CHAPTER 38

APPROPRIATE USE OF PERIOPERATIVE ANTIBIOTICS

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INTRODUCTION

Despite the abundance of research pertaining to perioperative antibiotic use in the literature, there continues to be a deficiency of well-controlled, large-scale studies specific to foot and ankle surgery. We utilize modifications of the current principles outlined in the orthopedic literature and apply them to podiatric surgery. Unfortunately antibiotics are commonly used indiscriminately in the perioperative period, and their usage is frequently a function of habit or tradition rather than sound medical principles. This paper will present a pertinent review of the literature and the most current and accepted indications for perioperative antibiotics in foot and ankle surgery.

INDICATIONS FOR ANTIBIOTIC PROPHYLAXIS

Trauma Surgery

Open Fractures. Although the efficacy of antibiotics in the treatment of open long-bone fractures is well-established, their importance in the treatment of open fractures of the foot and ankle has not been identified. The term prophylaxis in the traditional sense is somewhat ambiguous when discussing open fractures, since it is impossible to achieve the maximum concentration of antibiotics present at the time of insult. It must be noted that antibiotics only supplement a thorough and aggressive debridement.

Three goals must be accomplished for the successful treatment of all open fractures: the prevention of infection, the achievement of bony union, and the restoration of function.[1] The consolidation of the fracture site(s) and functional outcome are dependent on the first goal. Infection is the primary cause of non-union and instability following open fractures.[2] There are several underlying themes which dictate antibiotic administration for open fractures: 1. Antibiotics reduce the incidence of infection; 2. Antibiotics should be given with all open fractures; 3. The risk of infection is proportional to the severity of the injury (i.e. fracture stability and soft tissue envelope devitalization); 4. Most infections are caused by nosocomially acquired pathogens; 5. Antibiotic treatment should be initiated immediately.[1]

Current recommendations for anti-infective therapy are based on fracture stability and the degree of disruption of the soft tissue envelope. Cefazolin alone may be used for the treatment of type I open fractures.[1] A combination of cefazolin and an aminoglycoside, or a broad spectrum antibiotic such as Timentin may be reserved for more severe injuries.[1] Osterman et al.[3] demonstrated the effectiveness of tobramycin-impregnated beads in conjunction with systemic antibiotics in reducing infection rates with open fractures, however this may have limited application in the foot and ankle. The duration of anti-infective therapy following an open fracture remains debatable, with some authors advocating administration ranging from 1 to 3 days.[1,4,5] Templeman et al.[1] advocate continuation of antibiotics for 3 days following wound closure.

Closed Fractures. Malaligned fractures with significant displacement or intra-articular involvement must frequently undergo open reduction with internal fixation to restore function and to prevent post-traumatic arthritis. The Dutch Trauma Trial[6] clearly illustrated the need for perioperative antibiotics in the surgical treatment of closed fractures. This study of over two thousand fractures (88% lower extremity) demonstrated a significant reduction in the incidence of wound and early nosocomial infection with the use of a single dose cephalosporin. The research of Roth et al.[7] supports these findings. As with clean elective foot and ankle surgery, the prophylaxis is directed toward *anti-staphylococcal* coverage. Antibiotic prophylaxis is not indicated for fractures treated by closed reduction, as contamination of the fracture site is highly unlikely in these circumstances.[8]

Immunocompromise

It is generally believed that patients who are "immunocompromised" are candidates for perioperative antibiotics, however it may be difficult to identify specific host factors, which cause vulnera-

bility in the postoperative period. Particular disease states and/or their treatments may prevent the host immune system from defending against a surgical wound infection. Clinical research in support of this indication is indirect and originates from the treatment of patients who have undergone chemotherapy and developed a secondary leukopenia.[9] Therefore, since antibiotic administration reduces the risk of sepsis in this compromised population, it is assumed through extrapolation that antibiotics may be beneficial when given to patients with varying degrees of host defense impairment.

