Antibiotic prophylaxis plays an important role in the prevention of surgical site infections. For healthcare institutions to receive reimbursement, compliance with current measures introduced by the Surgical Care Improvement Project is required. Anesthesia providers commonly administer prophylactic antibiotics and are in the position to provide valuable input in the perioperative setting. This review provides a summary of the most common antibiotics used in the surgical setting—cefazolin, clindamycin, and vancomycin—and their implications to the anesthesia provider, such as proper dosing, targeting bacteria, and side effects.

Keywords: American Society of Health-System Pharmacists, anesthesia, antibiotics, Surgical Care Improvement Project.

Prophylactic antibiotics have become a necessity in most operations. In the United States, surgical site infections (SSIs) are currently the most common nosocomial infection, leading to the greatest costs among hospital-acquired infections.1 The morbidity and mortality risk are decreased by ensuring a clean and sterile surgical site, normothermia, normal blood glucose level, and adequate tissue oxygenation.1,2 Prophylactic antibiotic administration is another critical factor in the prevention of SSIs. For this reason, perioperative antibiotic administration is mandated by the Surgical Care Improvement Project (SCIP) protocol.3 Moreover, with rising healthcare expenses, antibiotics fulfill an important role in decreasing costs. Infections at the surgical site account for approximately $3.5 to $8 billion spent yearly because of a prolonged recovery and a 2 to 11 times longer hospital stay.2,4 One estimate suggests 60% of SSIs are preventable.5 Anesthesia providers can decisively contribute in preventing infections by optimizing antimicrobial dosing: considering the appropriate timing, dosage, and selection of the antimicrobial agent.6 Although SCIP measures help to attenuate nosocomial infections, more stringent safety checklists must be part of the perioperative setting to greatly minimize SSIs from present rates.7,8

This review focuses on 3 commonly administered antibiotics: cefazolin, clindamycin, and vancomycin. Because cefazolin is the most frequently administered antibiotic in the United States, it is crucial to be familiar with its perioperative implications.9 Clindamycin and vancomycin are often given as alternative agents to patients with a β-lactam allergy or a methicillin-resistant Staphylococcus aureus (MRSA) infection.

Anesthesia providers are commonly responsible for the timely administration of antibiotics in the perioperative setting. Unfortunately, there are minimal data available regarding the knowledge and practices of anesthesia providers in this important area. In 2006, researchers surveyed 221 members of what is now known as the Association of Anesthesia Clinical Directors regarding the responsibility, education, and selection of perioperative antibiotics by anesthesiologists.10 Eighty-three percent of respondents indicated that it was the primary responsibility of the surgeon to select the antibiotic, yet 82% indicated they believed there was insufficient education regarding the selection of the appropriate antimicrobial agent.10 Although the subject of antibiotic administration has received considerable attention in recent years, there is, to our knowledge, currently no published research available evaluating beliefs and practices of nurse anesthetists.

Timelines for Antibiotic Administration
The SCIP began in 2002 as the Surgical Infection Prevention project sponsored by the Centers for Medicare and Medicaid (CMS) and the Centers for Disease Control
and Prevention to decrease the incidence of SSIs in major surgical procedures. The project focused on multiple core measures for enhanced intraoperative patient monitoring, such as antibiotic timing and dosing, glucose and temperature monitoring, and venous thromboembolism prophylaxis. Because of high compliance rates of more than 95% in recent years, all but 1 SCIP core measure were retired effective January 1, 2015.11 The core measure still in place is SCIP-INF (Infection) -1. Its protocol states that all patients should have “received” prophylactic antibiotics “within one hour” before surgical incision. This protocol is further clarified by the SCIP in its subsequent description section: “Patients who received vancomycin or a fluoroquinolone for prophylactic antibiotics should have the antibiotics initiated within 2 hours before surgical incision” (emphasis ours).3

Stated in a somewhat similar manner, the American Society of Health-System Pharmacists (ASHP) recommends that administration of the first dose of antimicrobial “begin within 60 minutes before surgical incision” and administration of vancomycin and fluoroquinolones “should begin within 120 minutes of surgical incision” (emphasis ours). It is of interest that both the SCIP and ASHP provide only a vague description as to when antibiotics should be initiated (eg, a dosing window of 60 minutes for cefazolin and 120 minutes for vancomycin). For example, under existing SCIP measures and ASHP guidelines, it would be satisfactory to start an infusion of cefazolin 60 minutes before incision or 180 seconds before incision.3,12 When the use of a tourniquet is indicated for surgery, the ASHP and the American Academy of Orthopaedic Surgeons recommend that the antibiotic be completely infused before inflation.12,13

