CME

Administration of Parenteral Prophylactic Beta-Lactam Antibiotics in 2014: A Review

Ronald J. Gordon, MD, PhD

The role of the anesthesiologist in reducing the incidence of surgical-site infections by the administration of prophylactic parenteral beta-lactam antibiotics is reviewed. Suggestions are made with regard to timing, dosing, and method of administration of these drugs to potentially reduce the risk of surgical-site infection. (Anesth Analg 2015;120:877–87)

As of 2014, the administration of prophylactic parenteral antibiotics in the perioperative period is well embedded into the practice of anesthesia. In popular jargon, we "own it," and are responsible for assuring perioperative prophylactic parenteral antibiotics are given so as to optimize their effectiveness, thereby minimizing the incidence of surgical-site infections (SSIs). It is proper and fitting that this should be so, both because of our role as perioperative physicians and by virtue of our central position within the flow of the surgical patient's care. Before 2006, this was not the case. Prophylactic antibiotics often were given by the nursing staff, either on the hospital floor or in the preoperative holding area. However, the aggressive and comprehensive efforts of major figures in the health care establishment, such as Donald Berwick through the Institute for Healthcare Improvement and the "100,000 lives campaign,"[1] as well as the Centers for Medicare and Medicaid's (CMS) efforts to improve medical quality via the physician's quality reporting initiative, rapidly moved this responsibility to the anesthesia health care team. For us to be more than just technicians, administering medications ordered by the surgical resident or attending without having any input, we require an understanding of the pharmacokinetics and pharmacodynamics of prophylactic parenteral antibiotics. It is imperative that we act in a manner befitting our dual roles as the surgical team member responsible for providing safe and optimal operating conditions, as well as being a significant contributor to efforts to reduce longer-term perioperative complications.[2,3] Such complications include SSIs, chronic pain, perioperative myocardial and pulmonary events, and venous thromboembolic phenomena. To effectively provide such benefits to our patients, there must also be a mutually respectful symbiotic relationship between surgeon and anesthesiologist.[2]

The following discussion focuses on the problem of hospital-acquired infections (HAIs) after surgery. The proper administration of prophylactic beta-lactam antibiotics is then reviewed. It is common knowledge among medical providers that HAIs (or as they are more commonly known, SSIs) are a major perioperative complication and add markedly to the cost of health care for the American public. A recent study indicated that the annual cost associated with HAIs in the United States is approximately 9.8 billion dollars.[4] A significant component of these HAIs and costs occurs after surgical procedures.[4] For example, a SSI in a routine ventral hernia repair with mesh can add more than $100,000 to the patient's total cost of care.[a]

SSIs are the most common reason for hospital readmission after surgery.[b] In elderly patients, the complication of a deep incisional or organ space infection increases mortality by a factor of 4 and average hospital stay by 15.7 days.[5] The US Department of Health and Human Services' Administration on Aging website projects the number of elderly Americans will grow from 39.6 million in 2009 to 72.1 million in 2030. Hence, the importance of this issue with regard to patient morbidity, mortality, and health care costs will continue to increase. Historically, prevention and treatment of SSIs has been within the purview of the operating surgeon, but recently the complementary role of the anesthesia provider has received attention.[6–16] Our specialty has much to contribute in the battle against this major health care issue. Efforts to broaden the scope of anesthesia care, for example, with the development of the perioperative surgical home[17] or protocols for enhanced recovery after surgery,[18] increasingly focus on the role of the anesthesiologist in influencing long-term patient outcomes.[3,11,16]

Anesthetic interventions potentially effective in decreasing SSIs derive from 5 fundamental pathophysiologic principles:

1. SSIs develop after inoculation of bacteria of sufficient dose and virulence into tissue to overcome local host defenses, which in turn may be weakened by such factors as hypoxia, surgical stress, blood transfusion, pain, and hyperglycemia.

From the Department of Anesthesia, Naval Medical Center San Diego, San Diego, California; Department of Anesthesia, the Veteran's Administration Hospital San Diego, San Diego, California; and Department of Anesthesia, the University of California Medical Center, San Diego, San Diego, California.

Accepted for publication August 13, 2014.

Funding: None.

The author declares no conflicts of interest.

Reprints will not be available from the author.

The views expressed in this article are those of the author and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.

Address correspondence to Ronald J. Gordon, MD, PhD, Clinical Investigation Department (KCA), Naval Medical Center San Diego, 34800 Bob Wilson Dr., Suite 5, San Diego, CA 92134. Address e-mail to rjgordonmd@gmail.com.

DOI: 10.1213/ANE.0000000000000468

[a]Colavita PD, Zemlyak AY, Burton PV, Dacey KT, Walters AL, Lincourt AE, Tsirline VB, Augenstein VA, Kercher KW, Heniford BT. The expansive cost of wound complications following ventral hernia repair. American College of Surgeons Clinical Congress 2013. Walter E. Washington Convention Center, Washington, DC, October 7, 2013. Scientific Sessions. Available at: http://web2.facs.org/cc_program_planner/Detail_Session_2013.cfm?CCYEAR=2013&SESSION=SP04&GROUP=SP. Accessed June 21, 2014.

[b]Outpatient Surgery. February 2014. Available at: http://www.outpatientsurgery.net/surgical-facility-administration/infection-control/study-finds-ssis-the-best-predictor-of-surgical-readmissions--02-19-14. Accessed June 21, 2014.

2. The primary host defense is oxidative killing by neutrophils.
3. Neutrophils must be delivered in sufficient number to be effective, dependent in part on local capillary blood flow. Hypothermia, hypovolemia, and increased sympathetic tone decrease capillary blood flow whereas interventions that reduce sympathetic tone, such as neuraxial anesthesia, increase capillary blood flow.
4. The time from skin incision to a few hours after skin closure is a decisive period[6,19,20] during which infection is established. Modifications in anesthetic management to decrease SSIs are most effective when implemented during this decisive period.
5. To optimize effectiveness, prophylactic antibiotics must be administered at a proper time in sufficient dose and with sufficient frequency such that the maximum tissue concentration occurs at the time of incision[21–23] and tissue concentrations exceed the minimum inhibitory concentration (MIC) of potential microbial pathogens for the duration of the decisive period.[24]

It follows that anesthesiologists potentially may contribute to a reduction in the frequency of SSIs in many ways. Interventions suggested (but not necessarily proven) to be beneficial include frequent handwashing,[12–14] maintenance of intraoperative normothermia,[6,8,15,16] neuraxial anesthesia,[9] modest glucose control (maintaining blood levels <200 mg%),[25] induced hypercarbia,[6,7] increased inspired oxygen concentrations,[6,8,11] timely administration of prophylactic antibiotics,[15,24] minimization of operating theater traffic,[26] avoidance of blood transfusions,[8,26] and effective postoperative pain control.[6,11] Of these, perioperative temperature management and timely administration of prophylactic parenteral antibiotics have become accepted universally and are integrated widely into clinical practice in the United States. These latter 2 interventions also are included in the Surgical Care Improvement Project (SCIP) Module 1 on prevention of SSIs and in the CMS Physician Quality Reporting System (PQRS) measures 193 and 30:

PQRS Measure 193. Perioperative Temperature Management: Percentage of patients, regardless of age, undergoing surgical or therapeutic procedures under general or neuraxial anesthesia of 60 minutes' duration or longer, except patients undergoing cardiopulmonary bypass, for whom either active warming was used intraoperatively for the purpose of maintaining normothermia, or at least one body temperature ≥36°C (or 96.8°F) was recorded within the 30 minutes immediately before or the 15 minutes immediately after anesthesia end time.

PQRS Measure 30. Perioperative Care: Timely Administration of Prophylactic Parenteral Antibiotics: Percentage of surgical patients aged 18 years and older who receive an anesthetic when undergoing procedures with the indications for prophylactic parenteral antibiotics for whom administration of the prophylactic antibiotic ordered has been initiated within 1 hour (if fluoroquinolone or vancomycin, 2 hours) before the surgical incision (or start of procedure when no incision is required).

Most medical centers in the United States require anesthesia providers to be in compliance with these CMS measures, and within the realm of publicly reported quality yardsticks, they represent (along with the central line placement, PQRS Measure 76) the only publicly available means of assessing anesthesia care.[27] Current efforts by such organizations as the Anesthesia Quality Institute certainly will lead to much more comprehensive and useful assessments of anesthesia quality of care,[2,27] but at present, the CMS measures are all that is available. To be sure we "tow the mark" regarding compliance with these measures, starting in 2013 CMS imposed penalties (assessed in 2015) on anesthesia providers for noncompliance. It is disconcerting then, with so much riding on compliance with measure 30, that a number of editorials and studies by prominent authorities in the field call into question the clinical benefit of its enforcement. We are troubled by missives such as "Surgical Care Improvement: Should Performance Measures Have Performance Measures,"[28] "SCIP to the Loo,"[29] "Reducing the Risk of Surgical Site Infections: Did We Really Think SCIP was Going to Lead Us to the Promised Land?"[21] and "Is it time to refine? An exploration and simulation of optimal antibiotic timing in general surgery,"[30] all of which question the clinical benefit of enforcement of performance measure 30. A major goal of the SCIP project was the reduction of SSIs by 25%.[21] To date, despite the almost universal implementation of measure 30, very little if any reduction has occurred.[31] It is therefore a most appropriate time to revisit and reevaluate current literature on this topic.

