Review Article

Antibiotic Stewardship in Orthopaedic Surgery: Principles and Practice

Abstract

A thorough knowledge of the principles of antibiotic stewardship is a crucial part of high-quality orthopaedic surgical care. These principles include (1) determining appropriate indications for antibiotic administration, (2) choosing the correct antibiotic based on known or expected pathogens, (3) determining the correct dosage, and (4) determining the appropriate duration of treatment. Antibiotic stewardship programs have a multidisciplinary staff that can help guide antibiotic selection and dosage. These programs also perform active surveillance of antimicrobial use and may reduce *Clostridium difficile* and other drug-resistant bacterial infections by providing expert guidance on judicious antibiotic usage. The emergence of antibiotic-resistant pathogens, the geographical diversity of these infecting pathogens, and the changing patient population require customization of prophylactic regimens to reduce infectious complications. A multidisciplinary approach to antibiotic stewardship can lead to improved patient outcomes and cost-effective medical care.

The efficacy of prophylactic antibiotics for spine and total joint surgery has been well established. Until the 1960s, the use of prophylactic antibiotic therapy in orthopaedic surgery was controversial. Several early retrospective studies demonstrated higher infection rates with the use of prophylactic antibiotics. In 1961, Burke found that antibiotic administration was effective at reducing infection when administered 1 hour before the surgical incision was made. Multiple prospective human and animal studies have confirmed Burke’s findings, which were especially important for joint arthroplasty and spine surgery because of the high risk of infection associated with these procedures.

Despite the generalized use of prophylactic antibiotics in orthopaedic surgery, surgical site infections (SSIs) continue to be a major source of morbidity, mortality, and hospital cost. SSIs are the second most common cause of nosocomial infections, with an incidence of 2% to 5% in patients undergoing uncontaminated, extra-abdominal surgeries. In part, this is due to the increasing prevalence of antibiotic-resistant organisms. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections, in particular, have increased significantly over the past 30 years and have been a major source of SSI in orthopaedic procedures. The number of infections caused by gram-negative bacilli that are resistant to antibiotics is also increasing. A recent study performed at our institution showed that 50% of the culture-confirmed gram-negative SSIs had cefazolin-resistant gram-negative isolates. Because of changes in bacterial

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resistance patterns, recommendations for prophylactic antibiotic type and dosing and duration of treatment are evolving and becoming more complex. However, there are limited high-quality, level I or II studies on antibiotic stewardship in orthopaedic surgery.

We believe that the widespread use of antibiotic stewardship for prophylactic antibiotics will enhance patient care and reduce hospital costs by reducing the incidence of SSI. This is particularly relevant in a new health care environment in which institutions may start receiving payment for orthopaedic surgical procedures based on a defined-care fee structure. Antibiotic stewardship programs (ASPs) are staffed by multidisciplinary teams that provide recommendations on general dosage and antimicrobial selection, while performing active surveillance of antimicrobial use and authorizing the use of certain restricted antimicrobials. The teams consist of surgeons, infectious disease specialists, clinical pharmacists, and infection control and prevention practitioners. The goals of these programs are to decrease the incidence of hospital-acquired infections, control costs, and prevent complications associated with antibiotic use (eg, renal damage, *Clostridium difficile* infections). Strategies include determining the appropriate indications for antibiotic administration, selecting the best empiric antibiotic therapy based on the prevalence of infecting organisms, optimizing drug dosage (especially in overweight patients), and minimizing the duration of treatment to reduce opportunistic infections and the development of resistant strains.

### Antibiotic Stewardship in the United States

The Infectious Disease Society of America and the Society for Healthcare Epidemiology of America have published guidelines for developing an institutional program to enhance antimicrobial stewardship. Two core strategies were described. The first strategy is a prospective audit with intervention and feedback, which is designed as a review of the use of antimicrobial therapy. In this strategy, recommendations are made with respect to antibiotic selection, dose, route, and duration of treatment, while allowing the primary physician or surgeon continued control of prescription. The goal is to reduce inappropriate use of antibiotics. The second strategy involves prior authorization; certain antibiotics are only made accessible through an approval process. This strategy is used to reduce antimicrobial use and cost. For both strategies, the ASP team determines the dosing parameters and appropriate indications for antibiotic use.

