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Antibiotic utilization in open fractures

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Abstract

Open fractures are complex presentations with elevated risks of infection and nonunion due to a multitude of factors. Along with early surgical debridement, antibiotics have been heavily utilized and have become part of standard of care to reduce the risks of fracture-related infections. Many aspects of their use have been studied and debated. The early administration of intravenous antibiotics has been shown to significantly reduce the incidence of infection. Furthermore, current standards do not recommend prolonged antibiotic administration post wound closure. Recently, an increasing number of studies have assessed the utility of locally administered antibiotics. Clinical and basic science studies have been relatively supportive of their usage, but further studies are still warranted to further delineate their effects.

Keywords: antibiotics, infection, open fractures

1. Introduction

Open fractures of the lower extremity are severe orthopaedic injuries with increased risks for infection and nonunion. A multitude of factors such as severity of injury and host factors influence the incidence of infection.[1,2] Due to extensive soft tissue trauma and degree of contamination, bacteria can penetrate the damaged skin barrier and adhere to nonviable tissue or fixation devices.[3] Subsequently, biofilm formation makes these infections very difficult to treat. These infections in the setting of open fractures have an increased socioeconomic cost burden for all involved.[4] Therefore, the utilization of antibiotics in this clinical setting is now widely recommended to combat the risks of fracture-related infections.[5] This review aims to delineate the evidence for various aspects of this antibiotic utilization in the setting of open fractures.

2. Time to surgical debridement

Historically, it was widely accepted that emergent debridement of open fractures was essential for improving outcomes. The 6-hour rule had been frequently utilized as it was believed to reduce infection and nonunion rates.[6] Despite questionable initial evidence, the rule recommended that open fractures be operatively debrided within 6 hours from the time of the injury.

Pollak et al[7] evaluated 315 patients with lower extremity open fractures to assess the relationship between time to surgical debridement and incidence of infection. They found that time from injury to initial operative debridement was not associated with infection risk. Meanwhile, time from injury to admission at trauma center was found to be an independent predictor of the likelihood of infection.[7] This finding likely demonstrates the importance of early antibiotic coverage rather than time to surgical debridement.

A systematic review subsequently assessed the 6-hour rule in relation to infection and nonunion rates.[8] Three hundred sixty-five patients across 3 studies were included in this study. It was determined that judicious delays greater than 6 hours to operative debridement do not result in a statistically significant difference in infection, nonunion, and perioperative morbidity rates.[8]

Hendrickson et al[9] further expanded the time interval to 12 hours in their multicenter retrospective review of Gustilo-Anderson Grade 3B open tibia fractures. The overall deep infection rate within the 116 fractures included was only 5.2%.[9] They identified no significant difference in incidence of infection whether initial debridement occurred prior to or after 12 hours post-time of injury. Weber et al[10] completed a prospective cohort study of 736 patients with open fractures and found that infection was actually associated with increasing Gustilo grade or tibia/fibula fractures (as opposed to upper limb) and not time to surgery or antibiotics. However, the majority of patients did receive antibiotics within 3 hours of injury and therefore, this finding may not be surprising.[10] Furthermore, the same prospective cohort was analyzed to assess for factors associated with the development of nonunion or delayed healing.[11] Deep infection (OR = 12.75; 95% CI 6.07– 26.8), smoking (OR = 1.73; 95% CI 1.09–2.76), and Gustilo 3A fractures (OR = 2.49; 95% CI 1.30–4.78) were strongly associated with nonunion.[11]

Interestingly, in a retrospective study assessing 459 consecutive open fractures, Hull et al[12] found that among Grade II and III open fractures, there was a statistically significant increase in the rate of deep infection for each hour of delay. The relationship demonstrated an increase in infection rate of 3% per hour of delay. Meanwhile, the Grade I open fractures in their study did not develop deep infections. Deep infection was also associated

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with other factors such as the presence of a tibial fracture (OR = 2.44: 95% CI 1.26–4.73) and contamination of the fracture (OR = 3.12: 95% CI 1.36–7.36). This study suggested that delay in initial debridement may be safe for Grade I open fractures. Meanwhile, in high-grade open fractures early debridement may be beneficial especially in the setting of poor prognostic factors such as tibial site and presence of contamination.[12]