The remarks that follow relate primarily to the beta-lactam class of antibiotics. This group includes the penicillins, cephalosporins, and carbapenems and is widely used in clinical practice. The beta-lactams exhibit pharmacodynamic behavior suggesting the possibility of more effective utilization. In contrast to the fluoroquinolones and aminoglycosides, the beta-lactams (as well as clindamycin) work primarily via a process termed "time-dependent killing."[32] In time-dependent killing, the fraction of time the drug concentration exceeds MIC is the primary determinant of effectiveness.[32–40] The beta-lactams also demonstrate a limited postantibiotic effect (the ability to continue bacterial killing after the concentration of the drug is below MIC), whereas the fluoroquinolones and aminoglycosides exhibit primarily concentration-dependent killing and a pronounced postantibiotic effect.[32] For these latter drugs, the maximum concentration achieved and the area under the concentration-time curve are the most important variables. Drugs such as vancomycin exhibit both time-dependent killing and a moderate postantibiotic effect. Examples of the different drug classes are listed in Table 1. Beta-lactams such as cefazolin are also highly protein bound, and only the free or unbound drug has antibacterial activity.[42] To influence bacterial virulence by virtue of the inhibition of bacterial cell wall synthesis (the primary mechanism of action of the beta-lactams), the unbound drug must first achieve an effective concentration throughout the interstitial fluid.[40] In most literature on the subject, the terms "tissue concentration" and "interstitial fluid concentration" are used interchangeably, and that convention will be followed here. Thus, to be effective, the unbound drug must pass though the capillary membrane, diffuse throughout the interstitial fluid to reach the offending pathogens, and finally bind to the penicillin-binding proteins on the bacterial wall. This process by necessity takes time, dependent on such factors

Table 1. Pharmacodynamics of Representative Prophylactic Antibiotics

Antibiotic/class	Surgical procedure and routine pathogens	Mechanism of action	Postantibiotic effect	Usual dose in adults	Half-life with normal renal function	Redosing interval (1–2 half lives)
Cefazolin (first-generation cephalosporin, a beta-lactam)	Cefazolin is the most commonly prescribed of the prophylactic antibiotics; it is recommended for all clean surgeries and many clean-contaminated surgeries: coverage includes *S epidermidis*, *S aureus*, streptococci, and gram-negative aerobes	Time-dependent killing	Minimal	1–2 g, 3 g for patients ≥120 kg	1.2–2.2 h	3 h[a]
Cefuroxime (second-generation cephalosporin, a beta-lactam)	An alternative to cefazolin with similar coverage: slightly broader gram-negative coverage	Time-dependent killing	Minimal	1.5 g (this dose is traditionally used for all adult patients)	1–2 h	3 h
Cefoxitin (second- generation cephalosporin, a beta-lactam)	Clean-contaminated surgeries such as colon resection: enteric gram-negative bacilli, anaerobes esp. *Bacteroides*	Time-dependent killing	Minimal	2 g	0.7–1.1 h[b]	2 h
Cefotetan (second-generation cephalosporin, a beta-lactam)	Clean-contaminated surgeries such as colon resection, an alternative to cefoxitin: enteric gram-negative bacilli, anaerobes esp. *Bacteroides*. Commonly used in gynecological surgeries.	Time-dependent killing	Minimal	2 g	2.8–4.6 h	6 h
Clindamycin (lincosamide)	An alternative to cefazolin in IgE-mediated penicillin allergic patients: *S. aureus*, *S. epidermidis*, streptococci, anaerobes	Time-dependent killing	Moderate	0.9 g	2–4 h	6 h
Ampicillin-sulbactam (combination penicillin, beta lactamase inhibitor)	Clean-contaminated surgeries (often head and neck): common gram positives, gram negatives, anaerobes, enterococci	Time-dependent killing	No	3 g	0.8–1.3 h	2 h
Ciprofloxacin[c] (fluoroquinolone)	Enteric gram-negative bacilli (often used in urological procedures as a 0.5 g po dose)	Concentration-dependent killing	Pronounced	0.4 g	3–7 h	8 h
Vancomycin[c,d] (glycopeptide)	Often used for patients who are allergic to penicillin in place of cefazolin. Covers common gram positives, MRSA.	Mixed properties	Moderate	0.015 g/kg	4–8 h	Not applicable
Metronidazole (nitroimidazole)	Covers anaerobes including *Clostridium difficile*. Often used in combination with cefazolin for clean-contaminated surgeries, especially colon surgery	Concentration-dependent killing	Pronounced	0.5 g	6–10 h	Not applicable

MRSA = methicillin-resistant *Staphylococcus aureus*.

[a]The American Society of Health-System Pharmacists recommends 4 hours, but other institutions and authors suggest redosing at 3 hours.[c] Twice the minimum half-life of 1.2 hours would give a redosing interval of 2.4 hours. The shorter the redosing interval the greater the likelihood antibiotic concentrations will always exceed the minimum inhibitory concentration.

[b]As with most beta-lactams, this is markedly dependent on creatinine clearance.[41]

[c]Because these drugs cannot be administered by bolus infusion, secondary to undesirable side effects, administration times refer to the initiation of infusion.

[d]In very prolonged cases (more than 10–12 hours), either the creatinine clearance or a measured drug level could be used to determine the requirement for an additional dose of vancomycin.

as the free drug's diffusion coefficient and the average distance from blood vessel to tissue. For the obese patient, this average distance is increased,[43,44] and the antibiotic transport time is by necessity also increased. Finally, all things being equal, prophylactic antibiotic administration should be timed such that maximum tissue concentrations are achieved immediately before times of known bacterial seeding, for example, during skin incision or bowel entry in clean-contaminated cases.[21–23] Because it is well known that tissue concentrations of antibiotics vary significantly between skin, adipose tissue, muscle, and omentum secondary to variations in capillary perfusion,[45–48] striving for a maximum average tissue concentration at incision is most likely to ensure adequate antibiotic coverage at all sites of potential contamination.[21–23]

TIMING OF INITIAL DOSE OF PROPHYLACTIC PARENTERAL ANTIBIOTICS

As measure 30 is currently written, we are free to administer the selected antibiotic 60 minutes before skin incision, 30 minutes before skin incision, or 30 seconds before skin incision. We are free to administer the drug after tourniquet inflation in an orthopedic procedure, as long as that occurs before skin incision. Most authorities would consider administration of prophylactic parenteral antibiotics 30 seconds before skin incision or after tourniquet inflation (often during the surgical "time out") suboptimal care because the tissue levels of the drug at the commencement of surgery would be expected to be quite low. Deiner and Silverstein[16] stated it well when they noted, "if prophylaxis is started as soon as 1 minute before incision, the OR team is still in compliance from a regulatory perspective. Although this practice may follow the strict definition of the criteria, it certainly does not follow our understanding of the science and therefore the spirit of the criteria."

With these remarks as background, it is helpful to review in simple terms the science in question. Starting with the fundamental studies of Burke,[19,20] it has been demonstrated that for antibiotics to be effective in reducing the incidence of SSIs, they must be present at sufficient levels within the at-risk tissues at the time of bacterial inoculation and throughout the surgical procedure (principle 5 above).[24] The 2013 revised policy paper on prophylactic antibiotics developed jointly by the American Society of Health-System Pharmacists (ASHP), the Infectious Disease Society of America, the Surgical Infection Society, and the Society for Healthcare Epidemiology of America[24] (which P. S. Barie[49] refers to as a "must read must heed" for every surgeon) states:

"Successful prophylaxis requires the delivery of the antimicrobial to the operative site before contamination occurs. Thus, the antimicrobial agent should be administered at such a time to provide serum and tissue concentrations exceeding the minimum inhibitory concentration (MIC) for the probable organisms associated with the procedure, at the time of incision, and for the duration of the procedure."

[c]Surgical prophylaxis antibiotic guidelines. Rochester General Health System. September 2012. Available at: http://nebula.wsimg.com/9678632ff686d48917fa1a34bc83f4ef?AccessKeyId=FD7CB6ADC6CB16B0172B&disposition=0&alloworigin=1. Accessed June 21, 2014.

Because it is also desirous that antibiotic tissue concentrations be maximal at times of greatest risk, it follows that sufficient time must elapse after IV infusion for peak tissue and interstitial fluid concentrations to be achieved at incision. Weber et al.[50] note that for cefuroxime, drug administration less than 30 minutes before skin incision may provide insufficient time to achieve adequate tissue concentrations. Andersson et al.,[23] in discussing the strategy for antibiotic infusion, state "current knowledge suggests that this is approximately 30 minutes before incision in relation to the type of antibiotics with a half-life of 30 minutes." The authors then go on to suggest 15 to 45 minutes before incision or tourniquet application as an acceptable time span for infusion. Edmiston et al.[21] note that "pragmatically, the likelihood of achieving the maximum tissue concentration at 30–45 minutes before incision is greater than if the drug is bolused 5–10 minutes before incision." Stefánsdóttir et al.[51] also advocate administering the antibiotic 30 minutes before incision, again with a range of 15 to 45 minutes considered acceptable. Indeed, the overwhelming majority of available studies are consistent with an optimal preincision infusion time window between 15 and 45 minutes. Consistent with these empirical guidelines, the careful microdialysis studies of Toma et al.[45] demonstrate that for cefoxitin, the peak tissue concentration in adipose tissue is reached at an average time of 29 ± 11 minutes after rapid IV infusion.