Currently it is not known whether there is an optimal time for initiation of antibiotics within this 60-minute window (120 minutes for vancomycin or fluoroquinolones). Nevertheless, research has been done that demonstrated a significant difference in the rate of SSIs (1.6% vs 2.4%, P = .04) when quickly injectable antibiotics, such as cefazolin, were initiated “within 30 minutes” before incision rather than closer to 60 minutes before surgical incision.14,15 Of interest in these clinical studies, however, was the researchers’ decision not to include the timeline for completion of the antibiotic administration, which could be a significant variable in study outcomes. A similar outcome in the incidence of SSIs (3.4% vs 7.7%, P = .019) has been reported when vancomycin was initiated within 16 to 60 minutes as opposed to 61 to 120 minutes before incision during coronary bypass and valve replacement surgery.16 Despite these apparent improvements in SSI rates with initiation of antibiotic administration closer to skin incision, the ASHP and SCIP recommendations remain unchanged. According to the ASHP authors, the evidence from these studies was too weak to recommend further refining the dosing window.12 Until future research further clarifies the optimal timing for initiation of antibiotics, the aforementioned guidelines remain accepted best practice.

Cefazolin

Cephalosporins are one of the most commonly administered preemptive antibiotics for surgery in the United States.4 Cefazolin, which belongs to the first generation of cephalosporins, is often chosen as a primary prophylactic antimicrobial agent because of its advantageous profile; it is comparatively cheap, is safe with minimal side effects, and its pharmacodynamics have been well studied.12 In addition, cefazolin is considered a broad-spectrum, β-lactam antimicrobial agent that is available only for parenteral administration.12 Cefazolin directly destroys the targeted bacteria by inhibiting the cell wall synthesis instead of interrupting its reproduction.17,18 The inhibition of bacterial cell wall synthesis occurs through binding and interfering with enzymes called penicillin-binding proteins, which are necessary for the production of the pathogen’s cell wall.18 Cefazolin is able to permeate into most tissues with the exception of the brain.19 Cefazolin shows bactericidal activity primarily against gram-positive aerobic microorganisms, such as staphylococci and streptococci.12,17 Both pathogens have been the main cause of SSIs because they colonize on the skin and enter the body through the surgical site. The internal flora is ideal for opportunistic growth for these cocci as they permeate into internal organs.18

The effectiveness of the antibiotic depends on the lowest concentration it reaches to inhibit growth of a bacterium in an incubator, which is defined by the minimum inhibitory concentration (MIC). It is important to take into consideration that cefazolin has a different MIC for each bacterial species. The MIC for S aureus is 0.25 to 1 µg/mL and for Escherichia coli is 1.0 to 4.0 µg/mL.20 After intravenous (IV) administration of 2 g of cefazolin, its peak serum levels can reach 16 to 45 µg/mL within 30 minutes.21 The half-life of cefazolin is 1.8 hours and thus requires less frequent redosing.12 Current SCIP measures and ASHP guidelines recommend redosing of cefazolin after 2 half-lives have passed, meaning at about every 4 hours or in cases of substantial intraoperative blood loss (ie, greater than 1,500 mL).2,12 Cefazolin is filtered through the glomeruli and excreted by renal tubular secretion. In patients with renal insufficiency, which is defined as having a compromised creatinine clearance of less than 55 mL/min, redosing of cefazolin is not necessary because of the antibiotic’s prolonged half-life and increased unbound tissue concentration in those patient populations.12,22 Once the creatinine clearance is reduced to less than 35 mL/min, the Food and Drug Administration (FDA) recommends to give only half the recommended dose.20

Regarding the administration of cefazolin, a single-
dose vial of either 1 or 2 g can be mixed in sterile water to a concentration of 2.5 mL/g and injected over a minimum of 3 to 5 minutes. The authors acknowledge that administering this recommended reconstituted dose of IV cefazolin is not common practice (injecting 1 g of cefazolin in a total volume of 2.5 mL). On the contrary, it is not unusual to have a 1-g dose of cefazolin prepared in a total volume of 10 mL and 2 g prepared in a total volume of 20 mL. In contrast, an alternative dosing technique provided by the FDA includes administering 1 to 2 g of cefazolin in 50 mL or 100-mL solutions of normal saline, Ringer’s lactate, or 5% dextrose infused over approximately 30 minutes. The FDA-approved injection labels do not provide an explanation for the recommended prolonged infusion time vs the rapid injection time (3 to 5 minutes) for a single bolus.

