REVIEW

Current Concept Review: Risk Factors for Infection Following Open Fractures

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Abstract: Infection following open fracture is a significant source of morbidity and mortality. Therefore, a central tenet of treatment is to minimize the risk of infection. The initial risk of infection is determined by wound characteristics, such as size, soft tissue coverage, vascular injury, and contamination. While no consensus exists on optimal antibiotic regimen, early administration of prophylactic antibiotics, within an hour of injury, when possible, has been shown definitively to decrease the risk of infection. Infection risk is further reduced by early irrigation with normal saline and aggressive debridement of devitalized tissue. Patient factors that increase risk of infection following open fracture include diabetes mellitus, smoking, male gender, and lower extremity fracture.
Keywords: open fracture, antibiotic prophylaxis, trauma, infection

Introduction

Open fractures are serious injuries with a reported incidence of 30.7 per 100,000 persons each year.[1] Infection is a relatively common complication following open fracture with rates ranging as high as 52%.[2] The sequalae of infection from open fracture includes longer hospitalization, non-union, and in some instances amputation and even death. Therefore, strategies to minimize the risk of infection following open fractures are an essential element of the overall treatment of these injuries.

The risk of infection following an open fracture is determined by a variety of factors. The most prominent among them is the severity of the wound. Greater soft-tissue damage along with vascular compromise creates an environment that is more conducive to bacterial growth and subsequent infection. The extent and type of contamination determines the bacterial load and the species that could lead to infection. Most infections appear to be nosocomial in origin.[3] Patient factors such as smoking status, immunodeficiency, and diabetes have all been shown to increase an individual's susceptibility to infection.[4]

Mitigating the infection risk in open fractures requires a systematic multidisciplinary approach. Antibiotics should be administered as early as possible, though there is no general consent on the optimal regimen.[5] The timing of irrigation and debridement as well as wound management and closure remains a topic of debate. Surgical treatment of more extensive open injuries often involves coordination between plastics and orthopedics to restore functionality to the damaged extremity.

Though most of the important treatment factors have been identified, they still require optimization. The purpose of this article is to review what the current literature tells us about minimizing the risk of infection associated with open fractures.

Risk Factors for Infection Following Open Fractures

A variety of factors determine the clinical results following an open fracture and these elements will be review in this section. These factors include:

1. Severity of soft-tissue injury.
2. Extent and type of contamination.

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3. Timing of treatment.
4. Antibiotic prophylaxis.
5. Surgical treatment.
6. Patient factors.

Severity of Soft-Tissue Injury

The severity of soft-tissue injury occurs along a spectrum and grading systems attempt to classify open fractures into groups. Multiple classification systems for open fractures have been developed to facilitate treatment decision making, increase standardization in research, and ease communication between clinicians. Of these systems, the Gustilo-Anderson classification system (GACS) is most common.[6] Gustilo and Anderson first proposed the system in a 1976 retrospective review that split open fractures of the tibia into 3 types.[7] Type I fractures are clean, with a wound <1 cm and a simple fracture pattern. Type II fractures are clean with a wound >1 cm without significant soft-tissue damage, flaps, or avulsions. Type III fractures include any open fractures with multiple fragments, severe contamination, bone loss, significant soft tissue injury, vascular injury, or an associated segmental fracture.

The heterogeneity of injuries with varying risk levels of morbidity and mortality led Gustilo and Anderson to subdivide type III fractures into three groups.[2] Type IIIA is an open fracture with extensive soft tissue damage but maintains sufficient soft tissue coverage. Type IIIB is characterized by periosteal stripping, bone exposure, the need for additional soft tissue coverage, and often massive contamination. Type IIIC fractures are open fractures with an associated vascular injury requiring repair.

The risk of infection is closely tied to the extent of tissue damage, contamination, and damage to the vasculature. In the original studies, Gustilo et al[2,7] showed that type IIIA fractures carry a 4% rate of infection while IIIB and IIIC fractures have infection rates as high as 52% and 42%, respectively. Infection rates fell substantially in type I and II fractures (0–2% and 2.4% respectively). More recent publications showed a broader infection rate in type III fractures (2.8–40.5%).[8,9]

The extent of injury affects the infection rate through several mechanisms. By definition, an open fracture is contaminated from the onset. However, greater tissue exposure increases the surface area in which an infection can develop. Soft tissue and vascular damage decrease perfusion to an injury and thus limit the local immune response as well as wound healing. Together these factors increase the likelihood of infection in the setting of an open fracture.