It would be surprising indeed if antibiotic infusion 15 to 45 minutes before incision ensured optimal tissue and serum concentrations for every beta-lactam, but because the molecular size of most of these drugs are similar, it is not an unreasonable assumption. Clinical studies by Davies et al.[52] in which they compare cefamandole, cefuroxime, and cephradine in 60 patients with hip replacement are consistent with the premise. These authors note "we feel that the three agents when given at the same dose showed a similar pharmacokinetic profile; the choice of antibiotic for chemoprophylaxis for total hip replacement should be influenced by the likely pathogens and the cost of the drug."[52] As noted previously, for the morbidly obese patient, the average distance from capillary to tissue is increased,[43,44] suggesting that a longer diffusion time may be required for the antibiotic to reach maximum tissue levels. It would seem prudent therefore, based on the recommendations and clinical studies noted, to further tighten our antibiotic infusion time to 30 to 45 minutes when possible (the pragmatic suggestion of Edmiston et al.)[21] for the obese patient. In such a manner, we are more likely to achieve the goal of maximum tissue concentrations at the initiation of surgery. Before we can make this universal recommendation, however, the ASHP admonition that tissue concentrations should exceed MIC for the "duration of the procedure" also must be considered.

For those antibiotics with relatively short half-lives (e.g., cefoxitin 0.7–1.1 hours) or for lengthy procedures, the tissue concentrations may be inadequate in the latter stages of the operation (particularly for the morbidly obese patient, whose tissue concentrations may never achieve effective levels).[45–47] Hence, administering the antibiotic closer to incision (for example, 0–10 minutes) may provide an insufficient interval to maximize tissue concentrations at incision but may have the alternative benefit of increasing the

portion of the decisive period for which the antibiotic concentration exceeds MIC. This trade-off between assuring tissue concentrations are maximum at incision and maintaining tissue concentrations above MIC for the majority of the operative procedure suggests clinical studies may show conflicting results in terms of when to administer the initial antibiotic dose. For example, according to Dellinger[53]:

"Some have questioned whether giving the antibiotic too close to the time of incision might have less efficacy, but the data of van Kasteren et al. and others are reassuring in this regard. It is important to observe that, although there was no statistically significant difference between the results of administration of prophylaxis during the intervals of 30 to 60 minutes and 0 to 30 minutes before incision, the results during the 0- to 30-minute interval actually showed a lower rate of SSI, which lends no credence to the concern that administration of prophylaxis close to the time of incision might be less effective. However, for total hip arthroplasty, administration of prophylaxis during the 60 minutes before incision had equally good results. This may be because the average duration of operation was only 79 minutes, and thus, administration of prophylaxis even 1 hour before incision would be expected to achieve therapeutic levels of antibiotics throughout the duration of operation. The longer the operation, the more benefit is achieved by administration of prophylaxis as close as possible to the time of incision." Steinberg et al.[54] also argues against the concern over giving antibiotics too close in time to incision. We see 2 different factors at play with respect to antibiotic timing: (1) high tissue levels are desired at skin incision, which is more likely to occur when antibiotics are given approximately 15 to 45 minutes out; and (2) tissue levels above MIC are desired for the duration of the operative procedure, which is more likely to occur when the antibiotic is given immediately before incision. These concepts are illustrated in Figs. 1 and 2, wherein the stippled areas represent the time periods for which tissue concentrations are below MIC.

In other studies, in an analysis of 3836 patients using a single dose of cefuroxime, Weber et al.[50] found that administration of the antibiotic 30 to 60 minutes before incision more effective than administration 0 to 30 minutes before incision. Here again, these data are not inconsistent with the benefits of using the 15- to 45-minute time interval, but rather that time interval was not examined. Steinberg

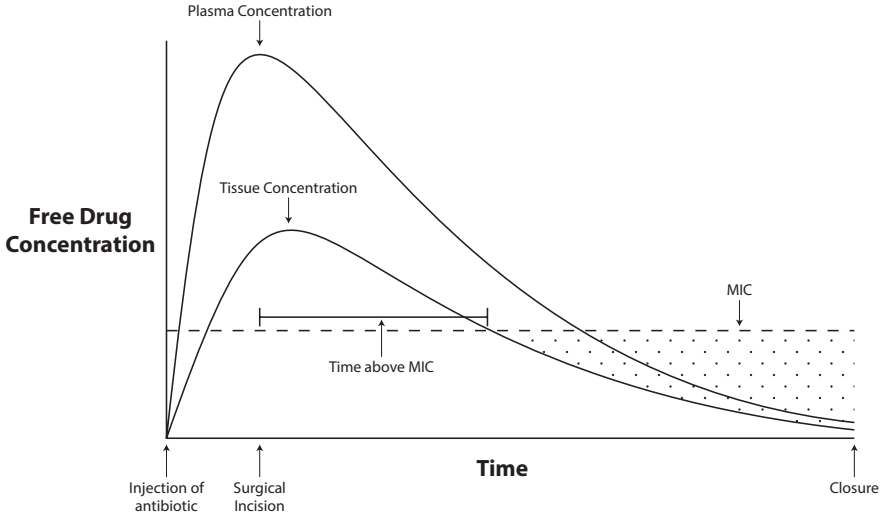

Figure 1. Schematic representation of plasma and tissue concentration of antibiotic compared with time when drug is administered approximately 30 minutes before incision. The stippled area represents the period during which antibiotic concentrations are subtherapeutic. For concentration-dependent antibiotics such as ciprofloxacin, the peak tissue concentration is the important variable. Ideally, this should be achieved simultaneously with surgical incision.

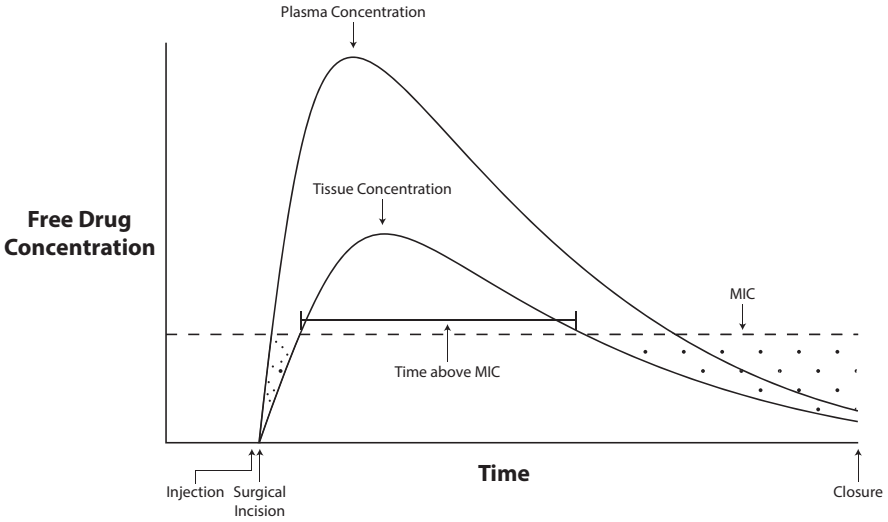

Figure 2. Schematic representation of plasma and tissue concentration of antibiotic compared with time when drug is administered immediately before incision. Note the time above minimum inhibitory concentration is increased in this example. The stippled area represents the period during which antibiotic concentrations are subtherapeutic.

et al.[54] studied data from 4472 cardiac, hip/knee, and hysterectomy cases and found the lowest rate of infection when antibiotics were given within 30 minutes of incision. An examination of their data demonstrates once again consistency with the 15- to 45-minute interval. In contrast, in a recent analysis of 32,459 Veterans Affairs surgeries, Hawn et al.[55] found greater rates of SSI for procedures during which the antibiotic was started more than 60 minutes before incision but not for antibiotics administered after incision. The authors concluded, "while adherence to (measure 30) is not bad care, there is little evidence to suggest it is better care." In Hawn et al.'s study, there was no limitation on the length of surgery, and redosing of antibiotics was not examined. Koch et al.[30] examined rates of SSIs in 6731 patients who underwent 7095 procedures. Their results were limited to procedures of less than 4 hours in duration. Four hundred forty-four patients developed a SSI. The authors found a continuous decrease in rates of SSI as the time between administration of antibiotics and surgical incision was shortened, with 4 minutes before incision as the optimal time for infusion. They concluded that antibiotic administration should be moved closer to incision time, in particular within 18 minutes of incision with a 95% confidence limit.[30]

In another study of 28,250 cardiac surgery patients, Koch et al. found that for cefuroxime initiation of administration of the antibiotic 15 minutes before incision resulted in the lowest SSI rate, whereas for vancomycin the optimal time to initiate infusion was 32 minutes before incision.[56] Here yet again the data are consistent with a range of 15 to 45 minutes leading to the lowest rate of SSIs. It is notable that available studies demonstrate that it does not take long for many antibiotics to achieve adequate tissue levels after bolus IV administration (in studies by DiPiro et al.[57] and Wong-Beringer et al.,[58] measurable tissue levels of cefoxitin and cefazolin and cefmetazole, respectively, were found within a few moments of infusion), but it does seem to require approximately 15 to 30 minutes for most cephalosporins to reach maximum tissue levels. Even in the study by DiPiro et al.,[57] not all patients had measurable tissue levels in muscle at 20 minutes. van Kasteren et al.[59] noted that for total hip arthroplasty procedures, optimal antibiotic administration times clustered around 30 minutes before incision, although the data did not reach statistical significance. A summary of some of the recent major studies on timing in the "SCIP era" primarily for the beta-lactams is listed in Table 2.