Supplemental strategies have been described, as well. These include prescriber education, structured guidelines on the use of certain antibiotics for specific conditions (eg, antibiotic type and duration of treatment for a urinary tract infection or a superficial soft-tissue infection), clinical pathways, automatic substitutions, and intravenous to oral conversion protocols. Studies with varying levels of evidence support the use of these strategies. Of these supplemental strategies, education (eg, conferences, student and house staff teaching sessions, written guidelines) is frequently used and is considered an essential part of any ASP. In two studies, antibiotic consumption decreased when core strategies were combined with a supplemental educational program, resulting in a savings of more than $913,236 over an 18-month period.

Nationally, many hospitals use some of the principles of antibiotic stewardship; however, the number of hospitals that have a formal program remains low. In a survey of 357 practitioners in various practice settings, 52% stated that their hospital did not have an ASP. Interestingly, the rates of adherence to some of the strategies of antibiotic stewardship (automatic dose adjustment, prescriber education, closed formularies, guidelines, clinical pathways) were similar among hospitals with a formal ASP and those without the program. Hospitals with an ASP were more likely to have a process in place for proactive pharmacy streamlining or de-escalation and were also more likely to have a process for dose optimization. Notably, approximately half of the hospitals surveyed that did not have an active ASP were in the process of developing a program.

ASPs have the potential to combat a variety of specific infectious disease issues, including the development of resistant organisms and the use of costly antibiotics when equally effective, less expensive alternatives exist. In a study of skin and soft-tissue infections at an academic medical center, Jenkins et al concluded that a substantial amount of healthcare resources were inappropriately allocated to the care of patients with these infections. Expensive imaging studies such as CT and MRI were noted to be low yield and overused. Additionally, the authors identified the use of broad-spectrum antibiotics and prolonged treatment courses as significant sources of waste and risk for antibiotic resistance. They concluded that improvements in care and savings could be achieved with the use of an ASP to target antibiotic use for soft-tissue and skin infections.

In a study on antibiotic stewardship, Fishman described antibiotic efficacy, antibiotic resistance, and the reduction of *C difficile* infection in the context of the use of fluoroquinolone for *Streptococcus pneumoniae* infections at the Hospital of the University of Pennsylvania. The antibiotic management team consisted of infectious disease physicians, clinical pharmacists, members of the microbiology laboratory staff, hospital...
drug resistance, and infection-control personnel. The team used guidelines for proper antibiotic use and established appropriate dosing and dosage intervals as well as an antibiotic restriction program that required prior approval of certain antibiotics. The team also used supplemental strategies, including ongoing educational initiatives. Clinical outcomes at this institution have demonstrated a 90% rate of appropriate antibiotic use compared with a 32% rate when not covered by an ASP. This improvement translated to a 91% cure rate with an ASP compared with a rate of 55% without ASP supervision. The failure rate was also significantly decreased from 31% without ASP supervision to 5% with an ASP.

The use of diagnostic tests designed to provide customized antibiotic regimens for patients has also been explored. Goff et al. found that advances in antimicrobial detection (eg, molecular assays) allowed for earlier targeted therapy for individual patients. Many of the assays described by the authors can detect specific microbes within hours; thus, the improvement in detection time can potentially reduce the use of broad-spectrum antibiotics and improve cure rates. Within an institution, laboratory test results that determine the sensitivity of isolated bacterial strains to different antibiotics in many patients can be used to create an antibiogram, which is a database that documents the type and frequency of pathologic organisms and antibiotic sensitivity. Therefore, regulating and designing an algorithmic approach to diagnostic testing may become an important component of the comprehensive ASP.

Customization of Antibiotic Regimens

Establishing appropriate antibiotic administration guidelines at an institution should take into account local practice patterns and antimicrobial resistance trends. Antibiograms provide valuable information with regard to the efficacy of specific antibiotics against certain pathogens and should be used to develop antibiotic guidelines. With regard to prophylactic antibiotic use in orthopaedic surgery, cefazolin continues to be the most commonly used agent despite growing antibiotic resistance. However, cefazolin may be inadequate at some institutions because of high rates of MRSA. For example, in a study performed at our institution, high-risk patients undergoing total hip or total knee arthroplasty or spine surgery were screened for MRSA and methicillin-sensitive Staphylococcus aureus (MSSA), and 3% were found to have nares colonized with MRSA. This pattern should alter local recommendations with regard to perioperative antibiotic prophylaxis in patients colonized with MRSA. Several studies have suggested that vancomycin be used for perioperative prophylaxis in patients at high risk of MRSA colonization and/or infection. Patients found to be colonized with MSSA still underwent the decolonization protocol but were given the standard weight-based antibiotic prophylaxis of cefazolin, cefuroxime, or clindamycin (based on patient allergies) instead of vancomycin.

