective procedures used for treating colonized, noninfected patients are decreasing the spread or a ward's risk of acquiring surgical-site infection in elective total joint arthroplasty patients. However, a previous study of 100 consecutive patients undergoing a primary hip or knee replacement in English hospitals found that drain tips or wound swabs did not culture positive for MRSA despite the presence of 33 patients on the ward with confirmed MRSA infection.[27] The authors of this study implicated strict ward isolation protocols as the main reason for reducing the spread of infections.[27] "Ring fencing" of the wards also has been shown to decrease the incidence of MRSA infection in total joint arthroplasty patients.[28] This practice involves placing all prescreened and MRSA-positive patients in the ring-fenced side of the ward. This practice, along with strict preventive precautions issued to staff and visitors, decreases the spread of resistant organisms.[28]

The Changing Profile of Periprosthetic Joint Infections

The rise in the incidence of infections caused by resistant organisms is a worldwide event. Struelens[29] reported on the prevalence of resistant organisms in hospital-acquired infections in Europe. This study demonstrated that the incidence of intensive care unit– and hospital-acquired infections was highest in Germany, Belgium, France, and Italy (United Kingdom not reported).[29] In these countries, 30% to 80% of intensive care unit–acquired infections were MRSA, whereas the rate for hospital-acquired MRSA infections was 5% to 27%. Ip and associates[30] reported on organism profiles in bacterial infections of total joint arthroplasties in Hong Kong. They reviewed a consecutive series of patients from 1995 to 2003 with an infected total joint arthroplasty. During the first 2 years of the study, there were no infections by MRSA or other antibiotic-resistant organisms. There were, however, 11 MRSA infections in the last few years of

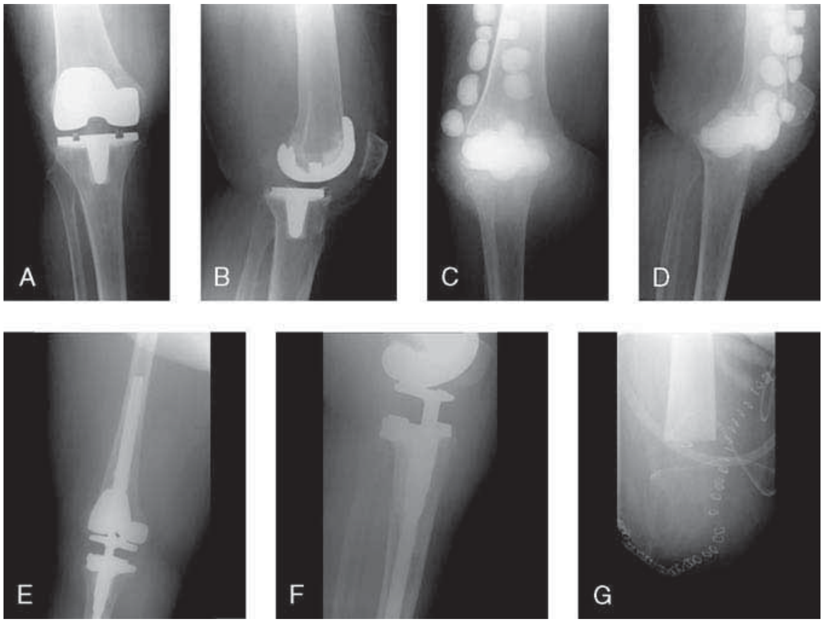

Figure 1 A 69-year-old woman who had a successful primary TKA 6 years ago from an outside facility now is experiencing pain after a bariatric procedure. A VRE hematogenous infection was diagnosed; the patient was treated with intravenous antibiotics for 6 months after a cement spacer was placed with beads. During her stage II procedure (stage I, resection arthroplasty with insertion of an antibiotic-laden cement spacer supplemented with 6 weeks of intravenous antibiotics; stage II, delayed reimplantation of the prosthesis), a frozen section revealed less than 5 cells per high-power field, so the revision TKA was done. She returned with frank pus at 3 months and underwent an above-knee amputation. **A** and **B,** AP and lateral views of the primary TKA. **C** and **D,** AP and lateral views of the resection arthroplasty with insertion of an antibiotic-laden cement spacer and cement beads. **E** and **F,** AP and lateral views of the revision prosthesis. **G,** AP radiograph of the above-knee amputation.