Finally, the British Association for Plastic Surgeons and Reconstructive and Aesthetic Surgeons along with the British Orthopaedic Association created their current standards for the management of open fractures.[13] They only recommend immediate surgical exploration of open fractures in the presence of: gross contamination, compartment syndrome, a dysvascular limb, and a multiply injured patient.[13] In the absence of these findings, their standards recommend surgical debridement to be completed within normal working hours and within 24 hours of the injury unless the wound involves agricultural, marine, or sewage contamination.[13] In essence, their standards refute the previously recommended debridement of all open fractures within 6 hours of the injury.[13]

3. Time to antibiotic administration

The importance of antibiotic utilization in open injuries has long been prioritized. Antibiotic administration timing had been shown to have an effect on wartime soft tissue wounds sustained by soldiers during the Falklands Campaign.[14] In the setting of open fractures, it has long been understood that antibiotic prophylaxis is an important factor for decreasing the incidence of deep infections.[1] Nonetheless, timing of antibiotic prophylaxis in the setting of open fractures was not always well understood and has historically been administered "as soon as possible." Patzakis and Wilkins[1] had demonstrated clear benefits of early antibiotic administration as those patients given antibiotics within 3 hours of injury had an infection rate of 4.7% while those administered greater than 3 hours had an infection rate of 7.4%. Meanwhile, a study of 237 consecutive open long bone fractures did not reveal a statistically significant difference in terms of the effect of antibiotic administration timing on incidence of infection.[15]

Initially, most studies grouped all open fractures together, regardless of location and Gustilo grade. Lack et al subsequently assessed 137 patients with Gustilo grade III open tibia fractures. They determined that delay in antibiotic administration greater than 66 minutes postinjury as well as delay of wound coverage greater than 5 days postinjury both independently predicted deep infection.[16] They made the strong recommendation to create management plans that recommend prehospital antibiotic administration to reduce the risk of infection in high-grade open tibia fractures. Harper et al[17] demonstrated that there are many logistical roadblocks to the timely delivery of antibiotic coverage. At their institution, cefazolin was delivered within an hour but logistical issues delayed the delivery of gentamycin as it was not typically stocked in close proximity.[17] Siebler et al[18] illustrated the effectiveness of a systemic performance improvement protocol targeting early antibiotic administration in increasing the percentage of open fracture patients receiving appropriate prophylactic antibiotics within 1 hour of admission.

4. Duration of antibiotic coverage

After antibiotics have been initiated in the setting of open tibial fractures, controversy still surrounds appropriate duration of dosing. Earlier studies and reports had suggested an adequate duration for antibiotic administration to be 3 to 5 days.[2,19,20] Another study recommended further antibiotic coverage for only 24 hours after wound closure.[21] Furthermore, some studies recommended 3 days of additional antibiotic coverage if another surgical procedure is required on the same site.[20,22] Dellinger et al[23] developed the first and only randomized, double-blind, prospective study specifically assessing duration of antibiotics in the setting of open extremity fractures. They randomized 264 open fractures to receive 24 hours or 5 days of postsurgical antibiotics. They found that a short course of antibiotics is as effective as a long course in terms of incidence of infection.[23] Recent reviews recommend 24 hours of antibiotic coverage after closure of Gustilo I and II injuries.[24] For grade III injuries, they suggest antibiotic coverage for 72 hours after injury but no longer than 24 hours after wound closure.[24] Nonetheless, there remains the need for a rigorous multicenter randomized control trial to assess the optimal duration of antibiotic coverage to reduce risk of infection, yet not increase risk of antibiotic resistance.[25]

5. Utilization of local antibiotics

Although systemic intravenous antibiotics have improved outcomes, local infection prophylaxis has historically been utilized in a variety of forms as well. Disrupted vascular anatomy in the setting of complex open fractures may result in decreased local tissue concentration of intravenously delivered antibiotics. With local antibiotics delivered directly to the traumatic site, this vascular deficiency may be bypassed and local tissue concentrations may be higher than could be achieved with intravenous antibiotics.[26] Furthermore, in the setting of internal fixation, local antibiotics may reduce the formation of biofilm and colonization of bacteria.[27]

A meta-analysis including 2738 patients from 8 studies assessed the effect of local antibiotic prophylaxis in the setting of open limb fractures.[28] Six studies utilized antibiotic loaded poly methyl methacrylate beads and 2 studies utilized local antibiotics without a carrier substance. Their analysis suggested a risk reduction of 11.9% in fracture-related infection if additional local prophylactic antibiotics were also given. Nonetheless, heterogeneity, potential bias, and low-quality studies limit this finding.