REDOSING OF PROPHYLACTIC PARENTERAL ANTIBIOTICS AND CONTINUOUS INFUSION

The plasma half-life of cefazolin is estimated at 1.2 to 2.2 hours.[24] As the plasma concentration decreases, so ultimately does the tissue concentration. Administering cefazolin 30 minutes before skin incision may lead to peak tissue levels at incision, but rapidly decreasing plasma and tissue levels thereafter. Giving cefazolin closer to the time of incision results in lower tissue concentrations at incision but greater tissue concentrations at closure. As emphasized previously, because cephalosporins work via time-dependent killing, it is the time above MIC rather that the maximum concentration reached, which determines effectiveness. The ASHP recommends redosing at intervals of approximately 2 half lives.[24] Hence, for cefazolin, a redosing interval of 4 hours is suggested, whereas for ampicillin-sulbactam, a redosing interval of 2 hours is suggested. Ho et al.[60] and Goede et al.[61] have also emphasized the importance of redosing. In Goede et al.'s study, the lack of redosing had the greatest noncompliance (45.1%) among the various SSI prevention measures analyzed. Those studies in which redosing was used indicate this in turn results in a sinusoidal or sawtooth type of concentration profile, with drug levels alternatively peaking and decreasing.[22] Many authors have suggested that a continuous infusion after the initial prophylactic bolus injection so that the total amount of drug infused stays the same for lengthy cases is much more in keeping with the pharmacokinetics and pharmacodynamics of the beta-lactams.[22,33–40] For example, if cefazolin is given at an initial dose of 2 g in a 100-kg individual and 3 hours later is redosed with an additional 2 g, with continuous infusion the drug is immediately started at a rate of 2 g over 3 hours after the initial bolus, so that at the end of 3 hours of surgery a total of 4 g has been given. In this manner, assuming the drug reaches a steady-state concentration, we conform to the optimal time-dependent killing concentration profile. Although clinical studies demonstrating a reduced rate of SSIs are not available, numerous authors have suggested such an approach to be beneficial.[22,33–40] Available data by Adembri et al.[22] measuring tissue levels in cardiac surgery patients shows a clearly beneficial effect on antibiotic concentrations in atrial tissue with continuous administration at the same total dose of cefazolin. In their study, plasma concentrations of cefazolin remained above MIC for >90% of the surgical procedure in 9 of 10 patients for continuous infusion, whereas only 3 of 10 patients in the bolus dosing group achieved plasma concentrations above MIC for >90% of the procedure at the same total dose. In addition to the pharmacokinetically calculated and expected decrease in antibiotic concentrations with time due to physiologic clearance, some surgeries also are associated with significant blood loss and fluid requirements. Both factors result in additional decreases in antibiotic tissue concentrations, either as a result of dilution or elimination. Current recommendations in this area are limited, but some authors recommend redosing for >1500 cm^3 of estimated blood loss.[24] Assuming an average blood volume of 5000 cm^3, 1500 cm^3 of blood loss would reduce plasma levels of antibiotics (assuming euvolemia) by 30%. Because blood volume varies significantly in the adult patient population, a better approach would be to calculate the total blood volume using the Lemmens formula (see next section) and redose at a 30% estimated blood loss.

WEIGHT-BASED DOSING AND OTHER ESTIMATES OF ANTIBIOTIC REQUIREMENTS

To simplify dosing schedules for commonly used beta-lactams, often 1 g of cefazolin, cefoxitin, or cefotetan is used for patients ≤70 kg and 2 g for patients ≥70 kg. For cefuroxime, 1.5 g often is used for all patients. In Chopra et al.'s[62] study on obese patients, a dose of 3 g of cefazolin was recommended for patients with a body mass index (BMI) >50. It is evident, however, that the 1.5-m tall, obese individual with a BMI of 50 will have a far smaller blood volume than

Table 2. Summary of Recent Timing Studies on Antibiotics

Publication year	Author	Number of procedures/SSIs	Timing recommendations	Study design	Comments
2013	Hawn et al.[55]	32,459/1497	Greater SSI rates for administration > 60 min before but not after incision. Concluded adherence to timely antibiotic administration did not improve care.	Retrospective cohort study using national Veterans Affairs patient-level data on orthopedic, vascular, colorectal, and gynecological procedures from 2005 to 2009	Did not consider redosing or limit duration of procedures studied.
2013	Koch et al.[30]	7095/444	Recommend moving infusion closer to incision time (0–18 min). But data are also consistent with 15- to 45-min window for infusion of antibiotics.	Prospective cohort study using National Surgical Quality Improvement Program data for 6731 patients who underwent 7095 general surgery procedures from 2006 to 2012	Excluded vancomycin and procedures longer than 4 h
2012	Koch et al.[56]	28702/590	Timing recommendations varied for vancomycin and cefuroxime but analysis of results suggests 15–45 min optimal infusion time for either drug.	Prospective cohort study undergoing cardiac surgery procedures from 1995 to 2008	Duration of procedures and redosing were not considered.
2009	Steinberg et al.[54]	4472/113	30 min before incision was optimal.	Prospective cohort study from 29 hospitals from randomly selected cardiac, hip/knee arthroplasty, and hysterectomy cases	Intraoperative redosing in cases >4 h appeared to reduce SSI risk, but only if preoperative dose was administered correctly.
2008	Weber et al.[50]	3836/180	For cefuroxime, 30–59 min was best. Did not examine 15- to 45-min time period.	Prospective observational cohort study of 3836 patients	No redosing noted.
2007	van Kasteren et al.[59]	1922/50	Total hip arthroplasty, relatively short procedures, 30 min before incision was optimal although data did not reach statistical significance.	Prospective observational cohort study of 1922 patients with hip arthroplasty	Noted advantage of giving antibiotic close to incision time: measurable tissue levels at end of procedure. Intraoperative redosing was not administered.

SSI = surgical site infection.

the 2.0-m tall individual with a BMI of 50, and in the former case, the initial plasma concentration of cefazolin will consequently be significantly higher. The ASHP recommends a dose of 3 g of cefazolin for patients who weigh ≥120 kg but does not discuss dosage modifications with increasing weight for many of the other beta-lactams. Once again, the 1.5-m tall individual with a weight of 120 kg will have a far smaller blood volume than the 2.0-m tall individual with the same weight. The matter is far from settled, and the few available studies on antibiotics and morbid obesity indicate current dosing regimens to be inadequate.[44–46,62,63]

Because serum antibiotic levels often are used as a surrogate for antibiotic tissue concentrations as well as reflecting to some degree the risk of toxicity, a more physiological approach to dosing commonly used beta-lactams would be to strive for the same initial plasma level of antibiotic. With serum concentration as a guide, and with the use of a minimum dose of 2.0 g of cefazolin, cefoxitin, or cefotetan for a 70-kg patient as a "floor," the calculated antibiotic dose is 0.00041 g/cm^3 of blood, using a blood volume of 70 cm^3/kg. Similarly, for cefuroxime, with a minimum dose of 1.5 g for a 70-kg patient as a floor,[24] the calculated antibiotic dose is 0.00031 g/cm^3 of blood.

To estimate blood volume in the obese patient, one useful tool is the Lemmens formula[44]:

$$\text{BV (actual blood volume in cm}^3\text{ / kg)} = \frac{70}{\text{square root}\sqrt{(\text{BMI} / 22)}}$$

where BMI is the patient's body mass index in kg/m.^{2} Therefore, the required dose of cefazolin, for example, to achieve the same initial plasma level for patients >70 kg (where W is the actual body weight in kg) is estimated as follows:

$$\text{Cefazolin dose (in gms)} = 0.135 \times \text{H (in meters)} \times \sqrt{\text{W (in kg)}}$$

For a morbidly obese patient with a height of 1.77 m and a weight of 157 kg (BMI = 50), the required dose would be 3.0 g, identical to the recommendation of Chopra et al.[62] For a morbidly obese patient with a height of 1.50 m and a weight of 113 kg (BMI = 50), the required dose would be reduced to 2.15 g, a result of the markedly decreased blood volume. Selecting 3 hours as the redosing interval (approximately 1.5 half-lives) for the former patient, the initial bolus would be followed by a continuous infusion at 1.00 g/h. Maintaining this antibiotic infusion until the patient's discharge from the postanesthesia care unit is more likely to maintain adequate blood levels in the (obese) patient throughout the entire

decisive period than a traditional dosing regimen.[21,45,46] Thus, as anesthesia providers, one possible and logical way we can address the troubling issue of ineffective antibiotic tissue levels for obese patients is by (1) calculating antibiotic dose based on the Lemmens formula with floors for cefoxitin, cefotetan, or cefazolin of 2 g and for cefuroxime of 1.5 g for a 70-kg patient and (2) for high-risk patients or patients in whom a SSI would be catastrophic, following the initial bolus dose by a continuous infusion. It is noteworthy that the Lemmens formula gives results in approximate agreement with the dosing weight calculations for aminoglycosides, which is not surprising because the toxicity of these latter drugs is also related to plasma concentration.

USE OF A TOURNIQUET

The anesthesiologist often is charged with the task of administering prophylactic antibiotics to patients for whom a pneumatic tourniquet is used. Use of a tourniquet creates unique problems with regard to antibiotic dosing. After tourniquet inflation, the affected limb is ischemic for the duration and oxidative neutrophil killing, the body's primary defense mechanism against pathogens, stops. Hence, pathogens weakened by the initial dose of antibiotics and more susceptible to host defenses remain viable while bacterial seeding from a variety of external sources continues during ischemia. This bacterial load is then integrated into the clot that forms after tourniquet release, making neutrophil killing more difficult.[64] Simultaneously, the blood infusing the affected limb after tourniquet release has a much lower antibiotic concentration, affected by the duration of tourniquet use and the half life of the specific antibiotic administered.[65,66] The literature on the topic is equivocal, and equal SSI rates are seen whether the antibiotic is given before or after tourniquet inflation.[65–67] It has been suggested that a tourniquet release dose is appropriate, as well as an initial dose at least 10 minutes but preferably longer before tourniquet inflation and skin incision.[67,68] Although evidenced-based studies are lacking, this approach has the weight of physiologic reasoning behind it, common to many of the anesthesia techniques we use.[69] On the other hand, the ASHP monograph makes the point that antibiotic administration before tourniquet inflation seems intuitively correct and does not discuss a tourniquet release dose.[24] In summary, it appears prudent to administer the first dose of antibiotic within the 15- to 45-minute time span before tourniquet inflation (being careful to satisfy the 1-hour PQRS requirement for antibiotic to incision time) and add an additional tourniquet release dose for those procedures in which occurrence of a SSI would be catastrophic, such as total knee replacement. Continuous infusions of antibiotics have no logical place in procedures involving a tourniquet.