According to Cimino et al.[10] rheumatoid arthritis (RA) affects the foot and ankle in greater than 90% of affected individuals at some time during the disease course. With this fact in mind, it is important to recognize potential risk factors and the need for antibiosis. A large number of studies have revealed a significant increase in postoperative complications among rheumatoid patients including an increase in surgical wound infections and dehiscence.[11-14] Medications used to combat the inflammatory nature of RA (i.e. antineoplastic agents, corticosteroids) may certainly increase the potential for postoperative wound infection through impairment of the immune response. Rayan et al.[15] found that many patients with RA have poor nutritional profiles, which may also contribute to the higher infection rates. Perioperative antibiotics in addition to a thorough medical history, evaluation of preoperative nutritional status and meticulous tissue handling will likely minimize postoperative wound complications.

Although diabetes is frequently discussed as a significant risk factor for the development of postoperative infection, it is primarily the poorly-controlled diabetic patient who presents an increased risk for surgical wound complications. Abnormalities in neutrophil function, cell-mediated immunity, and serum opsonin activity have been identified, however these cellular and biochemical malfunctions manifest in the presence of significantly elevated blood glucose.[16-19] In fact, in a review of over 3000 clean orthopedic procedures, Lidgren found no statistical difference in infection rates comparing diabetic and non-diabetic patients.[20] Shapiro notes that "although reports exist showing association of diabetes and postoperative infection in general, and orthopedic surgery, those studies reviewing very large series of surgical wound infections with multi-variate analyses have failed to show that diabetes is an independent risk factor."[19] There may be little to no additional risk in performing clean, elective surgery in a well-controlled patient.[21] Co-morbid disease (obesity, atherosclerosis, etc.) states often seen clinically with diabetes may contribute to increased infection rates.

The relationship between postoperative infections and HIV remains unclear. Joseph argues that although there may be significant defects in cell-mediated immunity, the neutrophil-mediated immunity remains largely intact.[21] Therefore, those infections in which the primary defense is white blood cells are not more prevalent in the nonneutropenic patient regardless of CD-4 lymphocyte count. There are no studies demonstrating an increase in surgical wound infection in the aymptomatic HIV-infected population. No difference in the "microbial spectrum" has been identified, however "atypical" manifestations of "typical" organisms have been reported.[21,22] The guidelines for perioperative antibiotic prophylaxis remain unchanged with respect to the HIV positive patient. A multidisciplinary approach will likely yield the most beneficial results, although no significant risk for postoperative infection has been demonstrated.

In addition, many other medical conditions including vascular occlusive disease, end-stage organ failure, malnutrition, hypoxia or extremes of age may create less than optimal conditions for immune system function and therefore require surgical prophylaxis.

Permanent Internal Fixation Devices/Implants

No study to date has established the efficacy of perioperative antibiotics in elective foot and ankle surgery utilizing internal fixation. This indication originates from the orthopedic literature concerning large joint arthroplasties. There has been, however, research demonstrating the deleterious effects of implant/host interaction which may promote the development of infection. Studies have shown implants may cause impaired wound healing, reduction of leukocyte phagocytosis/opsonization, and "bacterial trapping," in addition to providing a substrate for adherence of a glycocalyx slime layer.[23,24] Dobbins found that despite the absence of clinical infection, greater than 70% of the internal fixation of ankle fractures were colonized with a slime producing coagulase negative Stapylococcus.[21]

First metatarsophalangeal implant arthroplasty has been a recognized indication for antibiosis

despite the lack of research to support it. In comparison, anti-infective therapy in clean elective hand procedures lasting less than two hours including arthroplasties of the metatacarpophalangeal or proximal interphalangeal joints using silicone implants has not been proven efficacious.[25] With the re-invention and increasing popularity of the total ankle implant, prophylactic antibiotics must be considered. In spite of a low incidence of postoperative infection, antibiotics should be administered, because infection with these devices may yield devastating results.

It seems reasonable however, that prophylactic antibiotics should be utilized for reconstructive procedures of the midfoot, rearfoot and ankle requiring internal fixation. In addition, these procedures typically last greater than two hours which is a recognized risk factor for the development of postoperative infection.

Prolonged Surgery

Prolonged surgical exposure creates a larger window of opportunity for contaminants to enter the wound environment, which increases the potential for infection. Approximately 90% of contaminants found within the surgical site originate from the patient, operating room personnel or equipment and travel via airborne route.[21,26] Most of the literature signifies surgery greater than two hours in length to be an appropriate indication for prophylaxis, however there are few studies to demonstrate this.[7,27,28] As with other issues pertaining to foot and ankle surgery, there exists the lack of research to support this claim.