The METRC group completed the first-large multicenter, randomized, controlled trial assessing the efficacy of locally administered vancomycin powder in the setting of an open fracture.[29] Their goal was to assess deep surgical infection rates within 6 months with local vancomycin administration compared with those who did not receive it. Patient population ranged between 18 and 80 years of age and were of high-energy tibial plateau or pilon fractures treated with plate fixation. Those with closed fractures, infected at the time of enrollment, with vancomycin allergy or pregnant were excluded from the study. Patients randomized to the treatment group received 1 g of vancomycin powder topically before wound closure and the control group received standard of care without vancomycin. Thirty-six centers enrolled 980 patients in total with 499 in the control arm and 481 randomized to the treatment group.

Results presented at a recent Orthopaedic Trauma Association Annual meeting revealed the rate of deep surgical site infection to be 10.3% (95% CI 7.6–13.5) in the control group and 6.7% (95% CI 4.6–9.5) for the vancomycin treatment group with the resultant relative risk of 0.66 (95% CI 0.42–1.02; $P = 0.07$). Secondary analysis revealed 10% noninfection complication rate in both groups with the majority being nonunion or wound dehiscence. Post-hoc analysis of the deep infections interestingly demonstrated a rate of 7.8% for gram-positive bacteria within the control group with only 3.7% in the treatment group with relative risk of 0.48 (95% CI 0.27–0.85; $P=0.01$). Meanwhile, gram-negative-only infections were 2.1% in the control group and 2.6% in the treatment group with relative risk of 1.25 (95% CI .54–2.91; $P=0.66$). These findings are consistent with known vancomycin activity against gram-positive pathogens.

This was a well-balanced randomized control trial that was generalizable as multiple centers and surgeons had participated. Unfortunately, the study was still underpowered as it had lower effect size and control event rate than anticipated.

6. Conclusion

Open fractures of the lower extremity remain a problematic presentation in orthopaedic trauma due to their association with surgical site infections. Historically, several initiatives and techniques have been utilized and further expanded to reduce the incidence of infection. It has been clear and evident that early administration of systemic antibiotics has significantly reduced the risk of infection in both animal models as well as clinical studies. A variety of initiatives such as promoting prehospital arrival antibiotic delivery have also improved outcomes. Furthermore, studies have demonstrated that in the majority of circumstances, antibiotics should not be utilized for longer than 24 hours postwound closure. More recently, the utilization of local antibiotic powder has been studied and found to be promising. There is a need for future large RCTs that investigate the timing and the length of time for administration of antibiotics in the perioperative period.