Myriad antibiotic classes, such as carbapenems, penicillins, monobactams, and cephalosporins, contain a β-lactam ring in their molecular structure to help destroy and disrupt bacterial cell wall synthesis. (Figure 1) At the same time, this molecular structure has been shown to increase resistance and lead to cross-reactivity reactions. A minority of gram-positive bacteria are not sensitive to cefazolin, such as enterococci and MRSA bacteria. Additionally, the gram-negative anaerobe Bacteroides fragilis is resistant to cefazolin. Bacteria develop resistance to cefazolin by secreting β-lactamase, which destroys the β-lactam ring. For this reason, in operations at sites where the aforementioned resistant pathogens are found (eg, distal ilium, colon, appendix), non-β-lactam antibiotics should be administered (eg, gentamicin, vancomycin, and cefoxitin).

Cephalosporin Cross-Reactivity to Penicillin

The existence of the cross-reactivity between cephalosporins and penicillin is widely accepted. Because cephalosporins and penicillins both contain a β-lactam ring, IgE antibodies in individuals who are allergic to penicillins may also recognize and react against cephalosporin antigens (Figure 2).

It is important to determine whether a patient has a true penicillin allergy. A combination of not specifying the allergic response, polypharmacy, and a tendency of clinicians to overdiagnose self-reported penicillin allergies all compromise the reliability of allergy determinations and have led to reports of exaggerated cross-reaction rates between cephalosporins and penicillins. Furthermore, the initial manufacturing process of penicillins from the 1960s to the early 1980s was based on a cephalosporin mold, resulting in cross-contamination during the production of penicillins and subsequent falsely elevating cross-reaction rates to approximately 10% and higher.

To assess the clinical significance of a patient’s penicillin allergy, the clinician should determine the timeline of events between the penicillin administration and when the first signs of an allergic reaction were noted. Signs that occur within 1 to 72 hours after exposure to penicillin belong to the type 1 hypersensitivity reactions. These reactions are acute and IgE-mediated, yielding anaphylactic reactions, such as urticaria, angioedema, laryngeal edema, hypotension, and wheezing. Blood and skin tests are able to detect the IgE penicillin-specific mediators and confirm the allergy.

In contrast, late reactions occur after 72 hours and are classified as type 2, 3, or 4 hypersensitivity reactions and are not as life-threatening as type 1. Types 2 and 3 result in autoimmune responses, whereas type 4 hypersensitivity reactions lead to contact dermatitis. Current research shows cross-reactivity rates of 2% to 4% in patients with a penicillin allergy confirmed by a positive skin test result. The current available penicillin IgE skin test has a specificity of about 99% and a sensitivity of less than 20%, and it takes about 15 minutes until results are available. Assessing for evidence of an acute type 1 allergic reaction should be the primary goal for the anesthesia provider unless the patient has a history of a major non-IgE-mediated reaction (eg, Steven-Johnson syndrome or necrolysis). If a patient presents with a reported cefazolin allergy yet the skin test result is negative, administration of cefazolin is not contraindicated, nor does it increase the risk of adverse reactions. However, it would be prudent not to administer cefazolin in a patient who conveys a history of an allergic response or a patient who is unable to share his or her allergic history (eg, because...
of incapacitation or a neurodegenerative disease), especially if no skin test was performed. Preoperatively, a graded challenge dose (sometimes referred to as a test dose) may be helpful in assessing for an IgE-mediated cefazolin allergy, in which only a small fraction of the prescribed antibiotic (eg, one-tenth of the therapeutic dose) is injected.25,26

Recent research reported that the relative risk of having an anaphylactic response on injection of cephalosporins ranges from 0.1% to 0.001%.25 The risk increases by a factor of 4 in patients who are allergic to penicillin. The hasty determination of patients having a penicillin allergy along with healthcare providers consequently choosing alternative and more expensive agents has been proved to increase healthcare costs.28 Therefore, it is important when interviewing patients to carefully delineate the stated signs and symptoms of allergic responses. For further clarification, performing an IgE-specific skin test may be a helpful tool to eliminate the risk of anaphylactic reactions due to cefazolin administration.

