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Controversies in Perioperative Antimicrobial Prophylaxis

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ABSTRACT

Although clinical guidelines for antibiotic prophylaxis across a wide array of surgical procedures have been proposed by multidisciplinary groups of physicians and pharmacists, clinicians often deviate from recommendations. This is particularly true when recommendations are based on weak data or expert opinion. The goal of this review is to highlight certain common but controversial topics in perioperative prophylaxis and to focus on the data that does exist for the recommendations being made.

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Mandates to improve antibiotic stewardship and reduce unnecessary antibiotic use[1–4] have compelled healthcare institutions to take a closer look at the divide between guidelines for perioperative antibiotic prophylaxis and clinical practice,[5,6] highlighting the fact that human nature makes providing less inherently more controversial than providing more when it comes to antibiotic prophylaxis. Some of the more common reasons for using antibiotics unnecessarily in the perioperative setting include entrance into abdominal cavity, higher estimated blood loss, and longer procedures.[7] Although clinical guidelines for antibiotic prophylaxis across a wide array of surgical procedures have been proposed by a collaborative, multidisciplinary group of physicians and pharmacists,[8] widely cited, and reiterated,[9] clinicians often deviate from recommendations, especially when recommendations are based on weak data. The goal of this review is to highlight certain common but controversial topics in perioperative prophylaxis.

The principles of perioperative antibiotic prophylaxis are evidenced-based, but there are limitations. Available studies may include outdated surgical techniques, antibiotics that are no longer used, and newer antibiotics that have not been studied in the perioperative setting. Additionally, the operating environment has evolved over time to include significant reductions in circulating air particles and improvements in how those particles move relative to the patient. This has the potential to reduce infection rates and confound the impact of antibiotic prophylaxis.

Patient-related Considerations

Obesity, Large-volume Blood Loss, and Fluid Resuscitation

A several-fold increase in the risk of surgical site infections in patients with higher percent of body fat suggests the need for adjusted dosing of antimicrobial agents.[10] Obese patients have increased volumes of distribution, altered protein binding, metabolism, and elimination.[11–13] Vancomycin and gentamicin are commonly used antibiotics given at higher doses when used in obese patients. Limited evidence that suggests larger volumes of distribution in obese patients affect the clearance of gentamicin,[14] while the effects of obesity on the pharmacokinetics of vancomycin remain somewhat unclear.[15]

Current guidelines recommend 3 g of cefazolin dosing in patients with body mass greater than or equal to 120 kg.[8] This is a weak recommendation because of the paucity of data. One study found that in patients with body mass index of 40 or higher, higher body mass index was associated with reduced achievement of target serum cefazolin concentration after a 2-g initial dose and a second dose at 3 h.[16] A more recent study in bariatric surgery patients suggested that a single 2-g dose of cefazolin was sufficient to exceed mean minimum inhibitory concentration for methicillin-sensitive *Staphylococcus aureus* in adipose tissue samples.[17] Although a separate study did not show a significant difference, there was a trend toward increasing surgical site infections in patients not receiving the increased cefazolin dose.[18]

Guidelines from the United States and Canada recommend redosing prophylactic antibiotics in case of excessive blood loss, defined as more than 1,500 ml.[8,19] These recommendations are consistent with conclusions from two small studies in spinal surgery patients, one of which has demonstrated a correlation between blood loss and reduced tissue

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cefazolin concentration.[20,21] The volume of intravenously administered fluid has also been shown to correlate with serum and reduced tissue concentrations of antibiotics.[22] Some authors suggest that patients who receive more than 2,000 ml of intravenous fluid may need antibiotic redosing.[23]

Allergic Reactions and Cross-reactivity

Patients with reported penicillin allergy may have a 50% or higher likelihood of developing surgical site infections because of suboptimal performance of second-line agents.[24,25] Although vancomycin provides appropriate antimicrobial coverage for Gram-positive flora (the predominant cause of surgical site infections in clean procedures) from a microbiologic standpoint, the increased administration time of 1 to 2 h and time before incision (within 120 min)[8] has lead centers to try to time incision for 60 to 120 min after start of infection. Utilizing this protocol, Blumenthal *et al.*[24] found that less than 3% of patients received vancomycin within 60 to 120 min, although Garey *et al.*[26] actually found that the surgical site infection rate in cardiac surgery was lowest for patients whose infusion started 16 to 60 min before incision. Additional reasons for increased surgical site infections with vancomycin alone could be the underappreciated role of Gram-negative pathogens in these infections[27] and the greater effectiveness of cephalosporins as compared with glycopeptides for methicillin-sensitive *S. aureus*.[25]

