Prophylactic Antibiotics in Hip and Knee Arthroplasty

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Current Concepts Review

Prophylactic Antibiotics in Hip and Knee Arthroplasty

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- Prophylactic parenteral antibiotics have contributed to the present low rate of surgical site infections following hip and knee arthroplasty.
- Over the past decade, there has been a change in the pattern of methicillin-resistant *Staphylococcus aureus* infections from hospital-acquired to community-acquired.
- The findings of recent studies on screening programs to identify carriers of methicillin-resistant *Staphylococcus aureus* have been equivocal, with some studies showing that such programs reduce the rate of infections and others showing no effect on infection rates.
- Hospitals with antibiogram data that reveal high Staphylococcus resistance should consider use of vancomycin as a prophylactic antibiotic.

"Every operation in surgery is an experiment in bacteriology" – Moynihan[1]

Prophylactic antibiotics have been described as antibiotics given for the purpose of preventing infection when infection is not present but the risk of postoperative infection is present[2]. The goal of antimicrobial prophylaxis is to achieve serum and tissue drug levels that exceed, for the duration of the operation, the minimum inhibitory concentration for the organisms likely to be encountered during the operation[3].

While the benefits of preventing surgical infections are apparent, one must also keep in mind the disadvantages of excess antimicrobial use. All infections cannot be prevented by the use of prophylactic antibiotics. Each patient has a unique set of immune defenses against, and risks of, infection. The goal of surgical prophylaxis is to decrease the bacterial burden at the surgical site, not to sterilize the patient. Essentially, prophylaxis augments the host's natural immune defense mechanisms by increasing the amount of bacterial contamination needed to cause an infection.

Use of broad-spectrum antibiotics contributes to the development of multi-drug-resistant organisms. Similar to the rise in penicillin resistance, there has been, in the past decade, a rise in the prevalence of methicillin-resistant *Staphylococcus aureus* surgical site infections[4]. Infections due to resistant organisms are associated with a worse clinical outcome for each individual patient. In addition, the impact on hospital ecology may be detrimental to other patients, potentially leading to increased morbidity and costs. There must be a delicate balance between the use of antimicrobial agents to prevent infection and the overuse of antimicrobial agents, which is associated with the development of multi-drug-resistant organisms. Fortunately, studies done over the past fifty years have helped to provide the foundation for guidelines for appropriate antimicrobial prophylaxis.

Current Infection Rates Associated with Elective Primary Total Hip and Knee Arthroplasty

According to Medicare outcome data from 2003, primary total hip arthroplasty is associated with a ninety-day deep-infection rate of 0.24%[5]. The Surgical Site Infection Surveillance Service in Britain reported an overall infection rate of 2.23% in association with primary total hip arthroplasties; with superficial infections excluded, they reported a 0.23% rate of deep incisional infection (similar to the rate according to U.S. Medicare

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data) and a 0.18% rate of deep joint involvement[6]. The Surgical Site Infection Surveillance Service defines infections as being related to the operation if they occur within one year after the use of an implant and when they appear to be related to the procedure. Medicare outcome data for primary total knee arthroplasty reveal a ninety-day deep-infection rate of 0.4%[7]. Studies of large series of total knee arthroplasties have generally demonstrated rates of up to 2% at one year[8,9]. Most surgeons will therefore accept an average rate of deep infection of between 0.25% and 1.0% at one year after primary hip replacements and between 0.4% and 2% at one year after primary knee replacements[5-9].

Historical Perspective: Investigations of the Role of Prophylactic Antibiotics in General and Orthopaedic Surgery

Tachdjian and Compere, in a retrospective nonrandomized study of 3000 clean orthopaedic operations done with the use of multiple antibiotic protocols, found a more than twofold increase in the rate of infections in patients treated with perioperative antibiotics and therefore recommended against perioperative antibiotic use[10]. Burke was one of the first investigators to scientifically explore an effective period for the administration of perioperative antibiotics[11]. On the basis of experiments with dermal lesions in guinea pigs, he concluded that *Staphylococcus aureus* had a maximal susceptibility to an antibiotic when the antibiotic was present within the tissue before the bacteria were introduced. In 1970, in a study of mold arthroplasties and spinal fusions, Fogelberg et al. compared a group treated prophylactically with penicillin, given preoperatively, intraoperatively, and for five days postoperatively, with a control group not treated with antibiotics[12]. The prevalence of infections was 1.7% (two of 120) in the treated group and 8.9% (ten of 112) in the control group. During the time period of the study, the authors noted an increase in the prevalence of penicillin-resistant *Staphylococcus aureus* in all major orthopaedic wound infections in their hospital from 10% in the first year of the study, to 31% in the second year, and to 60% in the third year. This caveat highlights one of the basic tenets for the prevention of resistant infections; there must be a balance between the use of antibiotics and the avoidance of overuse of antibiotics in the prevention and treatment of infections.