Customization of the antibiotic regimen and dosage should include patient-specific recommendations based on pertinent exposure history and demographic information. One report found that 80% of patients who received the standard 1-gm dose of vancomycin were underdosed based on weight. Underdosing of antibiotics has the potential to create increased bacterial resistance to these antibiotics because the bacterial infections are only partially treated; this may have serious consequences. ASPs can play a key role in minimizing antimicrobial resistance by ensuring appropriate dosing with the implementation of formal weight-based guidelines and monitoring. Figure 1 provides a perfect example of the importance of weight-based dosing of antibiotics by showing the number of patients who were either underdosed or overdosed when given the standard 1-gm dose of vancomycin.

The incidence and risk factors for hospital-acquired C. difficile infection in a specific patient population should also guide the antibiotic regimen. Current evidence does not support the extended use of perioperative antibiotic prophylaxis (≥24 hours). Thus, timely discontinuation of prophylactic antibiotics following surgical procedures should be a targeted goal of orthopaedic ASPs. Risk factors for C. difficile infection specific to the orthopaedic population include inpatient hospitalization, antibiotics used for urinary tract infections, and the use of proton pump inhibitors. These high-risk patients require special attention with regard to the use and duration of antibiotics commonly associated with C. difficile infection.

Our Institutional Protocol

Our protocol incorporates aspects of the guidelines from all of the major healthcare agencies, including the Centers for Disease Control and Prevention and the Centers for Medicare and Medicaid Services as well as the Surgical Care Improvement Project. However, the protocol also has been customized based on our institutional experience with antibiotic stewardship and could be used as a guide for running an ASP.

Our protocol begins with pre-admission testing. All patients undergoing total hip or knee arthroplasty or spinal procedures are screened for S. aureus via a swab of the anterior nares.

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naries and are then treated perioperatively based on the culture results. Patients colonized with MRSA are treated preoperatively with a 5-day, twice-daily course of 2% mupirocin nasal ointment and are given chlorhexidine gluconate soap to shower with on the night before and the morning of surgery. Vancomycin is administered prophylactically at the time of surgery. In the literature, no consensus exists with regard to whether vancomycin should be substituted for cefazolin or added to it. At our institution, we use vancomycin in place of cefazolin because of the low prevalence of MRSA isolates that are resistant to vancomycin and the high rate of cefazolin-resistant MRSA isolates. Postoperatively, MRSA-colonized patients are placed on isolation precautions. Patients found to be colonized with MSSA are treated similarly except that they receive the standard antibiotic prophylaxis instead of vancomycin and are not placed on isolation precautions. Hutzler et al described a complete algorithm for preadmission screening. Implementation of a similar program is feasible and can result in a significant decrease in hospital-acquired MRSA infections.

In addition to patients undergoing total joint or spine surgery, the ASP is involved in the care of all hospitalized patients. The multidisciplinary team recommends antibiotics and dosage based on risk factors such as type of surgery, patient weight, and comorbidities. In accordance with the previously mentioned recommendations, these guidelines are customized to the specific institutional antibiogram. Figure 2 and Table 1 represent our hospital’s guidelines for dosage calculation. Additionally, the ASP is actively involved in restricting the overuse of medications. The program has a suggested duration for administration of specific antibiotics for common hospital infections, and consultation with an infectious disease specialist is required for approval of an extended period of antimicrobial administration.

Our ASP supplements the core strategies with ongoing institutional education and research. Guidelines have theoretical benefits; however, practical implementation is often more difficult. Communication is inherently important in the education and use of the program by physicians and hospital staff. Communication tools should aim to educate staff on the usefulness, effectiveness, and purpose of the ASP. For example, at our institution, an antibiogram is published to help house staff understand which antibiotics are preferred and which medications should be avoided based on clinical circumstances. Some institutions have implemented care pathways to direct medication choice, dosing, and duration of antibiotic therapy based on the type of infection. These pathways have been developed in the form of decision support aides, which can be integrated into an electronic medical record system.