Because 85 to 95% of patients with documented antibiotic allergy have negative skin testing,[28,29] further investigation into the individual reaction would optimize antimicrobial coverage and may decrease the frequency of surgical site infection. Formal allergy testing is feasible in patients with unclear types of reactions to penicillin or cephalosporins who are expected to undergo elective surgery.[30] Evidence of successful and safe penicillin skin testing carried out by intensivists suggests that perioperative physicians may also utilize such a test.[31]

In patients with documented or presumed immunoglobulin E–mediated reaction to penicillin (anaphylaxis, bronchospasm, or urticaria), current guidelines recommend against using cephalosporins or carbapenems for surgical prophylaxis.[8] It should be noted, however, that cefazolin has low cross-reactivity with penicillin because of a unique side chain[32] and carbapenems demonstrate less than 1% cross-reactivity with penicillin.[33] In a single center, not one of 282 patients with reported penicillin allergy suffered adverse consequences when administered cefazolin.[34] Furthermore, the majority of patients with immunoglobulin E–mediated reaction to penicillin can tolerate penicillin within a decade.[35] Thus, even in patients with documented immunoglobulin E–mediated reaction to a first-line antibiotic, formal allergy testing may demonstrate tolerance to penicillin if the reaction occurred in the distant past.[36]

Clinically Relevant Drug Interactions

A number of antibiotics used for surgical prophylaxis manifest significant interactions with other perioperative medications. The frequency of clinically significant interactions has not been adequately studied, but severe complications have been reported. For example, clindamycin, a commonly used second line agent for surgical site infection prophylaxis, may potentiate the effects of neuromuscular blocking agents and, if overdosed, can be fatal in the perioperative setting.[37,38] Experimental studies also suggest that both clindamycin and gentamicin act synergistically with rocuronium.[39] Other consistently reported interactions include profound sedative and cardiovascular effects of ciprofloxacin in patients taking methadone.[40,41]

Immunosuppressed Population

Antimicrobial prophylaxis may be warranted in any procedure performed in an immunocompromised host,[8] including patients receiving glucocorticoids, disease-modifying antirheumatic drugs, and anti–tumor necrosis factor agents for chronic inflammatory diseases. Increased frequency of surgical site infection with perioperative glucocorticoid use is biologically plausible and has been reported.[42] One subgroup analysis of 364 patients in a trial using steroids in cardiac surgery did not demonstrate increased frequency of surgical site infection in the steroid group,[43] whereas another study of patients on chronic steroids having lumbar fusion showed an association between steroid use and surgical site infection.[42] Surgical site infection may be impacted by the dose of steroid and the chronicity of its use. Studies of perioperative discontinuation of disease-modifying antirheumatic drugs also produced inconsistent results with respect to surgical site infection.[44] It is likely that ongoing treatment of inflammatory bowel disease with anti–tumor necrosis factor agents does not increase the frequency of surgical site infection after abdominal or large joint surgery.[45,46] However, one large study did demonstrate a 50% increase in organ space infections and anastomotic leaks in immunosuppressed Crohn's disease patients after elective colectomy.[47] In this study the immunosuppressive regimen included corticosteroids, which confounds the result. Acknowledging the low quality of available evidence that originates from studies of low-risk patients, the World Health Organization Global Guidelines for the Prevention of Surgical Site Infection suggest not discontinuing immunosuppressive medication before surgery for the purpose of preventing surgical site infection.[9,48]