Other Measures to Reduce Infection Rates

Sir John Charnley rigorously documented the results in his patients treated with his low-friction arthroplasty, and he utilized a methodical approach to the reduction of infections associated with this new procedure[13]. He investigated the effects of air contamination and surgical team contamination in the operating room while purposely avoiding the use of prophylactic antibiotics to allow for a study of aseptic technique. Charnley was able to reduce the infection rate associated with hip replacements from 7% (thirteen of 188) in 1960 to 0.5% (six of 1113) in 1970 by taking measures to reduce sources of exogenous infection in the operating room—i.e., clean air technology (laminar flow), reinforcement of surgical gowns, and double gloves.

In a multicenter study, Lidwell et al. followed up on Charnley's work with ultraclean air in the operating room by comparing the effects of conventional and ultraclean-air ventilation on the rate of postoperative infections[14]. The authors reported: "In the patients whose prostheses were inserted in an operating room ventilated by an ultraclean-air system the incidence of joint sepsis confirmed at reoperation within the next one to four years was about half that of patients who had the operation in a conventionally ventilated room at the same hospital." The authors also stated: "When all groups in the trial were considered together the analysis showed deep sepsis after 63 out of 4133 operations in the control group (1.5%) and after 23 out of 3922 operations in the ultraclean-air groups (0.6%)." This study reinforced the belief in the effectiveness of ultraclean air (laminar flow) and whole-body exhaust suits in reducing the prevalence of deep infection in patients treated with arthroplasty. The authors also recognized the large number of procedures needed to show a significant difference given the low rates of infection at the time. Lidwell et al. suggested that ultraclean air and antibiotic prophylaxis had independent and cumulative effects in preventing infections after joint replacement, although this was not directly studied.

Common Causes of Surgical Site Infections in Hip and Knee Arthroplasty

The choice of antibiotics used as prophylaxis requires an understanding of the common microorganisms that cause surgical site infections associated with hip and knee arthroplasties. Wound infections following clean surgical procedures are primarily caused by skin or exogenous airborne microorganisms since other reservoirs of bacteria, such as the gastrointestinal tract, are not entered.

Numerous studies have documented that gram-positive organisms are the most common bacteria causing infections associated with joint arthroplasty, with *Staphylococcus aureus* and *Staphylococcus epidermidis* causing the majority of the infections[5,15-17]. Enterococcus, Streptococcus, and gram-negative organisms such as *Escherichia coli,* Pseudomonas species, and Klebsiella species are less common but have been frequently reported[18]. These microorganisms can all be part of normal skin flora; hence, direct inoculation at the time of the operation as well as airborne contamination are the most likely causes of these infections.

Although *Staphylococcus epidermidis* is generally not considered pathogenic, infections surrounding a joint replacement prosthesis may be more difficult to treat because of the bacterial biofilms typically produced by *Staphylococcus aureus* and *Staphylococcus epidermidis* around orthopaedic implants[19,20]. This glycocalyx layer, which is formed on the surface of the orthopaedic devices, creates a complex environment for the bacteria. Numerous factors, including restricted penetration of antimicrobials into the biofilm, decreased bacterial growth rates, and expression of biofilm-specific resistance genes, all contribute to bacterial and biofilm resistance[21].

Antibiotic treatment can suppress the symptoms of the infection, but eradication usually requires removal of the device and its associated glycocalyx layer[19].

While the patient's endogenous flora is largely held accountable for surgical site infections, surgical team personnel and the operating room environment may also contribute organisms. Hare and Thomas described staphylococcal "dispersers" as people who are *Staphylococcus aureus* carriers and shed the organism in vast numbers[22]. Ritter also recognized the importance of the quantity of people in the operating room as a source of increased bacterial counts[23]. Members of the surgical team who have direct contact with the sterile operating field have been linked to unusual outbreaks. For example, an outbreak of *Serratia marcescens* surgical site infections in patients who had undergone cardiovascular surgery was associated with the use of artificial fingernails[24]. Anesthesia personnel also may play a role in postsurgical infections. Although not directly involved in the operative field, they perform a variety of procedures leading up to the operation. Outbreaks of bloodstream and surgical site infections have been linked to the reuse of propofol vials and other departures from acceptable protocols for anesthesiologists[25].

Properties of a Prophylactic Antibiotic

Bacteriostatic antibiotics limit the growth of bacteria predominantly by interrupting bacterial protein production or by inhibiting precursors in folic acid synthesis and DNA replication. These bacteriostatic agents inhibit the growth and reproduction of bacteria without killing them. Bactericidal antibiotics kill the bacteria. The beta-lactams accomplish this by inhibiting cell wall synthesis and inducing cytolysis[26]. Most of the prophylactic antibiotics used in orthopaedic surgery are categorized as bactericidal. These include the penicillins, the cephalosporins, vancomycin, and the aminoglycosides. Clindamycin, a lincosamide, is considered bacteriostatic. High concentrations of most bacteriostatic agents can be bactericidal, whereas low concentrations of bactericidal agents can be only bacteriostatic[26].