Implementation of a surveillance and research program is the final component of a successful ASP. As part of our program, follow-up research is conducted by the Division of Quality and Patient Safety to determine adherence to guidelines, changes in the microbial profile, resistance patterns, and infection rates. Report cards for individual divisions, departments, and/or institutions should be published and distributed on a regular basis. The division or committee that handles this program should also actively share its findings with the orthopaedic surgery community by publishing research based on the compiled data.

The development of an ASP can be a useful tool in establishing standardized methods to decrease hospital-acquired infections and control the development of antibiotic-resistant
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Figure 2

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* Infuse gentamicin 40 mg/mL preparation over 60 min.
* Dosing range 3–5 mg/kg

Our institutional antibiotic stewardship program recommendations for gentamicin dosing for adults undergoing total hip arthroplasty, hip fracture repair, or thoracic and/or lumbar spine fusion surgery.

Cost Analysis

Management of SSIs following orthopaedic surgery is expensive. For example, prosthetic infection following total joint arthroplasty often necessitates revision surgery. In a study of the economic burden of periprosthetic infection, revision surgery cost US hospitals $566 million, and that cost is expected to rise to $1.62 billion by 2020.32 Another study found that periprosthetic joint infections complicated by MRSA incur significantly higher cost than do infections caused by strains that are not resistant to antibiotics ($107,264 versus $68,053 per case; \( P < 0.0001 \)).33 Hospital-acquired \( C \) difficile infection is associated with a substantially longer hospital stay and higher cost of care compared with that of controls in several studies.27,34,35 Targeting hospital-acquired infections can help to reduce these medical costs.

An ASP can provide cost savings of up to $900,000 through the reduction of antibiotic misuse, iatrogenic infections, and antibiotic-resistant organisms.11,36,37 Most of the savings is probably attributable to reduced expenditure for antibiotic treatment. One prospective study reported that implementation of an ASP resulted in a 36% decrease in antimicrobial use without compromising clinical care.38 Other potential avenues of cost savings include reduction in the length of stay, 14-day reinfection rate, and readmissions attributed to reinfection.39 Scheetz et al40 analyzed the cost-effectiveness of an ASP that targeted infections of the bloodstream and estimated effectiveness based on quality-adjusted life years. They reported that the program was cost-effective, with a gain of approximately $2,367 per quality-adjusted life year gained. These studies suggest that an ASP can function as a self-sustaining program while providing improved quality of care. Establishing an ASP makes sense
from the perspectives of patient care and administrative and healthcare policy.

An ASP in Action

The following example demonstrates how an ASP can be used to enhance patient care in an orthopaedic practice. In a 69-year-old, obese patient (5 feet 6 inches tall, 100 kg with a BMI of 35.5) with a history of noninsulin-dependent diabetes who was diagnosed with right hip osteoarthritis and is a candidate for total hip arthroplasty, antibiotic stewardship would begin at the preadmission testing appointment, which typically occurs 2 weeks preoperatively. In addition to the routine medical clearance and anesthesia assessment, a swab of both of the anterior nares would be obtained and sent for culture to screen for MRSA colonization. If the culture tests positive for MRSA, the patient is treated with a 5-day course of intranasal 2% mupirocin ointment and would be required to shower with a chlorhexidine gluconate soap the night before and the morning of surgery. On the day of surgery, the patient would be checked for compliance as part of the standard preoperative nursing assessment. If the patient was noncompliant, mupirocin would be administered on the day of surgery and continued for a total of 5 days postoperatively. Additionally, the positive culture results would be noted in the patient’s chart, triggering the use of vancomycin for antibiotic prophylaxis and isolation.