References

1. Patzakis MJ, Wilkins J. Factors influencing infection rate in open fracture wounds. Clin Orthop Relat Res. 1989;36–40.
2. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. J Bone Joint Surg Am. 1976;58:453–458.
3. Metsemakers WJ, Kuehl R, Moriarty TF, et al. Infection after fracture fixation: current surgical and microbiological concepts. Injury. 2018;49:511–522.
4. Metsemakers WJ, Smeets B, Nijs S, et al. Infection after fracture fixation of the tibia: analysis of healthcare utilization and related costs. Injury. 2017;48:1204–1210.
5. Zalavras CG. Prevention of infection in open fractures. Infect Dis Clin North Am. 2017;31:339–352.
6. Bednar DA, Parikh J. Effect of time delay from injury to primary management on the incidence of deep infection after open fractures of the lower extremities caused by blunt trauma in adults. J Orthop Trauma. 1993;7:532–535.
7. Pollak AN, Jones AL, Castillo RC, et al. The relationship between time to surgical debridement and incidence of infection after open high-energy lower extremity trauma. J Bone Joint Surg Am. 2010;92:7–15.
8. Prodromidis AD, Charalambous CP. The 6-hour rule for surgical debridement of open tibial fractures: a systematic review and meta-analysis of infection and nonunion rates. J Orthop Trauma. 2016;30:397–402.
9. Hendrickson SA, Wall RA, Manley O, et al. Time to Initial Debridement and wound Excision (TIDE) in severe open tibial fractures and related clinical outcome: a multi-centre study. Injury. 2018;49:1922–1926.
10. Weber D, Dulai SK, Bergman J, et al. Time to initial operative treatment following open fracture does not impact development of deep infection: a prospective cohort study of 736 subjects. J Orthop Trauma. 2014;28: 613–619.
11. Westgeest J, Weber D, Dulai SK, et al. Factors associated with development of nonunion or delayed healing after an open long bone fracture: a prospective cohort study of 736 subjects. J Orthop Trauma. 2016;30:149–155.
12. Hull PD, Johnson SC, Stephen DJ, et al. Delayed debridement of severe open fractures is associated with a higher rate of deep infection. Bone Joint J. 2014;96-B:379–384.
13. BRITISH ASSOCIATION OF PLASTIC RAASB. Standards for the Management of Open Fractures of the Lower Limb. 2009.
14. Jackson DS. Sepsis in soft tissue limbs wounds in soldiers injured during the Falklands Campaign 1982. J R Army Med Corps. 1984;130: 97–99.
15. Al-Arabi YB, Nader M, Hamidian-Jahromi AR, et al. The effect of the timing of antibiotics and surgical treatment on infection rates in open long-bone fractures: a 9-year prospective study from a district general hospital. Injury. 2007;38:900–905.
16. Lack WD, Karunakar MA, Angerame MR, et al. Type III open tibia fractures: immediate antibiotic prophylaxis minimizes infection. J Orthop Trauma. 2015;29:1–6.
17. Harper KD, Quinn C, Eccles J, et al. Administration of intravenous antibiotics in patients with open fractures is dependent on emergency room triaging. PLoS One. 2018;13:e0202013.
18. Siebler J, Ogden B, Deans C, et al. A performance improvement project in antibiotic administration for open fractures. J Am Acad Orthop Surg. 2020;28:e34–e40.
19. Chan KM, Leung YK, Cheng JC, et al. The management of type III open tibial fractures. Injury. 1984;16:157–165.
20. Wilkins J, Patzakis M. Choice and duration of antibiotics in open fractures. Orthop Clin North Am. 1991;22:433–437.
21. Okike K, Bhattacharyya T. Trends in the management of open fractures. A critical analysis. J Bone Joint Surg Am. 2006;88:2739–2748.
22. Patzakis MJ, Wilkins J, Moore TM. Use of antibiotics in open tibial fractures. Clin Orthop Relat Res. 1983;31–35.
23. Dellinger EP, Caplan ES, Weaver LD, et al. Duration of preventive antibiotic administration for open extremity fractures. Arch Surg. 1988;123:333–339.
24. Mundi R, Chaudhry H, Niroopan G, et al. Open tibial fractures: updated guidelines for management. JBJS Rev. 2015;3:
25. Isaac SM, Woods A, Danial IN, et al. Antibiotic prophylaxis in adults with open tibial fractures: what is the evidence for duration of administration? A systematic review. J Foot Ankle Surg. 2016;55:146–150.
26. ter Boo GJ, Grijpma DW, Moriarty TF, et al. Antimicrobial delivery systems for local infection prophylaxis in orthopedic- and trauma surgery. Biomaterials. 2015;52:113–125.
27. Craig J, Fuchs T, Jenks M, et al. Systematic review and meta-analysis of the additional benefit of local prophylactic antibiotic therapy for infection rates in open tibia fractures treated with intramedullary nailing. Int Orthop. 2014;38:1025–1030.
28. Morgenstern M, Vallejo A, McNally MA, et al. The effect of local antibiotic prophylaxis when treating open limb fractures: a systematic review and meta-analysis. Bone Joint Res. 2018;7:447–456.
29. O'Toole RV, Joshi M, Carlini AR, et al. Local antibiotic therapy to reduce infection after operative treatment of fractures at high risk of infection: a multicenter, randomized, controlled trial (VANCO Study). J Orthop Trauma. 2017;31 (suppl 1):S18–S24.