The most important consideration in choosing an antibiotic for prophylaxis is its spectrum of action. While the chosen antibiotic may not cover the entire spectrum of organisms that may be encountered, it must be active against the bacteria that commonly cause postoperative infection. Other factors to consider include the pharmacokinetics and pharmacodynamics of the drug. Specifically, the agent must have a half-life that covers the decisive interval (the first two hours after incision or contamination) with therapeutic tissue concentrations from the time of incision to wound closure. Failure to maintain tissue concentrations of the drug above the minimum inhibitory concentration increases the risk of wound infection[27]. Repeat doses of antibiotics may be necessary if the procedure is long, if multiple transfusions are needed, or if the antibiotic is cleared rapidly[28]. The final consideration should be the cost associated with the use of the antibiotic, which should include the costs of drug monitoring, administration, repeat doses, adverse effects, and failure of prophylaxis (i.e., wound infection sequelae).

Prophylactic Antibiotics in Institutions with Low Bacterial Resistance

According to the Surgical Care Improvement Project (SCIP) Advisory Committee, part of a national initiative to reduce surgical morbidity and mortality by 25% by 2010, and the American Academy of Orthopaedic Surgeons (AAOS), the preferred antimicrobial for patients undergoing total hip or knee arthroplasty is cefazolin or cefuroxime (Fig. 1). The cephalosporins (specifically, cefazolin and cefuroxime) have been the antibiotics of choice for both the prophylaxis and the treatment of orthopaedic infections for at least three decades. Of these, cefazolin has been more extensively studied and used in the United States. Its favorable activity against gram-positive organisms and its effectiveness against most clinically important aerobic gram-negative bacilli and nonbacteroid anaerobes have contributed to its widespread acceptance. In addition, cephalosporins have excellent distribution profiles in bone, synovium, muscle, and hematomas[29]. Studies have documented that minimum bactericidal concentrations for most non-methicillin-resistant *Staphylococcus aureus* organisms are achieved rapidly in these tissues—i.e., within minutes after their administration[30,31].

Anaphylactic reactions to cephalosporins are rare events, but they do occur and thus have led to the recommendation against their use in patients with known anaphylaxis to other beta-lactam antibiotics. Some of the more common reactions include skin rash (a rate of 1% to 5%), eosinophilia (3% to 10%), diarrhea (1% to 10%), and pseudomembranous colitis (<1%)[29]. Clindamycin is currently the preferred alternative antibiotic for persons with an established allergy to a beta-lactam or with a contraindication to its use and at institutions with low rates of methicillin-resistant *Staphylococcus aureus* infection. Clindamycin has good bioavailability, and at thirty minutes after infusion has been shown to exceed the minimum inhibitory concentration for *Staphylococcus aureus* in both animal and human cortical bone samples[32].

The most severe adverse effect of clindamycin is *Clostridium difficile*-associated diarrhea (the most frequent cause of pseudomembranous colitis). While this side effect can occur with numerous antibiotics, it is classically linked to clindamycin use. Other side effects include the development of a rash, abdominal pain, cramps, and in high doses a metallic taste in the mouth.

Dosage of Parenteral Antibiotic Prophylaxis

The recommended dose of cefazolin is based on the patient's body mass, with 1.0 g for people who weigh <80 kg, and 2.0 g for those who weigh >80 kg. The adult dose of cefuroxime is 1.5 g. The recommended dose of clindamycin is 600 to 900 mg. It is recommended that, for extended operative times, cefazolin be readministered every two to five hours; cefuroxime, every three to four hours; and clindamycin, every three to six hours[33].

Timing of Parenteral Antibiotic Prophylaxis

Classen et al. studied the timing of administration of prophylactic antibiotics and the risk of surgical wound infections

AAOS Recommendations for the Use of Intravenous Antibiotic Prophylaxis in Primary Total Joint Arthroplasty[33]

Recommendation 1: The antibiotic used for prophylaxis should be carefully selected, consistent with current recommendations in the literature, taking into account the issues of resistance and patient allergies.

Currently, cefazolin, and cefuroxime are the preferred antibiotics for patients undergoing orthopaedic procedures. Clindamycin or vancomycin may be used for patients with a confirmed β-lactam allergy. Vancomycin may be used in patients with known colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or in facilities with recent MRSA outbreaks. In multiple studies, exposure to vancomycin is reported as a risk factor in the development of vancomycin-resistant enterococcus (VRE) colonization and infection. Therefore, vancomycin should be reserved for the treatment of serious infection with β-lactam–resistant organisms or for the treatment of infection in patients with life-threatening allergy to β-lactam antimicrobials.

Recommendation 2: Timing and dosage of antibiotic administration should optimize the efficacy of the therapy.