**Clindamycin**

Clindamycin is a lincosamide antibiotic derived from lincomycin and formulated from the amino acid trans-L4-n-propylhygrinic acid of the *Streptomyces lincolnensis* bacteria. Although structurally different from other macrolide antibiotics (Figure 3), such as erythromycin, the mechanism of action against microbes is similar. Bacteriostatic activity occurs by targeting the 50S ribosomal subunit, thereby inhibiting protein synthesis and halting bacterial reproduction.

Clindamycin is effective against gram-positive aerobic bacteria, including staphylococci, streptococci, pneumococci, as well as most gram-positive and gram-negative anaerobic bacteria. Enterococci and gram-negative aerobic organisms are resistant to clindamycin. In light of its spectrum of activity, clindamycin can be used to treat infections of the head and neck, respiratory tract, bone, soft tissue, abdomen, and pelvis. In SSI prophylaxis, clindamycin has been shown to be as effective as cefazolin.33 Earlier data from a prospective randomized controlled trial of 250 patients undergoing appendectomy revealed a lower rate of wound infection when clindamycin was used as the prophylactic antibiotic compared with cefazolin.34

Several synergistic mechanisms inherent to clindamycin, including opsonization, reduced bacterial toxin production; these mechanism and the postantibiotic effect enhance its effectiveness as an antimicrobial agent. Through a process called opsonization, in which a pathogen is marked for ingestion and destruction by a phagocyte, clindamycin enhances the phagocytic action of polymorphonuclear leukocytes. Even in subinhibitory concentrations (ie, serum levels that do not inhibit bacterial growth), clindamycin has been shown to opsonize S aureus, thereby increasing the uptake of leukocytes by the bacteria. Clindamycin has also been shown to suppress toxins produced by the same bacteria. In the case of streptococcal toxic shock syndrome, the release of streptococcal pyrogenic exotoxins, which cause massive cytokine release related to increased morbidity and mortality, were found to be significantly suppressed by subinhibitory concentrations of clindamycin. The postantibiotic effect, common in many classes of antibiotics, suppresses bacterial growth after initial dosing even at subinhibitory concentrations. In contrast to β-lactam drugs, which have either a clinically insignificant or “negative” post-antibiotic effect, clindamycin has variable yet significant postantibiotic effects, increasing its effectiveness as an antimicrobial agent.

The recommended IV dose of clindamycin is 900 mg in healthy adults or 10 mg/kg for pediatric patients (< 18 years). Safety and appropriate dosages in neonates (< 1 month) have not been established.12 The recommended maximum IV infusion rate is 30 mg/min diluted in a minimum of 18 mg/mL of normal saline or 5% dextrose in water (eg, a 900-mg dose should be diluted in a minimum of 50 mL of fluid and infused in no less than 30 minutes). Peak serum levels of IV administered clindamycin are reached in 30 minutes. Clindamycin is metabolized in the liver by cytochrome P450 enzymes. Serum elimination occurs at 3 hours in healthy adults and 2.5 hours in pediatric patients.32 Redosing is recommended after 6 hours of initial administration or after more than 1,500 mL of blood loss.12 Dosage adjustments in the elderly are not necessary because the pharmacokinetics are not altered.33 In patients with markedly decreased hepatic or renal function, elimination half-life is only slightly increased; therefore dosage adjustments are also not necessary.33 Dosing adjustments for obese patients are not currently available.

Current guidelines for antimicrobial prophylaxis in surgery recommend clindamycin as an alternative to cefazolin in patients with a documented β-lactam allergy. In hysterectomies, cesarean deliveries, appendectomies, and surgical procedures involving the gastro-duodenal tract, biliary tract, small intestine, colon, and rectum, it is recommended to use clindamycin in conjunction with aztreonam (a monobactam) or a fluoroquinolone such as ciprofloxacin.12

Clindamycin should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis, because it has been associated with *Clostridium difficile*-associated diarrhea. By disrupting the normal flora of the colon, overgrowth of clostridia may ensue, potentially leading to pseudomembranous colitis and colonic perforation if left untreated.36