ANTIBIOTIC SELECTION

Prophylactic antibiosis should be directed against the most probable *infecting* organisms, which may not be the most common *contaminating* organisms, but does not have to cover all the potential pathogens.[29] The goal of prophylaxis is to decrease the number of organisms below critical levels necessary to cause infection.[30] Consideration should also be given to the current hospital sensitivity-resistance patterns and the risk of adverse reactions. The primary infecting organisms in clean podiatric surgery are *Staphylococcus aureus,* followed by *Staphylococcus epidermidis.* Infections caused by aerobic gram-negative bacteria are less common.[23,25] *S. epidermidis,* which accounts for the largest percentage of prosthetic infections, possesses the ability to create an impenetrable slime glycocalx allowing it to adhere to the surfaces of implants.

Cephalosporins have been the mainstay for antibiotic prophylaxis and the current literature continues to support the use of cefazolin for clean orthopedic surgery. This first-generation cephalosporin has a long half-life, excellent anti-*staphylococcal* activity, is relatively inexpensive and has been shown to establish high serum and bone concentrations in comparison to other cephalosporins.[31] Cefazolin also provides adequate coverage of selected gram-negative organisms. Although some third generation cephalosporins and pencillin/ß-lactmase inhibitor compounds have been advocated for prophylaxis, they exhibit comparable or decreased coverage against staphylococcus in addition to an increased cost.[32-36] It is recommended that these agents be reserved for use in serious, complicated infections in hospitalized patients. Two grams of cefazolin are given preoperatively followed by 1 gram every 8 hours when indicated.

Vancomycin is indicated in antibiotic prophylaxis in several cases: documented anaphylaxis to penicillin allergy to cephalosporins; institutions with high occurrence of MRSA/MRSE infections; and patients who have had previous infections with MRSA/MRSE. Vancomycin has less antistaphyloccocal coverage than cefazolin and virtually no coverage of gram negative organisms. It is cautioned that indiscriminant use of vancomycin may encourage resistant strains of staph and enterococcus. One gram of vancomycin is given 1 hour prior to surgery and infused slowly over that hour. Postoperative administration consists of 0.5g-1.0g twelve hours after the first dose.

Clindamycin is a bacteriostatic agent primarily advocated for use in implant surgery because of its demonstrated ability to effectively penetrate the glycocaylx slime layer.[23] It provides adequate coverage of gram-positive cocci (MSSA, MSSE), in addition to some anaerobic coverage including bacteroides. As with vancomycin, clindamycin provides little if any gram-negative coverage. This agent has been criticised for its side effect profile, primarily diarrhea, in which the occurrence has reported to be as high as 20%.[23] Clindamycin is commonly used at the author's institution for antibiosis in patients with documented penicillin allergy. The usual dose is 900mg IV 30 minutes preoperatively with subsequent doses every 8 hours.

In the event that antibiotic prophylaxis fails

(i.e. postoperative infection) an alternate anti-infective agent should be selected for therapy.[9] The wound infection in this scenario is most likely due to a resistant pathogen not covered by the preoperative antibiotic.

TIMING OF ADMINISTRATION/ TOURNIQUET USE

Burke's[29] guinea pig model demonstrated a relationship between timing of administration and efficacy of prophylactic antibiotics. According to his work and others, prophylaxis has been shown to be most efficacious when maximum concentrations are achieved prior to wound contamination.[29] The effectiveness of antibiosis is greatly decreased when administration occurs in the subsequent time period following the initial incision. Current recommendations are to administer antibiotics 30 minutes prior to the skin incision with the exception of vancomycin which must be infused slowly over 1 hour.

Antibiotic administration five minutes prior to tourniquet inflation is necessary to achieve desired maximum tissue concentration in bone and soft tissue in the foot and leg.[37-39] Dosing near or following inflation will not allow for adequate perfusion and maximum tissue concentration at the time of incision.