Transplant Recipients

Antimicrobial prophylaxis and treatment in transplant recipients should be individualized and depend on the procedure performed, geographic epidemiology, and net state of immunosuppression.[8,49–51] Solid organ transplantations are clean-contaminated procedures in which skin flora, Gram-negative rods, and enterococci are the predominant surgical site infection pathogens.[8] Most opportunistic infections occur several weeks after the initiation of immunosuppression rather than in the immediate posttransplantation

period.[52] Thus, the recommended antimicrobial prophylaxis regimen for heart, lung, heart–lung, kidney, and pancreas transplantation procedures is a single dose of cefazolin.[8,51] Note that there is significant controversy regarding the duration of antibiotic prophylaxis, with many centers providing 48 to 72 h despite no evidence of improved outcomes and the potential for increased selection of resistant organisms.[53]

Known recipient or graft colonization, surgical technique, or complexity may justify escalation of the prophylactic regimen. For example, in patients with enteric drainage of the pancreas who are at high risk of fungal infections, fluconazole may be considered.[8] Surgical complexity, duration of surgery, and high surgical site infection rates also may necessitate broader antimicrobial prophylaxis in liver transplantation, although a Cochrane meta-analysis suggested the lack of evidence to support any one specific prophylactic regimen.[54,55]

Solid organ transplant patients presenting for nontransplant surgery are likely at increased risk of surgical site infection because of their immunosuppression. Evidence is accumulating on the outcomes of major surgeries in posttransplantation patients. However, no formal recommendations for antimicrobial prophylaxis in this patient population have been identified.[56,57]

Presence of Prosthetic Joints and Prosthetic Material

Prosthetic joints and cardiac devices are commonly encountered in patients having dental procedures. Current dental guidelines recommend against providing patients with prosthetic joints antimicrobial prophylaxis before dental procedures.[58] For patients with prosthetic cardiac valves or those who underwent valve or congenital heart disease repair with prosthetic material, recommendations from the American Heart Association (Dallas, Texas) suggest that antibiotic prophylaxis of infective endocarditis is reasonable during the following procedures: (1) dental procedures with manipulation of gingival tissue or periapical region of teeth or perforation of oral mucosa; (2) respiratory tract procedures; and (3) procedures on infected skin or musculoskeletal tissue. The American Heart Association does not recommend antimicrobial endocarditis prophylaxis in patients undergoing genitourinary or gastrointestinal tract procedures.[59]

Microbiome-related Considerations

Human skin teems with an estimated 3.8×10^{13} microorganisms, more bacteria than human cells. Microorganisms from the skin and nasal passages are the most likely origin of surgical site infection in clean operations.[60] The human gut is likewise home to a diverse microbial community. In disease and injury, including elective surgery, the microbial density and metabolite production can change dramatically.[61,62] Numerous planned and unplanned interventions in the perioperative period directly influence the gut microbiota. For example, both enteral and parenteral antibiotics cause dysbiosis by killing commensal organisms. The loss of benefit from commensal pathogens can occur through several known mechanisms such as loss of competitive niche exclusion, antimicrobial inhibitory peptides, and intraspecies communication (quorum sensing). Reduction of the skin microbiome by application of skin antisepsis and nasal decolonization are primary strategies for reduction of surgical site infection.[60] In colonic surgery, mechanical bowel preparation alone has a significant impact on the microbiota aside from removal of bulk contents. One randomized trial evaluating the effect of mechanical bowel preparation on fecal microbiota demonstrated marked reduction in some species (*Clostridium*, *Bifidobacteria*, *Lactobacillis*, and Enterobacteriaceae), whereas they did not see any decrease in *Enterococcus* and *Staphylococcus*.[63] Importantly, mechanical bowel preparation also disrupts the mucosal layer of the colon, which can affect intracellular signaling and luminal pH. The use of antibiotics and critical illness in postoperative or injured surgical patients has shown a dramatic change in our microbiome, with a particular change in loss of microbial diversity.[64] Marked alterations in the microbiome have been identified in patients with a long length of stay in the hospital and in patients who had a planned pancreaticoduodenectomy. The microbiome in 50 patients studied preoperatively demonstrated that the microbiome of these patients were enriched with *Klebsiella* and *Bacteroides* and were depleted of anaerobic taxa. Further, patients with a postoperative pancreatic fistula contained increased *Klebsiella* and decreased commensal anaerobes.[65] Although we are far from understanding the specific role of the gut microbiome in healing of surgical anastomosis, there is active investigation into this area.[61]