BIOFILMS

Many surgical procedures involve insertion of a foreign substance into the patient (pacemakers, mesh, prostheses, etc.). This is particularly true in the case of the extensive instrumentation involved in complex orthopedic procedures.[70] In all such cases, the development of a bacterial biofilm creates a formidable obstacle to infection control.[13,71] The development of a biofilm occurs in as little as 6 hours.[71] Hence, procedures involving mesh, instrumentation, and other foreign bodies necessitate more aggressive antibiotic prophylaxis. Until such time as molecules that interfere with biofilm production or facilitate penetration of the film with effective antimicrobials are routinely introduced into clinical practice,[72] the use of a beta-lactam bolus followed immediately by a continuous infusion may be justified.[73] Clear recommendations in the medical literature on this subject are not available.

OTHER COMMON CONSIDERATIONS

When to Avoid Prophylactic Antibiotics

Many other questions and issues occur in the course of selecting appropriate prophylactic antibiotic coverage, much of this relevant to the attending anesthesiologist. A significant and often-controversial issue concerns the actual need for antibiotics. The ASHP white paper discusses a number of situations for which antibiotics are not indicated. These include clean orthopedic procedures on the extremities without instrumentation, as well as clean head and neck procedures such as thyroidectomy or lymph node excision in low-risk patients. In addition, both the ASHP policy paper and the Medical Letter suggest that for low risk ASA I or II patients undergoing elective cholecystectomy, antibiotic prophylaxis is usually not indicated.[74] Other surgical procedures wherein antibiotics appear to have little or no place for low-risk patients include laparoscopic oophorectomies, tonsillectomies, and cystoscopies. To avoid delays, confrontations, and unpleasantries, all of these issues should of course be discussed in a cooperative and helpful exchange between the surgical and anesthesia teams and general policies and guidelines put in place. In situations in which prophylactic antibiotics may be avoided, their use should be discouraged because none of these medications are without potential harm. For example, *Clostridium difficile*, a rapidly growing health care problem and major contributor to morbidity and mortality in HAIs, is strongly associated with antibiotic administration[75] (as well as with the use of proton pump inhibitors and increased age, both increasingly common in today's surgical population), even when antibiotic use is restricted solely to prophylactic perioperative antibiotics.[76]

The Patient with a Penicillin Allergy

Traditionally, patients for whom cefazolin is the recommended antibiotic often are switched to clindamycin or vancomycin when they present with a history of a penicillin allergy. However, many authorities recommend that only in those situations where the patient's history is consistent with either an IgE-mediated penicillin allergy (urticaria, angioedema, anaphylaxis, bronchospasm) or a severe non–IgE-mediated reaction (interstitial nephritis, toxic epidermal necrolysis, hemolytic anemia, or Stevens-Johnson syndrome) is it necessary to switch out the cefazolin.[77–79] Even in these situations, there is at least some question if cefazolin need be avoided. Cross-sensitivity occurs when the R1 side chains of the penicillins and cephalosporins are similar, which perhaps surprisingly is not the case with cefazolin. Cephalosporins with R1 side chains similar to penicillins include cephalexin, cefaclor, and cefadroxil. According to *The Medical Letter*, for patients with mild-to-moderate reactions to penicillin G, ampicillin, or amoxicillin, the risk

associated with use of first- or second-generation cephalosporins with dissimilar side chains, or third- or fourth-generation cephalosporins, "appears to be very low."[78] Thus, reflexively dismissing cefazolin use with a vague history of any penicillin allergy should be reconsidered. We can certainly make our voices heard in these situations.

Practical Considerations in Drug Selection

It is generally agreed that antibiotic selection should target the most likely pathogens, and that targeting all potential pathogens is unnecessary and potentially harmful. The *Medical Letter's* 2012 recommendations for antibiotic selection take this approach. For many surgeries, cefazolin is the drug of choice.[74] The ASHP white paper reflects similar sentiment but gives a wider and much more detailed selection of appropriate antibiotics, with specific recommendations for a multitude of operative procedures.[24] The predictable culprits for different procedures vary by hospital, but it is common consensus that skin pathogens (*Staphylococcus aureus*, *Staphylococcus epidermidis*) are frequent offenders in clean surgeries, whereas enteric gram-negative microbes are found in many clean contaminated surgeries. The Center for Disease Control tracks common pathogens via the National Healthcare Safety Network, the most widely used infection-tracking system in the United States. According to the National Healthcare Safety Network, the top 5 most commonly reported pathogens are (1) *Staphylococcus aureus*, (2) coagulase-negative staphylococci, (3) *Escherichia coli*, (4) *Enterococcus faecalis*, and (5) *Pseudomonas aeruginosa*.[80]

CONCLUSIONS

It would certainly be unusual for an anesthesia provider to administer a medication in the absence of a thorough knowledge of the pharmacology, proper dosing, and indications for that medication, but this is often the case with parenteral prophylactic antibiotics. Glance and Fleisher[2] note if we are unwilling to share accountability for surgical outcomes, we run the risk of trivializing the specialty of anesthesiology. SSIs are one such frequent negative outcome, and because antibiotic administration is a cornerstone of prevention efforts, a thorough knowledge of the fundamentals of principles supporting appropriate selection and use is required.

If we consistently use well-understood pathophysiological concepts and current data with respect to the pharmacokinetics and pharmacodynamics of prophylactic antibiotics, it is highly likely we can reduce national rates of SSIs. We do not have the luxury of time to wait for the definitive large-scale clinical studies, so rare in modern anesthesiology.[81] Current evidence suggests that for most beta-lactams, a bolus dose at 15 to 45 minutes before incision is ideal and provides maximum interstitial fluid concentrations at the time of initial bacterial seeding. Because diffusion distances from capillary to pathogen are greater in obese patients, for this patient subset initiating antibiotic infusion 30 minutes or longer before incision is warranted on theoretical grounds. Koch et al.'s work is consistent with this premise, and for cefuroxime, patients with a BMI >30 had an optimal time for initiation of infusion of 39 minutes before incision versus 21 minutes for patients with a BMI < 30.[56] A current prospective study underway in Switzerland hypothesizes that antibiotics should be administered no earlier than 30 minutes before skin incision to minimize SSIs.[82]

The initial beat-lactam bolus dose should be followed by additional doses at every 1 to 2 half lives per the ASHP guidelines. For situations for which a SSI would be catastrophic, available literature and pharmacodynamic considerations suggest the initial bolus should be followed immediately by a continuous infusion such that the same total dose of drug is administered as in the case of redosing. Calculation of antibiotic dosing for obese patients is controversial, and although the simple expedient of giving 3 g of cefazolin for the 120-kg patient or alternatively for the patient with a BMI of ≥50 is acceptable, use of the Lemmens formula and blood volume dosing would seem prima facie preferable. Estimation of blood volume and using 30% of blood volume loss as an antibiotic trigger for redosing would also seem preferable to the unqualified recommendation of redosing for every 1500 cm^3 of blood loss in all patients. In the case of tourniquet use, a tourniquet release dose appears justified for those procedures in which a SSI would be devastating.

The pharmacokinetics and pharmacodynamics of antibiotics should guide their administration by the anesthesia provider. It is time for us to embrace our role in the overall surgical experience. We can do better. ■

DISCLOSURES

Name: Ronald J. Gordon, MD, PhD.
Contribution: This author wrote the manuscript.
Attestation: Ronald J. Gordon approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

ACKNOWLEDGMENTS

I would like to thank Dr. Charles E. Edmiston, Jr, Department of Surgery, Medical College of Wisconsin, for his interest and very helpful comments and suggestions.

REFERENCES

1. Berwick DM, Calkins DR, McCannon CJ, Hackbarth AD. The 100,000 lives campaign: setting a goal and a deadline for improving health care quality. JAMA 2006;295:324–7
2. Glance LG, Fleisher LA. Anesthesiologists and the transformation of the healthcare system: a call to action. Anesthesiology 2014;120:257–9
3. Sessler DI. Long-term consequences of anesthetic management. Anesthesiology 2009;111:1–4
4. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, Keohane C, Denham CR, Bates DW. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med 2013;173:2039–46
5. Kaye KS, Anderson DJ, Sloane R, Chen LF, Choi Y, Link K, Sexton DJ, Schmader KE. The effect of surgical site infection on older operative patients. J Am Geriatr Soc 2009;57:46–54
6. Sessler DI. Non-pharmacologic prevention of surgical wound infection. Anesthesiol Clin 2006;24:279–97
7. Akça O, Doufas AG, Morioka N, Iscoe S, Fisher J, Sessler DI. Hypercapnia improves tissue oxygenation. Anesthesiology 2002;97:801–6
8. Gifford C, Christelis N, Cheng A. Preventing postoperative infection: the anaesthetist's role. Contin Educ Anaesth Crit Care Pain 2011;11:151–6
9. Chang CC, Lin HC, Lin HW, Lin HC. Anesthetic management and surgical site infections in total hip or knee replacement: a population-based study. Anesthesiology 2010;113:279–84