the study. Of the four infections caused by *S epidermidis*, two had multiple drug resistance. Likewise, there were four *Escherichia coli* infections, two of which were resistant to multiple drugs.[30]

Fulkerson and associates[31] reported on the susceptibility of bacteria causing periprosthetic joint infection in 110 hip and 84 knee arthroplasty cases. They found that most of the infections were caused by *S aureus* and *S epidermidis*. Only 61% of the organisms in this study were sensitive to oxacillin.

Recently, 384 periprosthetic joint infection cases treated over a 10-year period at the Rothman Institute were surveyed (J Parvizi and associates, unpublished data presented at the 27th annual meeting of the European Bone and Joint Infection Society, Barcelona, Spain, 2008). A steady increase in the incidence of infections caused by methicillin-resistant *Staphylococcus* species was noted, with the incidence of MRSA increasing from 16% in 1999 to 37% in 2006, and for methicillin-resistant *S epidermidis* (MRSE), from 11% to 25% in 2006. The rise in the incidence of methicillin-resistant periprosthetic joint infection was true for infections at the Rothman Institute and those being referred to that center. Although the number of periprosthetic joint infection cases being referred to that institution had increased over the last few years, the proportion of periprosthetic joint infection with methicillin-resistant organisms had increased severalfold. Methicillin-resistant organisms (MRSA, MRSE) were found to be the most dominant infecting organisms over the last 3 years. The incidence of periprosthetic joint infection caused by methicillin-resistant organisms had surpassed those caused by methicillin-sensitive pathogens. In 1999, 27% of all the *S aureus* and *S epidermidis* species causing periprosthetic joint infection were methicillin resistant. The incidence of periprosthetic joint infection caused by methicillin-resistant organisms had increased to 55% by 2005 and 62% by 2006. VRE was identified in five cases (1.3%) during the years of study, with one case noted in each year. The outcome of these infections can be life changing for many patients, with a higher incidence of a poor outcome (Figure 1).

These recent reports highlight some important, and perhaps worrisome, findings. It appears that the incidence of periprosthetic joint infection caused by methicillin-resistant organisms is increasing. Although we believe that the trend observed at our institution is likely to be mirrored in other places, a larger database reporting such findings would have been ideal.

Operating Room Practices to Prevent Resistant Organism Infections in Primary TKAs

New pay-for-performance guidelines are being implemented by the Centers for Medicare and Medicaid Services such that prophylactic antibiotics are given within 1 hour before the start of TKA. The antibiotic to use, however, is often in question, especially among higher-risk patients. In general, the use of a first-generation cephalosporin is recommended. However, for those patients who are institutionalized or at higher risk from comorbidities such as diabetes or immunocompromised patients on prednisone, a broader-spectrum approach may be considered. The addition of gentamicin to the intravenous prophylaxis can add broader coverage, including gram-negative coverage, in these patients. It is also wise for all surgeons to investigate the profile of organisms within their own hospitals. This practice can aid in targeting known offending organisms within a community instead of acting solely on national standard recommendations. Again, the surgeon must be knowledgeable in the use of antibiotics and customize the approach for individual high-risk patients so as not to promote resistance in settings where the benefits may not be realized.