Numerous studies have demonstrated increased risk of postoperative infection in a vast array of surgical patients who are colonized with resistant pathogens such as methicillin-resistant *S. aureus*, extended spectrum β-lactamase producers, and carbapenemase-resistant Enterobacteriaceae.[66] Because of this known increased risk, it may be reasonable to alter preoperative preparation, especially for *S. aureus*, using strategies that may include preoperative screening and surface decontamination (mupirocin).[67] The decision to adjust perioperative antibiotic prophylaxis to cover known resistant species should take into account the procedure and reservoir of the resistant pathogen.[8,68,69]

Methicillin-resistant *S. aureus*

Several studies in cardiothoracic, gastrointestinal, and orthopedic procedures have demonstrated a correlation between colonization with *S. aureus* and the development of surgical site infection.[42] Guidelines produced by the American College of Surgeons (Chicago, Illinois) and the Surgical Infection Society (East Northport, New York) in 2017 identified this problem and noted that screening and decolonization should depend on baseline surgical site infection and methicillin-resistant *S. aureus* rates.[70] Guidelines from the American Society of Health System Pharmacists (Bethesda, Maryland) recommend

screening and decolonization for all patients colonized with S. aureus before total joint replacement and cardiac procedures.[8] Methicillin-resistant S. aureus bundles (screening, decolonization, contact precautions, and hand hygiene) are noted to be highly effective when all components are implemented. The guidelines further note that there is no specific standard decolonization strategy supported by the literature; nasal mupirocin has been used alone and in combination with chlorhexidine gluconate bathing. Povidone–iodine solutions have also been used to decolonize the anterior nares.[71–75] These methods should be performed close to the time of surgery to be effective, ideally within 3 months.[72]

The threat of postoperative methicillin-resistant S. aureus infection has caused some providers to prescribe vancomycin and vancomycin plus a -lactam for prophylaxis for a wide variety of procedures. In a review of more than 70,000 procedures matched by propensity scoring, vancomycin prophylaxis had a clear benefit for reduction of surgical site infection (in cardiac surgery only) but was associated with unintended harm, namely an increase in acute kidney injury across all populations studied. Screening and directed prophylaxis may maximize benefits while minimizing harm. When prescribed for methicillin-resistant S. aureus colonization, vancomycin as well as standard prophylaxis (e.g. cefazolin) should be administered in combination.[8] Finally, vancomycin should not be administered as prophylaxis to methicillin-resistant S. aureus–negative patients.[25,76]

Controversies in Selected Cardiac Procedures

Cardiac Implantable Electrophysiologic Devices and Infection

The use of implantable cardiac electronic device infections continues to rise.[73] Infections can occur as an infection of the generator pocket, the leads, and/or involve endocardial structures. Cardiac implantable electrophysiologic device infections now constitute 10% of all endocarditis cases.[74] There has been an increase in the incidence of infectious endocarditis, in part because of the increased use of cardiac implantable electrophysiologic devices.[75] Surveys document that physicians frequently administer antibiotics to these patients in nonstandard ways.[76] Complete cardiac implantable electrophysiologic device hardware removal should be performed for definite infectious endocarditis cases. Parenteral antibiotics should be given, but optimal timing for reimplantation is unknown.[75]

Antibiotic Envelope for Cardiac Implantable Electrophysiologic Device Infections

A randomized controlled trial assessing the safety and efficacy of an absorbable, antibiotic-eluting envelope was completed, with 3,495 people in the envelope group and 3,488 people in the control group. A total of 25 patients in the envelope group and 42 patients in the control group developed an infection that required the removal or revision of the cardiac implantable electrophysiologic device pocket; major cardiac implantable electrophysiologic device–related infections occurred in 32 patients in the envelope group compared to 51 patients in the control group. The use of an antibacterial envelope led to a significantly lower rate of revisions caused by infection and significantly fewer major cardiac implantable electrophysiologic device infections.[73] Given that the trial was international, prospective, and randomized, these results suggest this needs to be considered when implanting cardiac implantable electrophysiologic devices. However, an accompanying editorial noted that the number of cases of bacteremia and endocarditis was higher in the intervention group, and this finding leads one to question the efficacy of the envelope.[78]