Table 1

<table>
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<tr>
<th>Procedure</th>
<th>Patient Risk Factors</th>
<th>Antimicrobial Prophylaxis Regimen</th>
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<tr>
<td>Arthroplasty (knee, shoulder, elbow, hand, foot), cervical spine fusion, laminectomy, and diskectomy</td>
<td>Any risk factors</td>
<td>Cefazolin 1 g IV (2 g if pt weight is &gt;80 kg). Redose if the procedure is &gt;4 hr or there is major blood loss.</td>
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<td>Severe penicillin allergy or any cephalosporin allergy</td>
<td>Clindamycin 600 mg IV (redose if the procedure is &gt;4 hr or there is major blood loss) and gentamicin IV (no redose)</td>
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<td>History of MRSA infection or colonization, positive MRSA nasal culture in preoperative testing</td>
<td>Vancomycin weight-based infusion (redose if the procedure is &gt;8 hr) and cefazolin 1 g IV (2 g if pt weight is &gt;80 kg; redose if the procedure is &gt;4 hr or there is major blood loss) and gentamicin IV (no redose)</td>
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<tr>
<td>Hip arthroplasty, thoracic/lumbar spine fusion, hip fracture repair</td>
<td>Any risk factors</td>
<td>Cefazolin 1 g IV (2 g if pt weight is &gt;80 kg; redose if the procedure is &gt;4 hr or there is major blood loss) and gentamicin IV (no redose)</td>
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<tr>
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<td>History of MRSA infection or colonization, positive MRSA nasal culture in preoperative testing</td>
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<tr>
<td>Arthroscopy without implant</td>
<td>All</td>
<td>None required</td>
</tr>
</tbody>
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IV = intravenous, MRSA = methicillin-resistant Staphylococcus aureus

* For patients with known infection, all preoperative cultures should be reviewed to guide antimicrobial choices.

b Duration of perioperative prophylaxis is up to 24 hr only.

c All antibiotic infusions begin within 60 min prior to incision for knee arthroplasty with tourniquet. Infuse perioperative antibiotics before application of tourniquet (for vancomycin, infuse 1 g before application of tourniquet).

d History of anaphylaxis to penicillin constitutes severe allergy; for other minor allergic reactions (eg, rash) cefazolin may be used.

e Start gentamicin first because of the faster infusion time. Gentamicin exclusion criteria: creatinine clearance rate <20 mL/min, pregnancy, myasthenia gravis, or age >75 years. If excluded, substitute with aztreonam 2 g IV every 8 hr (redose if the procedure is >6 hr, reduce frequency to every 12 hr if creatinine clearance rate is <30 mL/min).

f Vancomycin IV weight-based dosing for perioperative prophylaxis: <70 kg, 1-g dose; 70-85 kg, 1.25-g dose; 86-100 kg, 1.5-g dose; >100 kg, 2-g dose.
precautions surgery to try to reduce the risk of exposing other patients to MRSA.

As part of the ASP protocol, the patient is weighed preoperatively to ensure accurate weight-based dosing of antibiotics. At our institution, weight-based dosing of vancomycin is 15 mg/kg. For this patient, 1,500 mg of vancomycin would be administered within an hour of the surgery, with redosing if the procedure lasts >4 hours. Furthermore, measures are in place to ensure that prophylactic antibiotics are discontinued after the

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Map of suggested elements of an antibiotic stewardship program (ASP). This map provides guidance on all of the steps required to establish an ASP, beginning with an assessment of current practices to identify current infection trends and available resources at the institution. Clinicians’ baseline knowledge and perceptions are also assessed. A core team of physicians, pharmacists, microbiologists and information technology (IT) experts is established. The team plans and implements the core strategies by targeting specific areas (eg, hospital-acquired infections). Analysis of the outcomes and financial impact of the interventions is an important part of the core team’s responsibilities. CAP = community acquired pneumonia, CPOE = computer physician/clinician order entry, UTI = urinary tract infection (Adapted with permission from Greater New York Hospital Association United Hospital Fund: Antimicrobial stewardship toolkit: Best practices from the GNYHA/UHF antimicrobial stewardship collaborative. http://www.gnyha.org/resourcecenter/?catid=51. Accessed September 12, 2014.)
standard 24 hours to decrease the risk of hospital-acquired *C. difficile* infection. These measures include standardized postoperative antibiotic orders with a specified number of doses, reminders within the electronic medical record to discontinue antibiotics, required authorization to continue antibiotics longer than 24 hours, and flags for the pharmacy when antibiotics are continued longer than 24 hours. With these simple interventions, data on the rates of MRSA colonization, weight-based dosing regimens, the rates of SSI, and the organisms responsible for these infections can be collected.