Prophylactic antibiotics should be administered within 1 h before skin incision. Due to an extended infusion time, vancomycin should be started within 2 h before incision. When a proximal tourniquet is used, the antibiotic must be completely infused before inflation of the tourniquet. Dose amount should be proportional to patient weight; for patients >80 kg, the doses of cefazolin should be doubled. Additional intraoperative doses of antibiotic are advised when the duration of the procedure exceeds one to two times the antibiotic's half-life or when there is significant blood loss during the procedure.

The general guidelines for frequency of intraoperative antibiotic administration are as follows: cefazolin every 2-5 h, cefuroxime every 3-4 h, clindamycin every 3-6 h, vancomycin every 6-12 h.

Recommendation 3: Duration of prophylactic antibiotic administration should not exceed the 24-hour postoperative period.

Prophylactic antibiotics should be discontinued within 24 h of the end of surgery. The medical literature does not support the continuation of antibiotics until all drains or catheters are removed and provides no evidence of benefit when they are continued past 24 h.

Fig. 1

AAOS recommendations for the use of intravenous antibiotic prophylaxis in primary total joint arthroplasty. (Reprinted, with permission, from: Prokuski L. Prophylactic antibiotics in orthopaedic surgery. J Am Acad Orthop Surg. 2008;16:283-93.)

in clean and clean-contaminated cases at a large community hospital[34]. In this study of 2847 patients, 313 (11%) were treated with arthroplasty. The authors found that the rate of infection was lowest for patients who had received an antibiotic from zero to two hours before the incision. They found that twenty-five (58%) of forty-three isolates from the surgical wound infections were resistant to the antimicrobial agent used, fifteen (35%) were susceptible, and three (7%) were not tested for susceptibility. When a proximal tourniquet is used in knee replacement surgery, the entire dose should be administered prior to inflation of the tourniquet[35]. Essentially, the timing of antibiotic prophylaxis should result in an adequate tissue level at the time of incision. Hence, both the AAOS and the SCIP recommend that prophylactic antibiotics be completely infused within one hour before the surgical incision.

Duration of Parenteral Antibiotic Prophylaxis

Many studies, in all of the surgical specialties, have been performed to compare durations of antibiotic prophylaxis, and the overwhelming majority have not shown any benefit in antibiotic use for more than twenty-four hours in clean elective cases[36-40]. In a retrospective review of their experience with 1341 joint arthroplasties, Williams and Gustilo found no difference in the deep-infection rate between a three-day and a one-day course of prophylactic antibiotics[41]. They emphasized the importance of a preoperative dose, which was 2 g of cefazolin.

Heydemann and Nelson, in a study of hip and knee arthroplasty procedures, initially compared a twenty-four-hour regimen of either nafcillin or cefazolin with a seven-day regimen and found no difference in the prevalence of infections[42]. They then compared a single preoperative dose with a forty-eight-hour regimen in a second group of patients and again found no difference in infection prevalence. A total of 466 procedures were performed during the four-year study period. No deep infections developed in either the one-dose or the forty-eight-hour antibiotic protocol group. A deep infection developed in one (0.8%) of the 127 patients in the twenty-four-hour protocol group and in two (1.6%) of the 128 patients in the seven-day protocol group, for an overall infection rate of 0.6% (three of 466). The authors recognized that, as a result of the small sample sizes, the study lacked the power to compare the one-dose and the more-than-one-dose categories. Mauerhan et al. compared the efficacy of a one-day regimen of cefuroxime with a three-day regimen in a prospective, double-blind, multicenter study of 1354 patients treated with an arthroplasty and concluded that there was no significant difference in the prevalence of wound infections between the two groups[43]. In the group treated with a primary hip arthroplasty, the prevalence of deep wound infection was 0.5% (one) of 187 for those treated with cefuroxime compared with 1.2% (two) of 168 for those who had received cefazolin. In the group treated with a primary knee arthroplasty, the rate of deep wound infection was 0.6% (one) of 178 for those who had received cefuroxime and 1.4% (three) of 207 for those who had received cefazolin. Both groups treated with primary arthroplasty received the first dose prior to the incision. On the basis

of studies such as these, the current position of both the SCIP and the AAOS is that postoperative administration of prophylactic antibiotics should not exceed twenty-four hours regardless of the use of catheters or drains.

Changing Epidemiology of Staphylococcal Infections

Over the past decade, hospitals and emergency rooms have seen a changing pattern of infections caused by Staphylococcus. In a pattern similar to that described in the first reports of penicillinase-producing strains of Staphylococcus in the 1940s, present resistant strains of Staphylococcus were reported in hospital settings and high-risk patient populations, such as intravenous drug users and people with chronic indwelling catheters[4]. Recent articles have described an alarming upward trend in the prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* strains in low-risk patients. One report from a large urban hospital in Chicago showed that the prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections increased 6.84-fold: from 24.0 cases per 100,000 people in 2000 to 164.2 cases per 100,000 people in 2005[44]. Additional studies from large county institutions in Dallas and Atlanta have demonstrated similar trends of increasing prevalences of community-acquired methicillin-resistant *Staphylococcus aureus,* with the conclusions being that this is now the predominant organism in skin and soft-tissue infections[45] (Fig. 2).

The prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* is probably lower in smaller, less dense community populations and varies between regions. However, because there is currently no systematic surveillance for antibiotic-resistant organisms in the community setting, the true prevalence of this organism is difficult to ascertain.

Resistant Surgical Site Infections

The choice of drug for prophylaxis should take into account the resistance patterns in the hospital. In a recent article by Fulkerson et al., the susceptibilities of *Staphylococcus epidermidis* and *Staphylococcus aureus* to cefazolin were only 44% and 74% at two high-volume academic centers in New York and Chicago[17]. Of the most common organisms infecting patients with a joint replacement at these hospitals, 26% to 56% were resistant to the standard recommended prophylactic agent. Thirty-three of the 194 infections in this report were diagnosed within four weeks after the surgery. Of these thirty-three infections, eight were due to *Staphylococcus epidermidis* and sixteen were due to *Staphylococcus aureus*. Only two of the eight *Staphylococcus epidermidis* infections and eleven of the sixteen *Staphylococcus aureus* infections were sensitive to cefazolin. These *Staphylococcus epidermidis* and *Staphylococcus aureus* infections were 100% sensitive to vancomycin (Fig. 3).

In a study of deep infections arising after hip and knee replacements over a fifteen-year period (from 1987 through 2001) at The Royal Orthopaedic Hospital and Queen Elizabeth Hospital in England, an infection developed after thirty-four (0.57%) of 5947 hip replacements and forty-one (0.86%) of 4788 knee replacements[46]. Twenty-two (29%) of the infections associated with joint replacement surgery were caused by microorganisms that were resistant to the antibiotic used for prophylaxis (cefuroxime). These included all three methicillin-resistant *Staphylococcus aureus* infections and all three *Pseudomonas aeruginosa* infections as well as eleven of twenty-seven

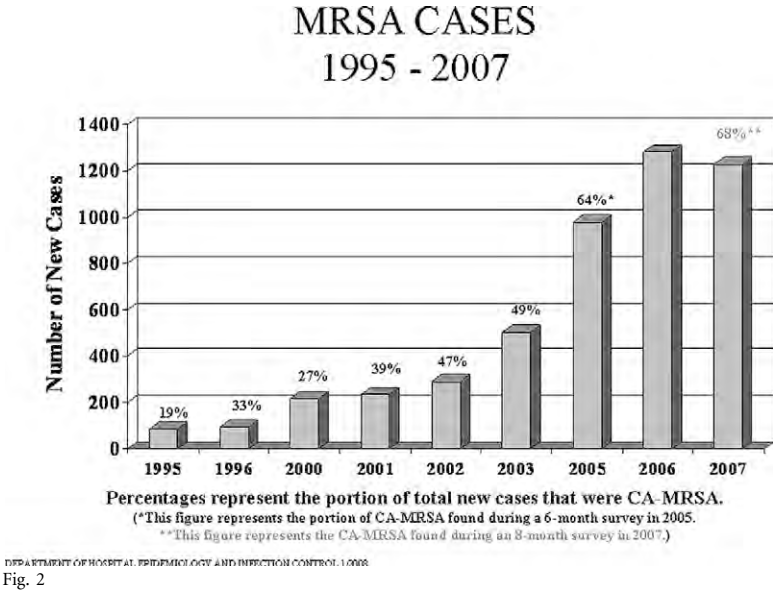

Fig. 2

A thirteen-year profile documenting the increasing numbers of all methicillin-resistant *Staphylococcus aureus* infections and the increasing prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections in a university hospital.

Antibiotic sensitivity, by classification, organism, and stage (%)

Organism	Antibiotic	Overall Sensitivity	Class A	Class B	Class C
Staphylococcus aureus	Cefazolin	74%	67%	74%	88%
	Clindamycin	75%	72%	76%	89%
	Gentamicin	89%	94%	86%	100%
	Vancomycin	100%	100%	100%	100%
Staphylococcus epidermidis	Cefazolin	44%	25%	47%	50%
	Clindamycin	68%	50%	70%	100%
	Gentamicin	87%	67%	90%	100%
	Vancomycin	98%	100%	98%	100%
Streptococcus sp.	Cefazolin	100%	100%	100%	100%
	Gentamicin	100%	N/A	100%	100%
	Vancomycin	100%	100%	100%	100%
Enterococcus sp.	Ampicillin	57%			
	Penicillin	50%			
	Vancomycin	54%			
Pseudomonas aeruginosa	Gentamicin	80%			
	Ciprofloxacin	60%			