Extracorporeal Membrane Oxygenation

Survey data regarding antimicrobial prophylaxis and surveillance practice patterns were obtained from extracorporeal membrane oxygenation coordinators and directors internationally.[79] Of 556 surveys that were sent out to the 172 extracorporeal membrane oxygenation centers, 223 (41%) responded, and 198 completed the survey. There was marked variability between centers; the majority of centers administer prophylactic antibiotics. Given the lack of high-quality evidence and a lack of randomized trials, this variability should perhaps be expected. Surveillance tended to include routine blood cultures despite a lack of evidence for such practice.[79]

The relative incidence of infections and the efficacy of prophylactic regimens was evaluated in a systematic review that included Extracorporeal Life Support Organization registry studies, as well as data from individual centers. Rates of infection ranged from 7.6% in neonates to 20.9% in adults.[80] In two single-center studies, all subjects received prophylactic antibiotics and had a prevalence of infections of 16.1% and 18.4%, respectively.[80,81] Bloodstream infections were predominant in most of the studies, ranging from 2.6 to 19.5% prevalence, and rates of respiratory infections ranged from 1.4 to 15.8%.[80] One review did not find a benefit for prophylactic antibiotics in two retrospective studies.[80] Given changes in the care of these patients, multicenter randomized trials of prophylactic antibiotics are needed.

Drug Dosing in Patients Receiving Extracorporeal Membrane Oxygenation

The pharmacokinetics of drugs appear to be affected in at least three ways during extracorporeal membrane oxygenation: drug sequestration by the circuit, increased volume of distribution, and altered drug clearance.[82] Drug sequestration can occur by drug binding to the circuit, which may also lead to the circuit serving as a reservoir of certain drugs. The factors that seem important for these phenomena are the oxygenator materials, the types of conduit tubing, the circuit age, and the composition of the priming solutions.[82] Drug characteristics that influence drug sequestration are multiple and include the molecular size, the negative log of

the acid dissociation constant (pKa), degree of ionization, lipophilicity, and predilection for plasma protein binding.[82]

In ammatory and pharmacokinetic changes can lead to changes in the volume of distribution of drugs. Changes in blood pH also change the volume of distribution, and acidosis can be a common occurrence in patients on extracorporeal membrane oxygenation. Finally, drug clearance appears to be lower than normal when patients are on extracorporeal membrane oxygenation; drug accumulation can occur, but the use of inotropic support and increased cardiac outputs may counter this accumulation.[83]

The recommendations from a recent review are to use -lactam antibiotics because they are utilized in other critically ill patients. The use of continuous vancomycin infusions during extracorporeal membrane oxygenation may help any extracorporeal membrane oxygenation-related pharmacokinetic changes. Recommendations for antifungal agents are sparse because of limited data. There are some data regarding voriconazole, suggesting a need for increased dosing because of sequestration.[83]

Bloodstream Infections in Extracorporeal Membrane Oxygenation Patients

Extracorporeal membrane oxygenation patients are at increased risk for bloodstream infections because they are in cardiogenic shock.[84] Large cannulae may be present for prolonged durations and are not easily exchanged if they become infected.[85] Finally, the presence of central lines and arterial catheters for prolonged periods may also increase the risk for bloodstream infection.[85]

Gram-negative rods were most frequently isolated from venous arterial–extracorporeal membrane oxygenation patients with bloodstream infection including Aeromonas hydrophilia/caviae, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa.[85] The venous venous–extracorporeal membrane oxygenation patients also had infections with Gram-negative rods including P. aeruginosa, A. baumannii, Burkholderia cepacia, and Enterobacter aerogenes, but they also had Candida infections. Notably, the venous arterial–extracorporeal membrane oxygenation patients in this study received prophylactic antimicrobial therapy with vancomycin and ceftriaxone for 4.8 All extracorporeal membrane oxygenation patients were bathed with chlorhexidine daily, and central lines are coated with minocycline/rifampin. Evaluation for infection was done if there was fever, leukocytosis, or purulence at an entry site.[85] Finally, bloodstream infection in extracorporeal membrane oxygenation patients was not associated with in-hospital mortality.[85]