In patients treated on an outpatient basis, the widespread use of the electronic medical record can serve as an efficient means of collecting data from physicians’ offices (and is used at our institution when available). The data can then be analyzed with respect to adherence and effect on infection rates to further adapt prophylactic antibiotic choice to address local antimicrobial patterns. Based on the data analysis, prophylactic antibiotics should be customized, and the rates of SSI may be lowered.

Up to 3 months postoperatively, the patient was recovering well but now presents with a potential peri-prosthetic joint infection of the hip. The patient’s probability of having a periprosthetic joint infection should be defined as low or high as recommended by the clinical practice guideline on diagnosis of peri-prosthetic joint infections of the hip and knee developed by the American Academy of Orthopaedic Surgeons. Astute decision and treatment point, the ASP team can be consulted to offer recommendations on whether the initiation of antibiotics is appropriate, what antibiotics should be administered, and the duration of treatment. Additionally, the infectious disease physician on the team (who will have experience treating orthopaedic surgery infections) can then assist with the selection of intravenous antibiotics based on the patient’s risk factors for specific pathogens and the local antibiogram developed by the ASP team. For example, after serological testing, if there is a high probability of infection, several questions arise with respect to the initiation of antibiotics: What antibiotic should be administered to the patient before cultures are obtained? Should oral or intravenous antibiotics be prescribed?

Given the high probability of infection, an aspiration of the involved joint should be performed before the initiation of antibiotic treatment; the aspirate should be sent for a microbiologic culture, and a white blood cell count and differential of the synovial fluid should be obtained. Once fluid culture has been obtained, antibiotic treatment should begin, with input from both the orthopaedic surgeon as well as the infectious disease specialist. It should be noted that perioperative antibiotic prophylaxis may be administered in patients who have already undergone joint aspiration. The ASP team will be able to adjust the antibiotic regimen to ensure that the selected antibiotic will provide adequate coverage without excessive use of broad-spectrum antibiotics that may lead to increased resistance patterns.

After medical optimization, the patient undergoes irrigation and débridement and either a one-stage or two-stage revision of the infected total hip arthroplasty based on the patient’s presentation, duration of symptoms, and surgeon preference. The ASP protocols may require collection of three or more cultures and tissue samples for cultures. Furthermore, based on the local trends in bacterial infections, the protocol may require that cultures from high-risk patients be kept for an extended period of time to maximize the growth of bacteria. It should be noted that, in patients from whom joint fluid has already been aspi-rated, preoperative antibiotic prophylaxis may be given. The ASP team can then determine the type, dosage, frequency, and duration of intravenous and/or oral antibiotic treatment based on the culture results. Entry of this data and the outcome of treatment in an ASP database can help determine future treatment regimens. As more patients are monitored and evaluated, the ASP recommendations should improve, tailoring treatment based on the experience of the institution that it serves.

ASPs can work for less complicated conditions, such as cellulitis or soft-tissue infections. The recommendations of these programs can be easily incorporated into a busy surgeon’s clinical practice.

### Summary

ASPs have the potential to be an invaluable resource for both orthopaedic surgeons and healthcare facilities in terms of improving patient care and reducing cost. These programs provide expert guidance on empiric and targeted antimicrobial therapy and create algorithms to monitor drug selection, dosing, and length of therapy. This guidance facilitates the elimination of extraneous and inappropriate antibiotic use, which can lead to decreased incidence of *C. difficile* infections. Moreover, institutional customization and monitoring of antibiotic regimens will allow ongoing research on the efficacy of ASPs and fine tuning of these programs to improve patient safety. With current increases in antimicrobial resistance, these programs will be crucial in maintaining the efficacy of our current antimicrobial agents. We recommend that other institutions consider initiating...
these programs with orthopaedic-specific recommendations.

Future research will be required to study the effectiveness of ASPs and their impact on patient care. Several types of studies will be required, including comparative studies of patient care with and without ASPs and retrospective reviews of infectious complications before and after implementation of these programs.

References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 9 and 26 are level I studies. References 1, 5, 6, 8, 15, 18-20, and 30 are level II studies. References 2, 7, 10, 11, 13, 17, 23-25, 27, and 32-40 are level III studies. References 16 and 21 are level IV studies.

References printed in bold type are those published within the past 5 years.