The GACS only demonstrates moderate interobserver reliability.[10,11] As a result, treatment recommendations and study results based upon the GACS should be interpreted with a degree of caution.

Another possible option for classifying open fractures is the Orthopaedic Trauma Association's open fracture classification system (OTA-OFC). The GACS was originally intended to only describe open fractures of the tibia, while the OTA-OFC was created to provide a common language for all open fractures.[12] The system stratifies open fractures by muscle, skin, and arterial damage along with degree of contamination and bone loss. Several studies have shown the OTA-OFC has increased accuracy in predicting complications following an open fracture (amputation, infection, etc.).[13,14] The OTA-OFC also more specifically defines different wound populations.[15] As such, well-designed randomized control trials using the OTA-OFC may be able to better identify populations that most benefit from specific treatment regimens.

However, the OTA-OFC has its own drawbacks. It is more complicated than the GACS and is not as well studied. It also has not demonstrated any large benefit in interobserver reliability when compared to the GACS.[16] Though the OTA-OFC may eventually supplant the GACS, the GACS currently forms the basis for most treatment paradigms.

Extent and Type of Contamination

Though all open fractures are contaminated, the extent and source of contamination impacts infection rates. Gross contamination alone is sufficient to elevate a fracture to Gustilo grade III regardless of wound size.[2] The elevated infection rate observed in Gustilo grade III compared to grade I and II injuries illustrates the increased infection risk associated with the extent of contamination. Furthermore, during the FLOW trial, the treating surgeons categorized each

wound as mildly, moderately, or severely contaminated. Wounds with mild, moderate, and severe contamination had 5%, 8%, and 23% infection rates, respectively.[17]

A large percentage of infections from open fractures are polymicrobial (20–35%) -the presence of multiple species of microorganism.[18] Polymicrobial infections following open fracture are associated with increased antibiotic requirements and more amputations.[19] Factors associated with the development of a polymicrobial infection after open fracture include a higher fracture grade (III); working in agriculture; the need for a blood transfusion; or the need for additional surgical debridement.[19]

A positive initial culture predicts the subsequent development of an infection following open fracture, but does not predict the colonizing organism.[3,20,21] In this sense, positive culture simply serves as an indicator of bacterial burden. When infection develops, isolated bacterial species often prove to be nosocomial in origin. The infecting species also appears to escape the chosen antibiotic prophylaxis.[3]

Compared with historical cohorts, rates of infection with MRSA, gram-negative bacteria, and polymicrobial infections appear to be increasing, indicating a possible need to reevaluate current antibiotic regimens.[22–24] One possible regimen used vancomycin and cefepime in place of cephazolin and gentamycin for grade III open fractures and showed a decreased infection rate.[24] However, no consensus exists regarding optimal antibiotic prophylaxis. While culture-based methods poorly predict infecting species, perhaps other methods may allow for more informed decision making around antibiotic prophylaxis.

The reliance on culture-based methods for identifying causative agents of infection is limited by inherent biases. Cultures will only produce microorganisms that grow well in isolation and under artificial laboratory conditions, which poorly demonstrates a wounds true bioburden.[21] Culture free methods, such as immunoassays or nucleic acid amplification testing, avoid these biases and produce a more complete report of the true bioburden associated with an open fracture. One study used culture-free methods to demonstrate that mechanism of injury (blunt vs penetrating) is strongly associated with microbial composition.[21] Further work is required to determine the association between microbiota and clinical outcomes in open fractures, but they may eventually assist in selecting appropriate antibiotic treatments.

In summarizing the effect and extent of contamination in open fractures it appears that the degree of gross contamination directly correlates with the overall risk of infection. The bacteria responsible for these infections have shifted over time with infection from MRSA becoming increasingly prevalent. In addition, wound culture poorly predicts the infecting species with culture-free methods possibly providing a clearer understanding of a wound's bioburden and better assistance in making informed antibiotic choices.