Controversies in Gastrointestinal Procedures: Bowel and Biliary Tract Prophylaxis

The idea of utilizing oral antibiotics to decrease perioperative infections began shortly after penicillin was discovered and was combined with purgatives to decrease microbial colonization. When the formal combination of mechanical bowel preparation and neomycin and erythromycin was introduced, surgical site infection rates were reduced from 43 to 9%.[86] In a review of 5,800 colorectal surgery patients, no signi cant di erence with mechanical bowel preparation versus no preparation in terms of leakage or surgical site infection were found.[87] Whether to use mechanical bowel preparation, oral antibiotics alone, or in combination with systematic antibiotics has remained controversial. A review of the results of the 2012 to 2015 American College of Surgeons National Surgical Quality Improvement Program database addressed the question as to what extent mechanical bowel preparation and antibiotic bowel preparation decreased infection after elective colorectal resection.[88] The combined mechanical bowel preparation/antibiotic bowel preparation when compared with no preparation had fewer surgical site infection (odds ratio, 0.39), organ space infection (odds ratio, 0.56), wound dehiscence (odds ratio, 0.43), and anastomotic leak (odds ratio, 0.54), all signi cantly lower. A 2014 Cochrane review found high quality evidence that antibacterial therapy targeting colonic pathogens reduced the risk of surgical site infection but could not determine whether this was attenuated by mechanical bowel preparation.[89] Antibiotic bowel preparation alone compared with no preparation also has signi cant bene ts, whereas mechanical bowel preparation alone did not. As such, for patients undergoing elective colon or rectal resection, both mechanical agents and oral agents are recommended whenever feasible.[90,91]

Unlike open cholecystectomy, the bene ts of antibiotic prophylaxis in patients undergoing planned elective laparoscopic cholecystectomy is controversial,[92] although some studies have suggested a decline in postoperative infection.[93,94] Patients who undergo more complex biliary, hepatic, or pancreatic surgery may have special considerations with respect to surgical site infection risk. Aside from the typical risk factors, these patients may have had recent contact with the healthcare system via procedures to further clarify their underlying anatomy/disease. Through endoscopic or transhepatic procedures, they may introduce or encourage potential future colonizing or infecting pathogens in the setting of partially obstructed biliary drainage systems. There appears to be a correlation between intraoperative biliary cultures and future pathogens identi ed at the time of infection.[95]

In a randomized controlled trial of 126 patients with planned hepatobiliary pancreatic surgery, patients received targeted prophylaxis based on known pathogens in biliary cultures versus standard prophylaxis, which was with either a second-generation cephalosporin or up to three antibiotics targeted for the resistant pathogens. Infection rates were high in both groups (43.5% in the targeted group and 71% in the standard group). This study suggests that multidrug-resistant colonization should be considered when using perioperative prophylaxis in high-risk hepatobiliary pancreatic surgery.[96] Duration of prophylaxis has also been controversial in liver surgery. Four randomized controlled trials have examined the issue of extended duration under the premise that

ongoing contamination related to bile leakage may occur after surgery and would incur added risk of surgical site infection. One study suggested that prophylaxis for up to 7 days postoperatively was bene cial,[97] whereas another study reported that 2 days were as e ective as 5 days.[98] A recent consecutive series of patients having a hepatic resection without biliary reconstruction reported no di erence in postoperative infection rates.[99] Last, a small randomized controlled trial that included major hepatectomy with extrahepatic bile duct resection and reconstruction compared 2 days versus 4 days of antibiotics and found no di erence in infectious complications between the two groups (30.2% in the 2-day group vs. 32.6% in the 4-day group).[100] These studies show diligence is required in identifying infectious complications given the high rate of occurrence, but extending antibiotic duration does not appear to confer bene t. No studies in this high-risk population have limited antibiotics to the operating room only, as recommended in recent guidelines.