10. Akça O, Melischek M, Scheck T, Hellwagner K, Arkiliç CF, Kurz A, Kapral S, Heinz T, Lackner FX, Sessler DI. Postoperative pain and subcutaneous oxygen tension. Lancet 1999;354:41–2
11. Kavanagh T, Buggy DJ. Can anaesthetic technique effect postoperative outcome? Curr Opin Anaesthesiol 2012;25:185–98
12. Hopf HW, Rollins MD. Reducing perioperative infection is as simple as washing your hands. Anesthesiology 2009;110:959–60
13. Roy RC, Brull SJ, Eichhorn JH. Surgical site infections and the anesthesia professionals' microbiome: we've all been slimed! Now what are we going to do about it? Anesth Analg 2011;112:4–7
14. Loftus RW, Muffly MK, Brown JR, Beach ML, Koff MD, Corwin HL, Surgenor SD, Kirkland KB, Yeager MP. Hand contamination of anesthesia providers is an important risk factor for intraoperative bacterial transmission. Anesth Analg 2011;112:98–105
15. Forbes SS, McLean RF. Review article: the anesthesiologist's role in the prevention of surgical site infections. Can J Anaesth 2013;60:176–83
16. Deiner S, Silverstein JH. Long-term outcomes in elderly surgical patients. Mt Sinai J Med 2012;79:95–106
17. Vetter TR, Goeddel LA, Boudreaux AM, Hunt TR, Jones KA, Pittet JF. The Perioperative Surgical Home: how can it make the case so everyone wins? BMC Anesthesiol 2013;13:6
18. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, McNaught CE, MacFie J, Liberman AS, Soop M, Hill A, Kennedy RH, Lobo DN, Fearon K, Ljungqvist O. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. Clin Nutr 2012;31:783–800
19. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. Surgery 1961;50:161–8
20. Burke JF. Preventing bacterial infection by coordinating antibiotic and host activity: a time-dependent relationship. South Med J 1977;70:24–6
21. Edmiston CE, Spencer M, Lewis BD, Brown KR, Rossi PJ, Henen CR, Smith HW, Seabrook GR. Reducing the risk of surgical site infections: did we really think SCIP was going to lead us to the promised land? Surg Infect (Larchmt) 2011;12:169–77
22. Adembri C, Ristori R, Chelazzi C, Arrigucci S, Cassetta MI, De Gaudio AR, Novelli A. Cefazolin bolus and continuous administration for elective cardiac surgery: improved pharmacokinetic and pharmacodynamic parameters. J Thorac Cardiovasc Surg 2010;140:471–5
23. Andersson AE, Bergh I, Karlsson J, Eriksson BI, Nilsson K. The application of evidence-based measures to reduce surgical site infections during orthopedic surgery—report of a single-center experience in Sweden. Patient Saf Surg 2012;6:11
24. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaeter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists (ASHP); Infectious Diseases Society of America (IDSA); Surgical Infection Society (SIS); Society for Healthcare Epidemiology of America (SHEA). Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt) 2013;14:73–156
25. Kao LS, Meeks D, Moyer DA, Lally KP. Peri-operative glycaemic control regimens for preventing surgical site infections in adults. Cochrane Database Syst Rev 2009;3:CD006806
26. Bryan CS, Yarbrough WM. Preventing deep wound infection after coronary artery bypass grafting: a review. Tex Heart Inst J 2013;40:125–39
27. Glance LG, Neuman M, Martinez EA, Pauker KY, Dutton RP. Performance measurement at a "tipping point." Anesth Analg 2011;112:958–66
28. Hawn MT. Surgical care improvement: should performance measures have performance measures. JAMA 2010;303:2527–8
29. Barie PS. SCIP to the loo? Surg Infect (Larchmt) 2011;12:161–2
30. Koch CG, Li L, Hixson E, Tang A, Gordon S, Longworth D, Phillips S, Blackstone E, Henderson JM. Is it time to refine? An exploration and simulation of optimal timing in general surgery. J Am Coll Surg 2013;217:628–35
31. Stulberg JJ, Delaney CP, Neuhauser DV, Aron DC, Fu P, Koroukian SM. Adherence to surgical care improvement project measures and the association with postoperative infections. JAMA 2010;303:2479–85
32. Varley AJ, Sule J, Absalom AR. Principles of antibiotic therapy. Contin Educ Anaesth Crit Care Pain 2009;9:184–8
33. Huang H, Huang S, Zhu P, Xi X. Continuous versus intermittent infusion of cefepime in neurosurgical patients with post-operative intracranial infections. Int J Antimicrob Agents 2014;43:68–72
34. Vondracek TG. Beta-lactam antibiotics: is continuous infusion the preferred method of administration? Ann Pharmacother 1995;29:415–24
35. McKinnon PS, Davis SL. Pharmacokinetic and pharmacodynamics issues in the treatment of bacterial infectious diseases. Eur J Clin Microbiol Infect Dis 2004;23:271–88
36. Waltrip T, Lewis R, Young V, Farmer M, Clayton S, Myers S, Gray LA Jr, Galandiuk S. A pilot study to determine the feasibility of continuous cefazolin infusion. Surg Infect (Larchmt) 2002;3:5–9
37. Nicolau DP, Nightingale CH, Banevicius MA, Fu Q, Quintiliani R. Serum bactericidal activity of ceftazidime: continuous infusion versus intermittent injections. Antimicrob Agents Chemother 1996;40:61–4
38. MacGowan AP, Bowker KE. Continuous infusion of beta-lactam antibiotics. Clin Pharmacokinet 1998;35:391–402
39. Roberts JA, Lipman J, Blot S, Rello J. Better outcomes through continuous infusion of time-dependent antibiotics to critically ill patients? Curr Opin Crit Care 2008;14:390–6
40. Douglas A, Udy AA, Wallis SC, Jarrett P, Stuart J, Lassig-Smith M, Deans R, Roberts MS, Taraporewalla K, Jenkins J, Medley G, Lipman J, Roberts JA. Plasma and tissue pharmacokinetics of cefazolin in patients undergoing elective and semielective abdominal aortic aneurysm open repair surgery. Antimicrob Agents Chemother 2011;55:5238–42
41. Isla A, Trocóniz IF, de Tejada IL, Vázquez S, Canut A, López JM, Solinís MÁ, Rodríguez GA. Population pharmacokinetics of prophylactic cefoxitin in patients undergoing colorectal surgery. Eur J Clin Pharmacol 2012;68:735–45
42. Singhvi SM, Heald AF, Schreiber EC. Pharmacokinetics of cephalosporin antibiotics: protein-binding considerations. Chemotherapy 1978;24:121–33
43. Fujii T, Tsutsumi S, Matsumoto A, Fukasawa T, Tabe Y, Yajima R, Asao T, Kuwano H. Thickness of subcutaneous fat as a strong risk factor for wound infections in elective colorectal surgery: impact of prediction using preoperative CT. Dig Surg 2010;27:331–5
44. Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. Obes Surg 2006;16:773–6
45. Toma O, Suntrup P, Stefanescu A, London A, Mutch M, Kharasch E. Pharmacokinetics and tissue penetration of cefoxitin in obesity: implications for risk of surgical site infection. Anesth Analg 2011;113:730–7
46. Edmiston CE, Krepel C, Kelly H, Larson J, Andris D, Hennen C, Nakeeb A, Wallace JR. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? Surgery 2004;136:738–47
47. Pevzner L, Swank M, Krepel C, Wing DA, Chan K, Edmiston CE Jr. Effects of maternal obesity on tissue concentrations of prophylactic cefazolin during cesarean delivery. Obstet Gynecol 2011;117:877–82
48. Stitely M, Sweet M, Slain D, Alons L, Holls W, Hochberg C, Briggs F. Plasma and tissue cefazolin concentrations in obese patients undergoing cesarean delivery and receiving differing pre-operative doses of drug. Surg Infect (Larchmt) 2013;14:455–9
49. Barie PS. Guidelines for antimicrobial prophylaxis in surgery: a must-read, must-heed for every surgeon. Surg Infect (Larchmt) 2013;14:5–7
50. Weber WP, Marti WR, Zwahlen M, Misteli H, Rosenthal R, Reck S, Fueglistaler P, Bolli M, Trampuz A, Oertli D, Widmer AF. The timing of surgical antimicrobial prophylaxis. Ann Surg 2008;247:918–26