There seems to be a rising trend in the United States and Europe to use antibiotics in cemented primary TKAs. In Europe, the predominant antibiotic is gentamicin; in the United States, tobramycin is used more often. In a randomized prospective clinical trial of 340 primary TKAs, Chiu and associates[32] compared the infection rates for patients who used cefuroxime bone cement (178 knees) with standard bone cement (162 knees). Significant reduction in deep infections was noted with the use of antibiotic bone cement ($P = 0.023$). Chiu and associates[33] conducted a second clinical trial on 78 diabetic patients treated with TKA for osteoarthritis of the knee. In this high-risk patient population, cefuroxime bone cement was used in group 1 (41 knees) and standard bone cement in group 2 (37 knees). There were no instances of deep infection in group 1, but this complication occurred in five knees (13.5%) in group 2 ($P = 0.021$). The possible drawbacks of the regular use of antibiotic-loaded bone cement may include an increased emergence of antibiotic-resistant organisms, increased possibility of an allergic reaction, and possible systemic toxicity.[34] This generates debate as to whether the use of antibiotics for cemented primary TKAs is appropriate standard treatment or whether antibiotic cement should be reserved for those patients with higher comorbid conditions such as diabetes or who are otherwise immunocompromised.[34-36]

Treatment and Outcome of TKA Infected With Resistant Organisms

Irrigation and débridement and exchange of modular parts, single-stage exchange arthroplasty, and two-stage exchange arthroplasty are common modes of treatment. Currently, two-stage exchange arthroplasty continues to be the main treatment strategy for periprosthetic joint infection in North America. This strategy involves removal of the infected prosthesis, placement of antibiotic-impregnated cement spacers, and delayed reimplantation.[37] Two-stage exchange arthroplasty is used for all periprosthetic joint infections, including those caused by resistant organisms. An important question is whether the treatment of infections caused by multiresistant organisms should differ from infections caused by all-sensitive pathogens. For example, should patients with MRSA infections have a more prolonged antibiotic treatment and should reimplantation be delayed further in these patients?[38] There are few or no data in the literature to guide surgeons in determining the optimal period of antibiotic treatment and the time to reimplantation. The period of time from resection arthroplasty to reimplantation appears to be quite variable in the literature, with a minimum of 6 weeks.[38-40]

Another issue is whether the type of infecting organism should influence the decision-making process for the treatment of acute periprosthetic joint infections that may be amenable to irrigation and débridement with retention of the prosthesis. Hartmann and associates[41] reported on 33 infected knee arthroplasties treated with irrigation, débridement, and intravenous antibiotics. Retrospective average follow-up was 4.5 years. There were 12 revisions and 21 primary arthroplasties. Thirty-two knees were treated with open irrigation and débridement, and one was treated arthroscopically. The reinfection rate was 61%. There was a statistically significant improvement in the success rate of knees irrigated and débrided within 4 weeks of the index surgery ($P = 0.05$). No statistically significant correlation was found between success and failure with regard to gender, age, preoperative diagnosis, previous surgery, length of intravenous antibiotics, or time from clinical symptoms to débridement. The analysis of the data from the Rothman Institute on 104 patients treated with irrigation and débridement of infected TKAs found that the failure rate for this treatment strategy was significantly higher when the infecting organism was methicillin resistant. A survey on the outcome of irrigation and débridement of infected TKA performed in five other centers in the United States also demonstrated similar findings (T. Fehring, MD, personal communication, 2007). There is a tendency

Table 1
Available Strategies and Pros and Cons in the Treatment and Prevention of Infections Caused by Resistant Organisms