Fig. 3

Antibiotic sensitivity by classification, organism, and stage. Class A = acute infections (occurring within four weeks after the index procedure), Class B = chronic infections (occurring more than four weeks after the surgery), and Class C = hematogenous infections (confirmed or suspected seeding from a remote site). (Reproduced from: Fulkerson E, Della Valle CJ, Wise B, Walsh M, Preston C, Di Cesare PE. Antibiotic susceptibility of bacteria infecting total joint arthroplasty sites. J Bone Joint Surg Am. 2006;88:1231-7 [Table E2 in supplementary material].)

coagulase-negative Staphylococcus infections. Sixty-four percent of the seventy-five infections were diagnosed within one year after the operation and therefore were considered to be related to the surgery, according to the criteria for defining surgical site infections[47].

In each of these reports, the recommended prophylactic antibiotic agents, cefazolin and cefuroxime, lacked activity against methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis*. The prevalences of these organisms as causes of infections are increasing according to the antibiogram data of numerous hospitals (Fig. 4).

Prophylactic Antibiotics in Institutions with High Bacterial Resistance

The routine use of vancomycin as a prophylactic antimicrobial, either alone or in combination with a cephalosporin, is controversial. Advisory statements defining the indications for the use of vancomycin are helpful but also contain some ambiguity. The AAOS information statement, "Recommendations for the Use of Intravenous Antibiotic Prophylaxis in Primary Total Joint Arthroplasty," states: "Clindamycin or vancomycin may be used for patients with a confirmed β-lactam allergy. Vancomycin may be used in patients with known colonization with methicillin resistant *Staphylococcus aureus* (MRSA) or in facilities with recent MRSA outbreaks."[48] A separate AAOS information statement, "The Use of Prophylactic Antibiotics in Orthopaedic Medicine and the Emergence of Vancomycin-Resistant Bacteria," states: "Vancomycin may be appropriate as a prophylactic antimicrobial for patients undergoing joint replacement at institutions that have identified a significant prevalence (e.g., >10-20 percent) of methicillin-resistant *S. aureus* (MRSA) and *S. epidermidis* among orthopaedic patients."[49] The Hospital Infection Control Practices Advisory Committee guideline also suggests that a high frequency of methicillin-resistant *Staphylococcus aureus* infection at an institution should influence the use of vancomycin for prophylaxis but acknowledges that there is no consensus about what constitutes a high prevalence of methicillin resistance[50].

Vancomycin

Vancomycin is a large tricyclic glycopeptide molecule that has historically been the first line of treatment for methicillin-resistant *Staphylococcus aureus* infections[51]. The bactericidal action of vancomycin is a result of the inhibition of bacterial cell wall synthesis through the disruption of peptidoglycan biosynthesis. It is active against most gram-positive organisms including *Staphylococcus aureus, Staphylococcus epidermidis* (including heterogeneous methicillin-resistant strains), streptococci, enterococci, and Clostridium. Vancomycin lacks activity against gram-negative bacteria, fungi, or mycobacteria. Similar to cefazolin, vancomycin reaches high concentrations in bone, synovial tissue, and muscle within minutes after administration[52,53].

Gram Positive Organisms (#) – All Sources																
Antimicrobic	Ampicillin	Cefotaxime	Ceftriaxone	Chloramphenicol	Clindamycin	Erythromycin	Gentamicin	Levofloxacin	Oxacillin[b]	Penicillin G	Rifampin[i]	Tetracycline	Trimeth/Sulfa	Vancomycin[h]	Gentamicin, High Level	Streptomycin, High Level
Breakpoints:																
Strep. Pneumoniae →		0.5	0.5	4	0.25	0.25				0.06		2	0.5/9.5	1		
Staphylococcus →					0.5	0.5	4	1	2[b]		1	4	2/38	2[h]		
Enterococcus →	8									8				4	S[a]	S[a]
Strep. pneumoniae, all sources (82)		95[g]	99[g]		94	78				72[c]		89	68	100		
Strep. pneumoniae, blood (15)		93[g]	93[g]		100	93				93[e]		100	86	100		
Strep. pneumoniae, CSF (2)		100[g]	100[g]							100				100		
Strep. pneumoniae, lower resp (52)		98[g]	100[g]		94	81				73[t]		90	75	100		
Staph. aureus, all (1805)					74	38	97	63	49		99	93	96	100		
S. aureus, not MRSA (881)					84	70	99	93	100		99	95	97	100		
S. aureus, MRSA (924)					66	8	95	34	0		99	91	95	100		
Staph., coagulase negative (206)					55		86	64	27		97	84		100		
Enterococcus species, all (713)	75									73				76[d]	73	72
Enterococcus species, not VRE (544)	95									93				100	78	82
Enterococcus species, VRE/VIE (169)	6									7				0	51	31

Fig. 4

Hospital antibiogram: a summary published at regular intervals of the results of an individual hospital's bacterial isolates susceptibility testing. MRSA = methicillin-resistant *Staphylococcus aureus,* VRE = vancomycin-resistant enterococci, and VIE = vancomycin-intermediate enterococci.

