Treatment

3.1. TREATMENT: ANTIBIOTICS AND NONOPERATIVE MANAGEMENT

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QUESTION 1: What is the most optimal prophylaxtic antibiotic coverage and treatment duration for open fractures of long bones?

RECOMMENDATION: The use of prophylactic antibiotics for open fractures of long bones has a protective effect against early infection. Antibiotics should be administered as soon as possible after the injury. The antibiotic of choice should target gram-positive organisms. Additional coverage for gram-negative organisms should be considered for patients with high-energy open fractures. Antibiotics should not be continued for more than 72 hours after wound closure.

LEVEL OF EVIDENCE:

- Efficacy of prophylactic antibiotics – Strong
- Timing of prophylactic antibiotics – Moderate
- Choice of antibiotics – Limited
- Treatment duration – Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Efficacy

Antibiotic administration has been shown to decrease the infection rate in open fractures in randomized controlled trials [1,2] as well as systematic reviews [3,4]. Patzakis et al. demonstrated for the first time the benefit of antibiotics in a prospective, randomized study [1], in which the infection rates for cephalothin versus penicillin with streptomycin versus no antibiotics were 2.3%, 9.7%, and 13.9%, respectively. In a Cochrane review data from 1,106 participants in eight studies were analyzed. The use of antibiotics had a protective effect against early infection compared with no antibiotics or placebo (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.29 to 0.65, absolute risk reduction 0.07 [95% CI 0.03 to 0.10]). [3]. Another more recent systematic review also suggested a large, consistent reduction in infection risk with antibiotic use (RR 0.37, 95% CI, 0.21 to 0.66) [4].

Timing

In a retrospective study of type III open tibial fractures by Lack et al., administration of systemic antibiotics more than 66 minutes after injury was significantly and independently associated with deep infection (odds ratio (OR), 3.78, 95% CI, 1.16 to 12.31) [5].

Based on the quality and quantity of available evidence, the initial strength of the recommendation for early administration of antibiotics would be limited. However, we can upgrade this recommendation to one of moderate strength based on the following factors: (a) there is strong evidence that antibiotics need to be given and (b) delaying the necessary administration of antibiotics does not convey any benefit that could balance the potential risk of increased infection rate with delayed administration.

Choice of Antibiotics

Target organisms for prophylactic administration should be contaminants in the wound. Studies evaluating the microbiology of open fracture wounds have consistently shown that most contaminants are gram-positive organisms [6,7]. A study of 616 type I and II open fractures of the tibia reported that bacterial contamination at the fracture site consisted of a similar distribution of gram-positive (75 to 78%) and gram-negative (22 to 26%) species upon arrival at the emergency department, at the start of the operation, and at wound closure [6]. Methicillin-resistant *Staphylococcus aureus* (MRSA) were absent among the strains isolated at these stages [6].

The importance of antibiotics covering gram-positive organisms (usually a first-generation cephalosporin) is widely agreed upon. However, the necessity of coverage against gram-negative organisms or against anaerobes remains controversial.

No studies in the literature have directly compared gram-positive coverage to combined gram-positive and gram-negative coverage. Patzakis et al. recommended addition of aminoglycosides in all open fractures and reported a reduction in the infection rate from 14.6% in open tibias treated with a cephalosporin (from 1976 to 1977) to 4.5% in open tibias treated with both a cephalosporin and an aminoglycoside (1979 to 1980). However, this was not a direct comparison but instead a comparison of patients treated in different time periods in two prospective studies [8]. Gustilo et al. reported that 77% of cultures isolated from infected open fractures were of gram-negative bacteria and advocated addition of aminoglycosides for type III open fractures [9]. Similarly, Vasenius et al. in a randomized controlled trial of clindamycin vs. cloxacillin reported high surgical site infection (SSI) rates in type III open fractures and advocated addition of an aminoglycoside in these severe open tibia fractures [10].

Contamination of open fracture wounds with gram-negative organisms, although less frequent, still occurs [6,7] and a severe open fracture may be misclassified due to limitations in the interobserver agreement of the Gustilo-Anderson classification [11]. However, the SSI rates of Gustilo type I and II fractures have been consistently low in the literature even with narrow-spectrum antibiotics that mainly target gram-positive species [9].

Therefore, administration of a first-generation cephalosporin is recommended for Gustilo I and II fractures [12–14] and additional administration of an antibiotic with good gram-negative coverage is recommended in Gustilo type III (e.g., aminoglycoside or 3rd generation cephalosporins) [13,14,15,16]. Aminoglycosides may cause nephrotoxicity, especially in the setting of renal disease or dysfunction; therefore, renal function should be considered beforehand. Pannell et al. reported that gentamicin use during treatment of open fractures does not lead to increased rates of renal dysfunction when used in patients with normal baseline renal function [17]. Unfortunately, renal function is often not known at the time of initial admission of antibiotics.

Anaerobic coverage (e.g., penicillin, clindamycin or metronidazole) is recommended in the presence of potential clostridial contamination (e.g., fecal contamination or farm-related injuries) [13,14]. However, no study has compared anaerobic coverage in such injuries. A group developing guidelines for combat injuries that are severely injured and contaminated did not recommend anerobic coverage, but instead emphasized early and thorough debridement.

The emergence of antimicrobial resistance in bacteria has created concerns about the adequacy of current antibiotic protocols, especially against MRSA. However, a randomized controlled trial comparing vancomycin and cefazolin versus only cefazolin in 101 patients with open fractures found no difference in the infection rates between the groups: 19% in the group receiving vancomycin and cefazolin versus 15% in the cefazolin only group [18]. As a result, the routine use of vancomycin in open fractures cannot be recommended based on available data.

Duration

Two randomized controlled trials compared one to five days of antibiotics in the management of open fractures [6,19]. Both studies reported that the infection rates were similar in the one-day and the five-day groups and advocated against the prophylactic administration of antibiotics for five days. However, no randomized controlled studies have compared one-day, two-day, or three-day antibiotic prophylaxis. A retrospective case control study of 1,492 open fractures by Dunkel et al. showed after multivariate analysis that there was no significant difference in infection risk for one-day prophylaxis compared with longer regimens [20]. Although the OR for infection in the two/three-day group compared to the one-day group was 0.6 (95% CI, 0.2 to 2.0) in all fractures and 0.3 (95% CI, 0.1 to 3.3) in type III fractures. These lower ORs were not found to be significant.

Prolonged prophylactic administration of antibiotics beyond 72 hours is not recommended. In the absence of additional data for type I and II open fractures we would recommend administration of antibiotics for at least 24 hours after wound closure, but not to exceed 72 hours. In type III fractures we recommend 72 hours of antibiotic administration or 24 hours after closure or soft tissue coverage of the wound, in agreement with existing guidelines [13,15,16,21].

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