Strategy	Protocol	Pro	Con	Our Recommendation
Preoperative screening	Treatment with nasal mupirocin for 5 days and shower or bath with 2% triclosan	Efficacy in producing negative cultures May reduce incidence of MRSA infections	Cost Fear factor for patients Little proof that negative cultures are indicative of "eradication" of organism	Insufficient evidence to support its implementation for all patients May be used for patients undergoing complex surgery, those with previous history of MRSA/MRSE, or high-risk patients such as those who are immunocompromised
Prophylactic antibiotics with activity against MRSA/MRSE	Vancomycin (1 g) administered over 1 hour and completed at least 30 minutes before surgery Daptomycin (6 mg/kg)	Effective against resistant organisms Reduces infections by MRSA/MRSE	Cost (particularly the newer antibiotics) Time wastage (vancomycin needs to be administered slowly to prevent red-man syndrome) May cause emergence of resistant organisms such as VRE	We currently recommend vancomycin for patients with: Remote or recent history of MRSA infections Careers involving contact with MRSA Institutionalized patients Proven penicillin allergy Treatment of infections caused by unknown organisms
Antibiotic-impregnated cement	Vancomycin (4 to 6 g per 40-g pack of cement) Gentamycin- or tobramycin-impregnated cement (dose variable)	Reduces incidence of infection based on Scandinavian registry data Reduces reinfection	Cost May cause emergence of resistant organisms	Use antibiotics in cement for high-risk patients (for example, immunocompromised, diabetics) Use high-dose antibiotics in cement for use as a spacer or during reimplantation for periprosthetic joint infection cases
Surgical intervention	Irrigation and débridement with retention of components	Retains prosthesis Less morbidity Avoids period of disability with spacer	Less effective than exchange arthroplasty May prolong period with infection	Reserve for patients who are infirm and frail and who cannot tolerate two-stage exchange arthroplasty Not suitable for compromised hosts
Two-stage exchange arthroplasty	Removal of implants and débridement with insertion of antibiotic spacer followed by delayed reimplantation	Effective strategy for the treatment of periprosthetic joint infection	Cost High morbidity	Should be used for patients with MRSA/MRSE Delay reimplantation until serology is normal and aspiration of antibiotics is negative Have low threshold for doing exchange spacer for patients with abnormal serology Consider suppressive therapy for immunocompromised patients

MRSA = methicillin-resistant *S aureus*, MRSE = methicillin-resistant *S epidermidis*, VRE = vancomycin-resistant enterococcus

among surgeons dealing with periprosthetic joint infection on a regular basis to favor removal of the prosthesis, even in cases of acute infection, when the infecting organism is methicillin resistant.

There is currently little information in the literature to provide guidance in treating periprosthetic joint infection caused by resistant organisms. What appears to be emerging is that the outcome of treatment of periprosthetic joint infection caused by resistant organisms such as MRSA appears to be less optimal than that of infection caused by sensitive organisms.[4,39] In a study of 70 patients with periprosthetic joint infection, with equal numbers of infected hips and knees, the success of two-stage exchange arthroplasty was 48% for hips and 18% for knees when the offending pathogen was methicillin resistant. When the periprosthetic joint infection was caused by methicillin-sensitive organisms, the success rate was 81% for hips and 89% for knees.[4] Volin and associates[40] compared the outcome of two-stage exchange arthroplasty in 46 patients with periprosthetic joint infection caused by resistant and nonresistant pathogens. They found that the failure rate of the procedure was significantly higher (11.1%) when the infecting organism was resistant to antibiotics, compared with 5.4% when the organisms were sensitive to antibiotics.

The high failure rate of the treatment of periprosthetic joint infection caused by resistant organisms also has been our experience. Many of the patients with periprosthetic joint infection caused by MRSA or MRSE have had a much more protracted course and worse outcome at our centers. This underscores the fact that a more stringent treatment strategy should be used when treating infections caused by resistant organisms (Table 1). It is important to implement a series of strategies aimed at reducing the spread of resistant organisms and preventing infections caused by these pathogens (Table 1).

Summary

There appears to be a worrisome trend in the rise of resistant organisms in the community and hospitals, which has translated to an increase in the incidence of periprosthetic infections caused by these antibiotic-resistant organisms. Strict policies and protocols may need to be implemented to prevent the spread of these organisms and deal with these challenging infections when they arise. There is an urgent need for studies evaluating the impact of the rise in the incidence of infections caused by resistant organisms in general and orthopaedic infections in particular.

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