Controversies in Urologic Procedures: Chronic Indwelling Catheters

The topic of antibiotic prophylaxis for the insertion or removal of urinary catheters has generated numerous articles and reviews.[101–106] Although there has been documented e cacy in the prevention of urinary tract infection with gentamicin use before removal of catheters, the use of gentamicin around the insertion and removal of urinary catheters before surgery has been discouraged by national recommendations. In one interventional study, rates of use on insertion went from 42 to 2% and on removal from 28 to 3%. In the nal 40 weeks of this study, no gentamicin was used for either indication. Importantly, there were no signi cant di erences in perioperative bacteriuria, surgical site infection, or acute kidney injury in this study.[107]

Controversies in Orthopedic Procedures

Different Administration Protocols for Antibiotic Prophylaxis in Joint Replacements

Prosthetic joint infection is an expensive and destructive complication for patients. The only "accepted" antibiotic prophylaxis is within 1 h of the surgical incision, which decreases surgical site infection in primary joint surgeries.[108,109] Single-center studies of adding a 1-g dose of vancomycin to the cephalosporin prophylactic antibiotic documented a lower rate of prosthetic joint infection in primary total knee arthroplasties and total hip arthroplasties.[110] Notably, these patients also received antibiotic cement.

Another more controversial technique of prophylaxis is the administration of antibiotics into the bone, or intraosseous regional administration, to increase antibiotic concentrations near the prosthetic joints.[111,112] These studies have been small, and although they have shown increased concentrations of antibiotics, they have not evaluated patient outcomes.

Intraoperative vancomycin powder has also been evaluated as a strategy to prevent infection. These studies have not been randomized. In one retrospective study of 115 patients,[113] 42 had received intraoperative vancomycin. There were no signi cant di erences in the number of surgical site infections, need for multiple antibiotics, reoperations, or length of stay between the control group and vancomycin powder recipients.[113]

Neurosurgery

A randomized, prospective, multicenter trial is underway assessing the safety and e cacy of topical vancomycin in neurosurgical patients undergoing a craniotomy or noninstrumented spine procedures. A report on the adverse events and microbiology pro les from the rst year of enrollment has just been published.[114] Systemic absorption of the topical vancomycin was monitored by measuring serum vancomycin levels at 6 and 12 h after wound closure. Microbial cultures were done of the anterior nares and surgical site before draping, 48 h after wound closure, and at 2 weeks and 3 months after surgery. Serious adverse events were reported in 5 of 257 control patients and 2 of 514 patients who were in the treatment group; therefore, no signi cant di erence in serious adverse events or adverse events occurred between the groups. Serum vancomycin levels in patients who received topical vancomycin but no intravenous vancomycin were 6.3 ± 1.8 micrograms/ml. Microbiologic studies documented that topical vancomycin did not change the risk of S. aureus colonization after cranial surgery in an interim report, but nal results are still pending.[114]

External Ventricular Drains

A consensus statement has been formulated by the Neurocritical Care Society (Chicago, Illinois) given the paucity of high-quality clinical data. The group involved included neurologists, neuroinfectious experts, internists, pharmacotherapy professionals, and nurses.[115] The infection rates of external drains have been reported between 0 and 32% with typical rates of about 10%.[115] The de nition of infection varies; the Centers for Disease Control and Prevention do not require positive cerebrospinal uid cultures, whereas other authors do.[116,117]

The recommendation from the Neurocritical Care Society was for one dose of antimicrobials before external ventricular drain insertion (low-quality evidence); they recommended against the use of antimicrobials for the duration of external ventricular drain placement (low-quality evidence). The Neurocritical Care Society did recommend using antimicrobial-impregnated catheters (moderate-quality evidence) and using intraventricular antimicrobials to treat ventriculostomy-related infections when there was a failure to respond to intravenous antibiotics or the

organisms involved had very high minimum inhibitory concentrations that would be difficult to achieve in the cerebrospinal fluid (moderate-quality evidence).[115] More recent studies have confirmed that prolonged antibiotics are associated with an increase in nosocomial infections[118] and do not provide more protection.[119]

Conclusions

Significant controversies in antimicrobial prophylaxis remain, and there are numerous opportunities for improving practice through rigorously designed and implemented studies. More antibiotics are not always more effective in reducing surgical site infection. There are significant gaps between guidelines and practices, predominately with duration of antibiotic prophylaxis exceeding current consensus guidelines.

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Competing Interests

The authors declare no competing interests.

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