Adverse reactions to vancomycin such as infusion-related pruritus and erythema can occur. Red man syndrome, a pruritic, erythematous rash on the upper trunk and face that is occasionally accompanied by hypotension, is associated with its rapid infusion and histamine release in approximately 5% to 13% of people[54]. This has led to the recommendation that vancomycin be administered slowly, at a rate of 1 g over sixty minutes. The recommended dose, which is based on body mass, is 10 to 15 mg/kg, up to a limit of 1 g, in patients with normal renal function[55]. When vancomycin is used for prophylaxis, its infusion should begin one to two hours before initiation of the operation (compared with within one hour for cefazolin) to ensure that the entire dose is administered and adequate concentrations are in the tissues prior to the surgical incision[56]. For extended operative times, repeat administration is recommended in six to twelve hours[33].

Nephrotoxicity and ototoxicity occur in <1% of patients, with nephrotoxicity being associated with concomitant aminoglycoside use. Other complications include hypersensitivity rash, reversible neutropenia, and drug fever. Daptomycin should be considered as an alternative for people with known anaphylactic or severe reactions to vancomycin.

Studies of Parenteral Prophylaxis with Vancomycin

In a study of patients treated with cardiac surgery who had been randomized to prophylaxis with either cefazolin or vancomycin for twenty-four hours, there was no difference in the observed surgical site infection rate between the groups but there was a difference in the types of surgical site infections[57]. Patients who had received cefazolin and in whom a surgical site infection later developed were more likely to be infected with methicillin-resistant *Staphylococcus aureus,* whereas patients who had received vancomycin were more likely to be infected with methicillin-susceptible *Staphylococcus aureus.* This finding suggests that the choice of prophylaxis changed the flora of infections but not the rate of infections[3].

Ritter et al. studied 241 patients who had been given a single dose of vancomycin and gentamicin preoperatively and concluded that this regimen provided safe and effective antibiotic prophylaxis at a reasonable cost[58]. There were no early infections in this small retrospective case series. Savarese et al. reported on a series of 233 arthroplasties (ninety-six knee, 133 hip, and four shoulder procedures) with 1 g of vancomycin given one hour before and six hours after the operation[59]. Within a minimum twenty-four-month observation period, there were two knee infections (2%), one with *Morganella*

morganii and one with *Staphylococcus epidermidis* (sensitivity not mentioned). The authors noted that "the choice of the antibiotic was based on the epidemiological knowledge of the literature and the experience on the ward" and concluded that vancomycin provided effective prophylaxis in high-risk cases.

The reluctance to use vancomycin as a prophylactic agent can be traced to a time when there were limited antibiotics available to treat methicillin-resistant *Staphylococcus aureus* as well as when antimicrobial profiles did not support its use in this capacity. In addition, the fear of promoting possible vancomycin-resistant strains of staphylococci and the emergence of vancomycin-resistant enterococci caused physicians to be appropriately cautious about its use.

Vancomycin Resistance

The use of oral vancomycin to treat pseudomembranous colitis contributed to the emergence of vancomycin-resistant enterococci[51]. The first staphylococci with reduced susceptibility to vancomycin were reported in Japan in 1997[60]. These staphylococci, labeled "vancomycin-intermediate *Staphylococcus aureus*," did not possess the resistance genes but had a reduced susceptibility to vancomycin. Since then, other strains with reduced susceptibility (heteroresistant vancomycin-intermediate *Staphylococcus aureus*) as well as resistant strains (vancomycin-resistant *Staphylococcus aureus*) have been identified but occur infrequently[61]. To help combat these resistant strains, new antibiotics that greatly expand the pharmacologic arsenal have been introduced. These newer antibiotics include linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline. Whether a single preoperative parenteral dose of vancomycin is associated with increased vancomycin resistance or decreased vancomycin susceptibility has not been demonstrated. Conversely, prolonged exposure to antibiotics has been identified as a risk factor for promoting bacterial resistance[38,62].

Role of Screening for Methicillin-Resistant *Staphylococcus aureus*

The potential for increased resistance to vancomycin, combined with the goal of reducing the threat of resistant organisms, has led investigators to examine the role of screening patients' endogenous flora to assist in the prevention of surgical site infections. In this scenario, prophylactic antimicrobials may be modified depending on the results of the screening test. Patients may be screened to determine whether they are colonized with drug-resistant bacteria. If they are, attempts at eliminating these drug-resistant bacteria can be made. This approach has been used with success in The Netherlands and is thought to be a contributor to the fact that ≤1% of *Staphylococcus aureus* isolates are methicillin-resistant there. At forty-nine hospitals in The Netherlands reporting to the European Antimicrobial Resistance Surveillance System during the years 1999 through 2004, only fifty-eight (0.78%) of 7420 cultures were positive for methicillin-resistant *Staphylococcus aureus* isolates[63].