POSTOPERATIVE ANTIBIOTICS

Despite mounting evidence and research stating the ineffectiveness and potential pitfalls of prolonged postoperative antibiotic administration, many surgeons continue to subscribe to this practice. In fact, it is not uncommon for many physicians to prescribe oral antibiotics at minimal recommended doses for 3-5 days following surgery (i.e. Keflex 500 bid). There are several inherent flaws with this practice. First, there is no conclusive evidence that supports postoperative antibiotics beyond the 24-hour time period. Nelson et al.[40] concluded that "preventive antibiotics used for 24 hours or seven days are equally effective in controlling sepsis in orthopedic surgery." Numerous studies comparing short-term versus long-term prophylaxis have not demonstrated an increase in the infection rates among the short-term recipients[19,25,40-42] A 24-hour dosing regimen may be utilized if the patient is significantly compromised, surgery is extensive or lasts greater than 2 hours. If these circumstances are not present, then the initial preoperative dose is adequate.[23,43]

Secondly, perioperative antibiotics continue to aid in the selection of multiresistant pathogens. Conte et al.[41] concluded that prophylaxis greater than 4 days has been associated with altered antimicrobial sensitivities of infecting organisms.[25] No detrimental effects however have been shown following a 24-hour course of postoperative antibiotics.[25] Certain clinical scenarios, such as open fractures, complex reconstruction and procedures involving compromised hosts, may necessitate the need for additional antibiotic administration in the postoperative course.

ADVERSE EFFECTS OF PERIOPERATIVE ANTIBIOTICS

Although the occurrence of adverse effects with perioperative antibiotics is infrequent, the possible complications should not be overlooked. One of the most frequently reported side effects with antibiosis is antibiotic associated diarrhea (AAD), specifically pseudomembranous colitis.[25] The incidence has been reported to be as high as 6% following the use of some cephalosporins.[29,43] However with widespread use of prophylaxis and the small number of reported cases, C. difficile colitis remains an unusual complication.[44] Of the patients who develop C.difficile colitis, those who receive perioperative prophylaxis comprise the largest group.[45] AAD, although associated with specific drugs (i.e. clindamycin and cephalosporins), may be caused by any antibiotic regardless of dose, duration or route of administration.

As mentioned previously, another consequence of widespread and injudicious use of antibiotics is the possibility of emergence of multiresistant pathogens with or without secondary superinfection. Current research indicates that antibiosis can alter the resident skin flora and may impart resistance.[46] Both methicillin and gentamycin-resistant coagulase negative staphylococci can be detected in high numbers on the skin of surgical patients within 5 days of exposure to perioperatively administered cephalosporins, however it is not yet known whether these bacteria are able to overcome the colonizing flora to contaminate the surgical site.[44]

Allergic reactions to antibiotics have been well-documented in the literature.[44,47,48] Penicillin allergies have been reported in 5-10% of the adult population.[25,29,49] Allergic reactions to cephalosporins are much more infrequent and are rarely life-threatening.[47] Despite the low incidence of cross reactivity between

ß-lactam antibiotics, many authors do not advocate the use of prophylaxis with a cephalosporin agent in patients with a history of an immediate or accelerated reaction to penicillin, such as hypotension, bronchospasm, or urticaria.[23, 29,48]

In addition to the previously-mentioned risks, antibiotic administration beyond documented indications is a financial burden to the healthcare industry. Heydemann et al.[50] estimated that the excess cost for antibiotic administration for 48 hours (instead of a single preoperative dose) per 100,000 would reach 8 million dollars. This is a significant cost for an unproven treatment.

CONCLUSION

Although definitive guidelines for antibiotic prophylaxis in elective and emergency foot and ankle surgery do not exist, podiatrists should utilize basic principles of prophylaxis with the knowledge of its potential hazards. Continued research is needed to define the surgical indications for antibiosis in our surgical scope. Certainly, antibiotic selection is a surgeon's preference, however cefazolin is the agent of choice in the non-penicillin allergic patient undergoing elective surgery. The duration of antibiotic use should be minimized to prevent possible complications, and antibiotic administration past the 24-hour period has not been shown to be more efficacious. The injudicious use of antibiotics will continue to select for multi-resistant organisms in addition to increasing the already exaggerated cost of medical care.

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