51. Stefánsdóttir A, Robertsson O, W-Dahl A, Kiernan S, Gustafson P, Lidgren L. Inadequate timing of prophylactic antibiotics in orthopedic surgery. We can do better. Acta Orthop 2009;80:633–8
52. Davies AJ, Lockley RM, Jones A, el-Safty M, Clothier JC. Comparative pharmacokinetics of cefamandole, cefuroxime and cephradine during total hip replacement. J Antimicrob Chemother 1986;17:637–40
53. Dellinger EP. Prophylactic antibiotics: administration and timing before operation are more important than administration after operation. Clin Infect Dis 2007;44:928–30
54. Steinberg JP, Braun BI, Hellinger WC, Kusek L, Bozikis MR, Bush AJ, Dellinger EP, Burke JP, Simmons B, Kritchevsky SB; Trial to Reduce Antimicrobial Prophylaxis Errors (TRAPE) Study Group. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. Ann Surg 2009;250:10–6
55. Hawn MT, Richman JS, Vick CC, Deierhoi RJ, Graham LA, Henderson WG, Itani KM. Timing of surgical antibiotic prophylaxis and the risk of surgical site infection. JAMA Surg 2013;148:649–57
56. Koch CG, Nowicki ER, Rajeswaran J, Gordon SM, Sabik JF 3rd, Blackstone EH. When the timing is right: antibiotic timing and infection after cardiac surgery. J Thorac Cardiovasc Surg 2012;144:931–937.e4
57. DiPiro JT, Vallner JJ, Bowden TA Jr, Clark BA, Sisley JF. Intraoperative serum and tissue activity of cefazolin and cefoxitin. Arch Surg 1985;120:829–32
58. Wong-Beringer A, Corelli RL, Schrock TR, Guglielmo BJ. Influence of timing of antibiotic administration on tissue concentrations during surgery. Am J Surg 1995;169:379–81
59. van Kasteren ME, Manniën J, Ott A, Kullberg BJ, de Boer AS, Gyssens IC. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. Clin Infect Dis 2007;44:921–7
60. Ho VP, Barie PS, Stein SL, Trencheva K, Milsom JW, Lee SW, Sonoda T. Antibiotic regimen and the timing of prophylaxis are important for reducing surgical site infection after elective abdominal colorectal surgery. Surg Infect (Larchmt) 2011;12:255–60
61. Goede WJ, Lovely JK, Thompson RL, Cima RR. Assessment of prophylactic antibiotic use in patients with surgical site infections. Hosp Pharm 2013;48:560–7
62. Chopra T, Zhao JJ, Alangaden G, Wood MH, Kaye KS. Preventing surgical site infections after bariatric surgery: value of perioperative antibiotic regimens. Expert Rev Pharmacoecon Outcomes Res 2010;10:317–28
63. Barbour A, Schmidt S, Rout WR, Ben-David K. Soft tissue penetration of cefuroxime by clinical microdialysis in morbidly obese patients undergoing abdominal surgery. Int J Antimicrob Agents 2009;34:231–5
64. Soriano A, Bori G, García-Ramiro S, Martinez-Pastor JC, Miana T, Codina C, Maculé F, Basora M, Martínez JA, Riba J, Suso S, Mensa J. Timing of antibiotic prophylaxis for primary total knee arthroplasty performed during ischemia. Clin Infect Dis 2008;46:1009–14
65. Richardson JB, Roberts A, Robertson JF, John PJ, Sweeney G. Timing of antibiotic administration in knee replacement under tourniquet. J Bone Joint Surg Br 1993;75:32–5
66. Akinyoola AL, Adegbehingbe OO, Odunsi A. Timing of antibiotic prophylaxis in tourniquet surgery. J Foot Ankle Surg 2011;50:374–6
67. Bannister GC, Auchincloss JM, Johnson DP, Newman JH. The timing of tourniquet application in relation to prophylactic antibiotic administration. J Bone Joint Surg Br 1988;70:322–4
68. Bicanic G, Crnogaca K, Barbaric K, Delimar D. Cefazolin should be administered maximum 30 min before incision in total knee arthroplasty when tourniquet is used. Med Hypotheses 2014;82:766–8
69. Horlocker TT, Brown DR. Evidence-based medicine: haute couture or the emperor's new clothes? Anesth Analg 2005;100:1807–10
70. Kasliwal MK, Tan LA, Traynelis VC. Infection with spinal instrumentation: review of pathogenesis, diagnosis, prevention, and management. Surg Neurol Int 2013;4:S392–403
71. Stewart PS. Theoretical aspects of antibiotic diffusion into microbial biofilms. Antimicrob Agents Chemother 1996;40:2517–22
72. Romanò CL, Toscano M, Romanò D, Drago L. Antibiofilm agents and implant-related infections in orthopaedics: where are we? J Chemother 2013;25:67–80
73. Høiby N, Bjarnsholt T, Givskov M, Molin S, Ciofu O. Antibiotic resistance of bacterial biofilms. Int J Antimicrob Agents 2010;35:322–32
74. Antimicrobial prophylaxis for surgery. Treat Guidel Med Lett 2012;10:73–8
75. Silva JM. Recent changes in Clostridium difficile infection. Einstein (Sao Paulo) 2012;10:105–9
76. Carignan A, Allard C, Pépin J, Cossette B, Nault V, Valiquette L. Risk of Clostridium difficile infection after perioperative antibacterial prophylaxis before and during an outbreak of infection due to a hypervirulent strain. Clin Infect Dis 2008;46:1838–43
77. Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: a literature review. J Emerg Med 2012;42:612–20
78. Cephalosporins for patients with penicillin allergy. Med Lett Drugs Ther 2012;54:101
79. Haslam S, Yen D, Dvirnik N, Engen D. Cefazolin use in patients who report a non-IgE mediated penicillin allergy: a retrospective look at adverse reactions in arthroplasty. Iowa Orthop J 2012;32:100–3
80. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, Kallen A, Limbago B, Fridkin S. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol 2013;34:1–14
81. Devereaux PJ, Chan MT, Eisenach J, Schricker T, Sessler DI. The need for large clinical studies in perioperative medicine. Anesthesiology 2012;116:1169–75
82. Mujagic E, Zwimpfer T, Marti WR, Zwahlen M, Hoffmann H, Kindler C, Fux C, Misteli H, Iselin L, Lugli AK, Nebiker CA, von Holzen U, Vinzens F, von Strauss M, Reck S, Kraljević M, Widmer AF, Oertli D, Rosenthal R, Weber WP. Evaluating the optimal timing of surgical antimicrobial prophylaxis: study protocol for a randomized controlled trial. Trials 2014;15:188

Prophylactic Perioperative Antibiotic Administration: Is It Time to Infuse Our Practices with New Approaches?

Nikolaus Gravenstein, MD,* Jeffrey T. Fish, PharmD,† Kenneth P. Klinker, PharmD,‡ and Douglas B. Coursin, MD§

We hope many are inspired, as were we, by Gordon's provocative Review Article in this issue titled "Administration of Prophylactic Beta-Lactam Antibiotics in 2014: Review."[1] Given that nearly a century ago, Lord Moynihan already considered every operation an experiment in bacteriology, it is encouraging that our specialty has, over the past decade, accepted ownership of timely perioperative prophylactic antibiotic administration.[2] In some institutions, this has decreased the surgical site infection (SSI) rate, but several large, well-done prospective studies have not been able to establish a clear benefit of strict adherence to the Surgical Care Improvement Project Measure 1 that calls for administration of the appropriate prophylactic antibiotic in a window that precedes surgical incision, but not by >60 minutes (120 minutes in the case of vancomycin or fluoroquinolones).[3,4] Despite the concerns over the efficacy of current perioperative antibiotic prophylaxis guidelines, the timing of prophylactic antibiotic administration remains an institutional quality marker throughout American hospitals. This begs the question of why there seems to be a disconnect between consistent timely antibiotic administration and a measurable reduction in the SSI rate. Could it be that we have satisfied the administrative requirement without sufficient thought given to the process of preventing these infections? Gordon politely suggests that this is indeed the case and calls on us to be clinicians and not simply technicians as it relates to prophylactic antibiotic administration in the acute perioperative period.

The time surrounding incision and the early postoperative recovery period has been coined the "decisive period" for an infection establishing a foothold or being prevented.[5] It is during this period that host defenses and prophylactic antibiotics play a key role in the prevention of SSIs.

Based on the classic work of Miles et al.,[5] SSIs may be amplified by low skin blood flow—his team used epinephrine-induced vasoconstriction. A wound edge retractor or cold air and evaporation might create a locally similar effect during surgery. Miles et al. also found that antibiotics concurrently administered during the induced vasoconstriction were effective in preventing infection, but this benefit waned as the interval between antibiotic administration and inoculation grew.

The decisive period is our time. It is our opportunity to make another difference in patient outcomes. The practice of anesthesiology is one of the applied pharmacology and we should practice accordingly as it relates to antibiotics. Gordon reviews antibiotic choice, timing of initial dose, dosing, redosing, patient size, penicillin allergy, and use of tourniquet considerations. The entire review is worth considering, but the concepts of intelligent pharmacodynamic and pharmacokinetic dosing and redosing in operative patients are perhaps the most provocative and important ones. They are also conceptually familiar.

Very simply, most antibiotics, including the β-lactams, for example, cefazolin, cefuroxime, and cefoxitin, used for SSI prophylaxis exert their bactericidal effect through a mechanism referred to as time-dependent killing with little postantibiotic effect.[6] For time-dependent kill antibiotics with short half-lives, the best strategy may be frequent administration of smaller doses to ensure that tissue concentrations remain above the minimal inhibitory concentration (MIC) (usually 4 times the MIC for the β-lactams) required to ensure efficacy. The β-lactam class of antibiotics is most effective if its concentration is maintained above the target MIC for a sufficient time, that is, the decisive period.[7,8] Unlike the quinolones, metronidazole, and aminoglycosides, which manifest a concentration-dependent killing and have a significant postantibiotic effect, the β-lactams have little-to-no postantibiotic effect. In other words, when β-lactam concentrations fall below the MIC, they no longer have a meaningful antibiotic effect. That is a pharmacodynamic reality. Put this in context with the typical bolus administration of 2 g of cefazolin (3 g if the patient weighs >120 kg). The very high initial peak plasma level rapidly redistributes into the tissue (which Gordon reminds us is crucial to appropriate timing

From the *Department of Anesthesiology, University of Florida, Gainesville, Florida; †Department of Critical Care, University of Wisconsin Hospitals, Madison, Wisconsin; ‡UF Health Shands Hospital, Gainesville, Florida; and §University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

Accepted for publication September 28, 2014.

Funding: None.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

Address correspondence to Nikolaus Gravenstein, MD, Department of Anesthesiology, University of Florida College of Medicine, PO Box 100254, Gainesville, FL 32610. Address e-mail to ngravenstein@anest.ufl.edu.