**Vancomycin**

Vancomycin (Figure 4) is a glycopeptide and is predomi-
nantly active against gram-positive bacteria, including staphylococci and streptococci strains. Glycopeptides, including vancomycin, exert their bactericidal action through the inhibition of bacterial cell-wall synthesis. Vancomycin is primarily renally excreted and has a MIC of 2 µg/mL for treating most gram-positive microorganisms, including MRSA. Vancomycin distributes widely into various tissues and body fluids, even permeating into the cerebrospinal fluid, making it a treatment option for meningitis. The SCIP guidelines recommend initiating vancomycin within 2 hours before surgical incision. Vancomycin can induce serious infusion rate–dependent hypersensitivity reactions from histamine release, known as red man syndrome (RMS). An infusion of 1 g of vancomycin over 2 hours releases a notably lower amount of histamine compared with administering 1 g of vancomycin over 1 hour. For this reason, safe infusion rates of vancomycin have been determined to be at a maximum of 15 mg/min or 1 g/h, with the tendency to infuse slower if time permits. These rates ensure decreased release of histamines and consequently reduced risks of RMS. Signs and symptoms of a hypersensitivity reaction include acute rash in the neck and head area, pruritus, hypotension, and angioedema. Signs of RMS can be noticed from 4 to 10 minutes after starting the infusion. Its treatment primarily consists of immediately stopping the vancomycin infusion as well as administering antihistamines, such as diphenhydramine, 50 mg. For attenuation of adverse effects, 1 g of vancomycin is infused slowly and diluted in a minimum of 200 mL/g of IV solution using either normal saline, lactated Ringer’s, 5% dextrose, or sterile water. Patients with comorbidities or who are on an antihistamine regimen are less likely to experience RMS.

The essential difference between vancomycin and β-lactam antimicrobials, such as penicillin or cefazolin, is that vancomycin lacks a β-lactam structure. Hence, vancomycin is not susceptible to β-lactamases, which are enzymes produced by bacteria for resisting β-lactam antimicrobials, and therefore is used as first-line treatment in cases of MRSA infections. Vancomycin has an adult half-life of 4 to 8 hours and a dosing recommendation of 15 mg/kg for adults and pediatric patients aged 1 to 18 years. Because of its long half-life, no redosing is usually warranted.

In summary, vancomycin is used as an alternative bactericidal agent for surgical procedures in which the patient has a history of a cefazolin allergy or of MRSA. The primary reason it is administered or not used in selected cases include either its relatively narrow bactericidal spectrum against gram-positive and very few gram-negative pathogens or extra fluid is required to administer the antimicrobial agent to patients. The latter is applicable in patients with fluid restrictions, such as those with heart failure or treated with renal dialysis. Vancomycin must be diluted, according to the manufacturer’s recommendation, to a minimum of 2.5 to 5 mg/mL (eg, 1 g mixed with 200 mL of diluent) and infused over 60 to 120 minutes (ie, 10-15 mg/min) to prevent thrombophlebitis and RMS.

Figure 3. Molecular Structure of Clindamycin

Figure 4. Molecular Structure of Vancomycin

**Conclusion**

The first-generation cephalosporin, cefazolin, is often chosen as a primary prophylactic antimicrobial agent because of its advantageous profile; it is comparatively inexpensive, has minimal side effects, and destroys the most potent aerobic gram-positive bacteria that cause SSIs (ie, staphylococci, streptococci). For patients with β-lactam allergies, the lincosamide clindamycin is the first-line alternative agent because it does not contain a β-lactam ring. Besides having bactericidal activity against the same bacteria as those of cefazolin, clindamycin kills anaerobic gram-positive and gram-negative bacteria.
Vancomycin resembles clindamycin in many respects in that it too does not contain a β-lactam ring and thus serves as an alternative agent to cefazolin. Vancomycin is considered the first-line treatment in patients with MRSA infections. Because of complications associated with vancomycin, such as RMS, prolonged infusion times, and potential bacterial resistance, cefazolin and clindamycin are still the preferred antimicrobials.

The latest guidelines for prophylactic antibiotics from the ASHP provide important updates such as “initiation of antibiotics within 60 minutes of incision” instead of at the “start of anesthesia.” The dosing guidelines for cefazolin, vancomycin, and clindamycin have also been updated in the latest ASHP document of 2013 (Table). Redosing of antibiotics should be performed if the surgical procedure exceeds 2 half-lives of the antimicrobial or there is blood loss greater than 1,500 mL.12,42 Financial incentives and reimbursements from CMS require continual adherence to SCIP measures. Because anesthesia providers are actively involved in the administration of perioperative antibiotics, education about the most commonly used antimicrobials remains a high priority to ensure low SSI rates, limit hospital expenses, and increase good patient outcomes.

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DISCLOSURES

The authors have declared no financial relationships with any commercial entity related to the content of this article. The authors did discuss off-label use within the article.