Timing of Treatment

The timing of treatment of open fractures is important. In principle, early administration of prophylactic intravenous antibiotics allows the antibiotics to begin aiding the immune system before excessive replication of bacteria occurs. Similarly, early surgical debridement and irrigation of the open wound in the operating room will decrease or eliminate the bacterial load associated with the open wound and minimize the risk of chronic bacterial contamination of the wound. A washout of the contaminated open wound in the emergency room prior to formal surgical management has been proposed and does seem logical. However, the effect of this treatment strategy has not been formally studied.

Early antibiotic prophylaxis has been demonstrated to unequivocally reduce the risk of infection following an open fracture.[25–27] Most surgeons deem a period of less than 1 hour as the optimal time to antibiotic administration, which is substantiated in the literature.[9,25]

Timing to formal surgical irrigation and debridement remains an area of contention. Traditionally, 6 hours was considered the standard to minimize infection risk following an open fracture. However, a 2015 prospective observation study extended the time limit to 12 and even 24 hours with no significant effect on infection rates.[28] More recently, a meta-analysis of observational studies showed an increased infection risk in grade IIIA fractures and higher when irrigation and debridement was delayed more than 12 hours.[29] Based on these studies early surgical irrigation and debridement should be emphasized to minimize infection risk. Surgical treatment should be performed no later than 24 hours post-injury for grade I and II open fractures and within 12 hours for grade III open fractures, although earlier treatment may be preferable.

The optimal timing of wound closure also remains unclear. For several decades delayed closure was accepted as it allowed for multiple rounds of debridement. However, many infections related to open fractures are of nosocomial origin,[3] which suggests earlier wound coverage could limit infection risk. Indeed, several studies have reported lower infection rates with primary closure of wounds associated with grade IIIA fractures and lower.[30–32] Regardless of fracture grade, the risk of infection increases significantly after 5 days without definitive wound coverage.[9] Therefore, the optimal timing of wound closure depends on clinical judgement of fracture grade, and should occur quickly following adequate debridement.

Antibiotic Prophylaxis
Choice of Systemic Antibiotic

The traditional recommendations for antibiotic prophylaxis have been a first-generation cephalosporin for type I and II fractures with the addition of an aminoglycoside for type III fractures. The first-generation cephalosporin provides gram-positive coverage, while the aminoglycoside adds gram-negative coverage. Fecal or soil contamination called for the addition of a penicillin due to the increased likelihood of infection from a clostridium species. The Eastern Association for the Surgery of Trauma (EAST) made more conceptual recommendations with gram positive coverage in type I and II fractures with the addition of gram-negative coverage for type III. Fecal or soil contamination still calls for the addition of a penicillin.[33]

Actual practice deviates significantly from the EAST guidelines. A recent multicenter study from across the US and Canada showed that 45% of patients with type III fractures received cephazolin monotherapy.[34] Even when only type IIIB and IIIC fractures were considered, 42% of these patients did not receive any gram-negative coverage, in direct contradiction to EAST guidelines.[34] The lack of adherence to established protocols may have several possible explanations. Most of the literature around antibiotic recommendations is observational, and a recent meta-analysis of existing randomized controlled trials showed no significant difference between antibiotic regimens in preventing infection.[26] Aminoglycosides also carry the risk of nephrotoxicity, a risk which increases in the setting of hypotension which is not uncommon in polytrauma cases associated with open fracture.

Support for deviation from traditional guidelines comes from a 2014 publication by Rodriguez et al.[25] They established an alternative protocol that removed aminoglycoside and glycopeptide antibiotics. Instead grade I/II fractures were treated with cefazolin (clindamycin if allergic), and grade III fractures were treated with ceftriaxone (clindamycin and aztreonam if allergic). The series included 174 patients (73 post protocol, 101 pre-protocol) in which data was gathered prospectively from the post-protocol patients and compared to retrospective data from pre-protocol patients. The study showed no significant change in infection rates related to open fractures between the pre- and post-protocol patients.