DOI: 10.1213/ANE.0000000000000541

of the first bolus administration) and interstitial compartments and is for a time higher than the MIC. All is good if the operation is short enough that tissue levels sufficiently exceed the MIC for the decisive period (Fig. 1). The typical operation in community surgery centers is <1 hour and is approximately 1.5 hours in inpatient facilities. By comparison, in academic centers, the duration of the same surgeries is roughly twice as long.

In the case of cefazolin, with a half-life of only 1.2 to 2.2 hours, if you are redosing it at least every 2 half-lives as recommended by the American Society of Hospital Pharmacists, redosing is due every 3 to 4 hours.[9] Your patient may well be below the target MIC threshold level before the redose is due.[10,11] In the case of cefoxitin, with a 1-hour half-life and a 2-hour redosing strategy, the risk of falling below the target MIC occurs earlier. To put a time-dependent effect antibiotic such as cefazolin into context, think of an anesthetic, or even a sedative, where to ensure an adequate anesthetic we give a bolus dose for induction followed by frequent boluses or a continuous infusion. This same principle can be applied to antibiotic administration. Yes, an infusion. An infusion is simply continuous administration of very small boluses. Is the infusion complicated to calculate or administer? No, not at all. The antibiotic redose infusion is simply set so that at what would have been your next bolus dose time, the redose infusion dose is just in. For a 2 g every 4-hour cefazolin redose interval, the infusion would begin immediately after the first 2 g dose and run at 500 mg/h. If your institution uses a 3-hour cefazolin redosing interval, the redose infusion is run over 3 hours. In the case of cefoxitin, with a 2 g every 2-hour schedule, the infusion would run at 1 g/h for the duration of the procedure. A potentially important benefit of this approach is that in the acute postoperative period, there is still a high plasma/tissue level during the time that is still considered to be within the decisive period window (Fig. 1).

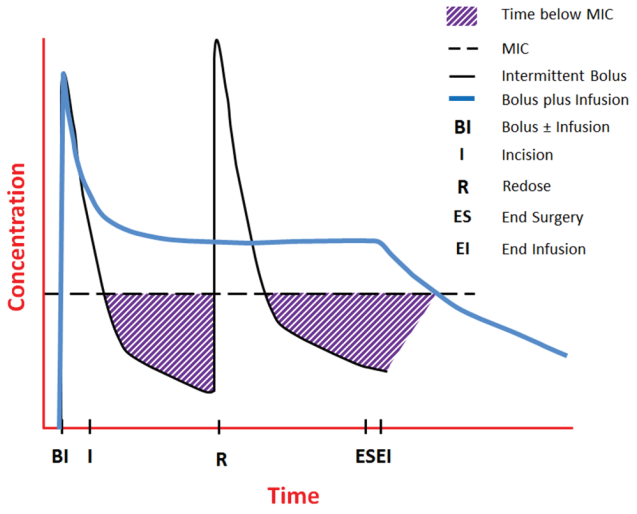

Figure 1. An intentionally exaggerated schematic displays a plot of antibiotic concentration versus time using intermittent bolus dosing (solid black line) versus bolus followed by continuous infusion (teal line) in relation to a target minimal inhibitory concentration (MIC) (dashed line). The "decisive period" is from I to shortly after end surgery. The time below MIC during the decisive period is represented by the crosshatched. BI = bolus ± infusion; I = incision; ES = end surgery; EI = end infusion. Modified from Abdul-Aziz MH, Delhunty JM, Bellomo R, Lipman J, Roberts JA. Continuous β-lactam infusion in critically ill patients: the clinical evidence. Ann Intensive Care 2012;2:37.

The current antibiotic prophylaxis guidelines are prescriptive and not necessarily based on patient- or operation-specific factors. The existing approach is an all or nothing one; the medication was given, yes or no, within 1 hour of incision, yes or no. Unanswered are factors such as was the right drug and dose administered? Was sufficient time allowed for adequate tissue penetration? Was the drug redosed in a timely manner or would a continuous infusion of a β-lactam provide a better infection prevention of the surgical site milieu?

Dr. Gordon nicely addresses why many patients who receive β-lactam prophylaxis might be better or best served if they received a loading dose and then a continuous infusion. This would result in drug concentrations above the target MIC from incision throughout the surgery and wound closure. We have delivery systems readily available to do so and it does not require greater doses of medication to maintain a sufficient MIC multiple. He bases his discussion on sound pharmacodynamic and kinetic principles; ones we routinely apply daily.

Why should antibiotic use and delivery be different than the routine use of sedatives, amnestics, analgesics, and paralytics, which we administer regularly and confidently, often as continuous infusions based on familiar principles? Antibiotics are not magical, but they are only as effective as our ability to choose the right one(s) and administer them in a manner that results in adequate tissue concentrations for an appropriate time frame. There is a clear analogy between surgical antibiotic prophylaxis and the current Surviving Sepsis recommendations.[12] The latter emphasize the need to quickly identify the most likely infectious pathogen (skin, bowel, or bladder flora or pathogen coverage for intraoperative prophylaxis) and select the best option for definitive treatment. We must remember to think beyond just reflexive administration of cefa-"something" and make certain we pick the appropriate drug to prophylax against the most likely bug. Whatever we choose to administer should be for short-term prophylaxis only and dosing should be discontinued within <24 hours. In sepsis, empiric broad-spectrum antibiotics with rapid de-escalation within 48 hours as causative factors are identified and provision of the appropriate dose at the appropriate time, as soon as possible, ideally within 1 hour of diagnosis. Surviving sepsis recommends a <3-hour delay for initiation of definitive broad-spectrum antibiotics. This dramatically impacts survival.[13] In septic patients, the incorrect drug or a delay of >12 hours markedly increases mortality. Analogously unsophisticated prophylactic antibiotic administration risks otherwise potentially avoidable SSIs. Of note, some practitioners now advocate continuous infusions of time-dependent antibiotics in septic intensive care unit patients, but the best practice remains unknown.[14,15] With regard to achieving target plasma prophylactic β-lactam concentrations, there is a clinical trial scheduled to start in 2014 that will formally address the question as it relates to plasma drug levels of cefazolin in major abdominal surgery patients: http://clinicaltrials.gov/show/NCT02058979.

Enhanced understanding of the basic principles of antibiotic administration related, in part, to drug class, patient characteristics, and surgical type and location will be bolstered by this review. Gordon outlines several areas where it would be helpful to have more prospective data. Like so much in our pharmacologic practice, 1 size, 1 time, 1 way does not always result in global benefit or benefit for an individual patient. Now that we have reliably conquered preincision prophylactic antibiotic administration, the next opportunity for our specialty is to tackle the surrounding nuances to optimize β-lactam antibiotic prophylaxis.

DISCLOSURES

Name: Nikolaus Gravenstein, MD.
Contribution: This author contributed to the editorial review, analysis, and manuscript preparation.
Attestation: Nikolaus Gravenstein approved the final manuscript.
Name: Jeffrey T. Fish, PharmD.
Contribution: This author contributed to the editorial review, analysis, and manuscript preparation.
Attestation: Jeffrey T. Fish approved the final manuscript.
Name: Kenneth P. Klinker, PharmD.
Contribution: This author contributed to the editorial review, analysis, and manuscript preparation.
Attestation: Kenneth P. Klinker approved the final manuscript.
Name: Douglas B. Coursin, MD.
Contribution: This author contributed to the editorial review, analysis, and manuscript preparation.
Attestation: Douglas B. Coursin approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

REFERENCES

1. Gordon RJ. Administration of prophylactic beta-lactam antibiotics in 2014: a review. Anesth Analg 2015;120:877–87
2. Moynihan GB. The ritual of surgical operation. Br J Surg 1920;8:27–35
3. Lee FM, Trevino S, Kent-Street E, Sreeramoju P. Antimicrobial prophylaxis may not be the answer: surgical site infections among patients receiving care per recommended guidelines. Am J Infect Control 2013;41:799–802
4. Hawn MT, Vick CC, Richman J, Holman W, Deierhoi RJ, Graham LA, Henderson WG, Itani KM. Surgical site infection prevention: time to move beyond the surgical care improvement program. Ann Surg 2011;254:494–9
5. Miles AA, Miles EM, Burke J. The value and duration of defence reactions of the skin to the primary lodgement of bacteria. Br J Exp Pathol 1957;38:79–96
6. Craig WA. Choosing an antibiotic on the basis of pharmacodynamics. Ear Nose Throat J 1998;77:7–11
7. Drusano GL. Pharmacokinetics and pharmacodynamics of antimicrobials. Clin Infect Dis 2007;45 Suppl 1:S89–95
8. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol 2004;2:289–300
9. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA; American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195–283
10. Adembri C, Ristori R, Chelazzi C, Arrigucci S, Cassetta MI, De Gaudio AR, Novelli A. Cefazolin bolus and continuous administration for elective cardiac surgery: improved pharmacokinetic and pharmacodynamic parameters. J Thorac Cardiovasc Surg 2010;140:471–5
11. Edmiston CE, Krepel C, Kelly H, Larson J, Andris D, Hennen C, Nakeeb A, Wallace JR. Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? Surgery 2004;136:738–47
12. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165–228
13. Lilly CM. The ProCESS trial—a new era of sepsis management. N Engl J Med 2014;370:1750–1
14. Korbila IP, Tansarli GS, Karageorgopoulos DE, Vardakas KZ, Falagas ME. Extended or continuous versus short-term intravenous infusion of cephalosporins: a meta-analysis. Expert Rev Anti Infect Ther 2013;11:585–95
15. Shiu J, Wang E, Tejani AM, Wasdell M. Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections. Cochrane Database Syst Rev 2013;3:CD008481