In a recent study, Robicsek et al. evaluated universal surveillance for methicillin-resistant *Staphylococcus aureus* surveillance at three affiliated hospitals in what they described as the first large-scale universal-admission methicillin-resistant *Staphylococcus aureus* surveillance program[64]. These hospitals reported a reduction by more than half in health-care-associated methicillin-resistant *Staphylococcus aureus* bloodstream, respiratory, urinary tract, and surgical site infections occurring during the stay in the hospital and in the thirty days after discharge. Perl et al. performed a randomized, double-blind, placebo-controlled study comparing nasal mupirocin with a placebo in general, gynecologic, neurologic, or cardiothoracic surgery[65]. They concluded that there was not a significant reduction of surgical site infections by *Staphylococcus aureus* overall but the nasal mupirocin did reduce the rate of infections among patients who were previously *Staphylococcus aureus* carriers.

Kalmeijer et al. performed a randomized, double-blind, placebo-controlled study of nasal mupirocin in patients undergoing elective orthopaedic surgery involving the implantation of devices into the hip, knee, or spine[66]. A *Staphylococcus aureus* surgical site infection developed in five (1.6%) of 315 cases in the mupirocin group compared with eight (2.7%) of 299 in the placebo group, which was not a significant difference. Two recent articles on preoperative nasal decolonization in patients undergoing orthopaedic joint replacement procedures did show a reduction in surgical site infections with resulting economic gains for the hospital[16,67].

Local Antibiotic Prophylaxis

The aminoglycosides are another class of antibiotics that have been used in a prophylactic fashion, being that they are administered locally rather than parenterally. They cause bacterial cell death by an intracellular mechanism, binding to a 30S subunit of the ribosome and thereby inhibiting protein synthesis. Buchholz et al. were, we believe, the first to report on the addition of aminoglycoside antibiotics to Palacos bone cement in a large series of exchange arthroplasties[68].

Josefsson et al. reported on a series of 1688 consecutive total hip arthroplasties followed for ten years in a randomized, prospective, controlled study comparing parenteral prophylactic antibiotics (cloxacillin, dicloxacillin, cephalexin, or phenoxymethyl penicillin) with local prophylactic antibiotics (gentamicin bone cement)[69,70]. The investigators concluded that each parenteral antibiotic provided equivalent efficacy in reducing infections and that it might be beneficial to use parenteral antibiotics and antibiotic bone cement concurrently. There were no cases of nephrotoxicity, ototoxicity, or allergic reactions in the patients receiving gentamicin bone cement.

The United States Food and Drug Administration (FDA) has approved the use of premixed antibiotic bone cement (either gentamicin or tobramycin) for prophylaxis in a second-stage reimplantation following a previous infection at the site of an arthroplasty, but not as prophylaxis in routine primary arthroplasties. The present commercially available preparations of aminoglycoside-impregnated bone cements provide elution concentrations that are bactericidal against nonresistant and methicillin-resistant Staphylococcus organisms along with susceptible aerobic gram-negative organisms[71]. These anti-

biotic bone cements provide broad antibacterial coverage with a low allergy profile.

Overview

The present low prevalence of surgical site infections associated with hip and knee arthroplasty has made interventions designed to reduce infections difficult to study given the large number of patients required to allow for a significant conclusion to be made. Measures related to operative technique as well as operating-room environment have contributed to a reduction in infections. In addition, measures directed at improving the antibacterial properties of the host tissues, such as parenteral use of prophylactic antibiotics, have also been studied, verified, and accepted across most surgical specialties. For the last three decades, the cephalosporins (cefazolin and cefuroxime) have been the preferred antimicrobials, with proven success, for prophylaxis for hip and knee arthroplasty. The increasing rates of community-acquired infections caused by methicillin-resistant *Staphylococcus aureus* and the increasing percentage of resistant organisms documented in numerous hospital microbiologic profiles have created a scenario whereby cefazolin or cefuroxime alone might not be the appropriate prophylaxis in all surgical settings. An ongoing collaborative effort between a hospital's infectious disease experts and its joint replacement surgeons is necessary to provide the best protection against the organisms most likely to be of concern. At our institution, in which the rate of *Staphylococcus aureus* resistance to cefazolin is 50% and the rate of *Staphylococcus epidermidis* resistance to cefazolin is 70% for all sources of infection, we have added a preoperative dose of vancomycin along with the cefazolin to provide prophylaxis against these resistant organisms and the other common bacterial causes of infection in patients treated with joint replacement. The use of vancomycin along with cefazolin is endorsed by our hospital Infectious Disease Committee, which allows us to be in compliance with pay-for-performance measures. ■

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