Shifts in the micro-biotic landscape that occur over time also support reevaluation of traditional guidelines. In their original study, Gustilo and Anderson found gram-negative bacteria caused 24% of infections in type III fractures.[7] Their follow-up study found 77% of infections in type III fractures came from gram-negative species.[2] This change likely reflects an increased use of antibiotics with gram-positive coverage and infections caused by bacteria that escape that coverage. More recently, a growing number of infections related to open fractures have been due to colonization with methicillin-resistant Staph. *aureus* causing some surgeons to recommend alternative antibiotics such as vancomycin, aztreonam, piperacillin/tazobactam, or ceftriaxone as first-line prophylaxis in type III fractures.[22,34] Furthermore, a 2017 study showed evidence of seasonal and regional variation in incidence and causative organism in infection following open fracture.[35]

Taken together, the current studies highlight the complexities associated with identifying the optimal approach to antibiotic prophylaxis in patients with open fractures. A protocol-based approach may be effective in decreasing variation in care. However, identifying the optimal protocol will require further research and protocols will likely vary between regions and require periodic reevaluation.[35] Establishing an antibiotic regimen for open fractures based on a hospital's specific infection profile may be beneficial. Though wound culture is relatively ineffective in predicting the causative species of an infection, culture-independent methods may with time influence antibiotic selection.[3,20,21] Culture-independent methods of identifying bacteria are tests, such as polymerase chain reaction (PCR), that can identify the

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general type of bacteria within hours without the need to grow the bacteria in the laboratory. These types of tests have the advantage of being fast, sensitive, and can identify multiple different types of organism. However, without a culture, sensitivity to specific antibiotics cannot be assessed.

Until completion of further studies, current evidence most strongly supports the use of some form of gram-positive prophylaxis in all fracture types, while little to no high-quality evidence supports the addition of gram-negative prophylaxis.[26,27,36] In actual practice, the most common regimen is cephazolin monotherapy regardless of fracture grade.[34] The success of protocols such as that proposed by Rodriguez et al[25] demonstrates the possibility of alternative antibiotic choices.

Duration of Antibiotic Administration

Controversy remains pertaining to the question of duration of antibiotic administration following open fractures. Most surgeons indicate that the literature does not clearly identify the optimal duration of antibiotic prophylaxis. However, the duration of antibiotics administration tends to increase with increased fracture grade.[37]

The EAST guidelines recommend discontinuing antibiotics within 72 hours of the injury or within 24 hours after achieving soft tissue coverage.[33] A variety of other guidelines exist concerning duration of antibiotic treatment with recommendations as high as 7 days.[27] A prospective study with 1234 patients showed a median of 2 days on antibiotics following wound closure. Duration increased with increased contamination or presence of multiple fractures.[34]

A recent meta-analysis of randomized controlled trials found no difference in infection risk following open fractures of all grades between 1 versus 3–5 days of antibiotic administration.[26] However, the authors did note a high risk of bias and therefore low to moderate confidence in the study's results. Stennet et al[17] showed that the wound contamination level affected the optimum duration of antibiotic prophylaxis. Extended antibiotic prophylaxis increased infection risk in mildly contaminated wounds. In severely contaminated wounds extended antibiotic prophylaxis significantly decreased infection risk.

Role of Local Antibiotic Administration

Local antibiotics have been used in conjunction with systemic antibiotics for decades as prophylaxis in open fractures. A recent study showed that more than 30% of patients receive some form of topical antibiotic as part of their prophylactic treatment.[34] Typically, either antibiotic powder or antibiotic impregnated cement beads are used. Local antibiotics maximize target tissue concentrations with minimal systemic toxicities.

Two different meta-analyses showed a significant decrease in infection risk with application of local antibiotics[8,38] The decreased infection risk was particularly pronounced with increased fracture severity.[8] The majority of the included studies within the meta-analyses focused on antibiotic impregnated cement, but also included two studies with direct application of antibiotic to the wound (vancomycin powder and an aqueous gentamicin solution). In all cases, the overall risk of infection was decreased with local antibiotics.

Given the increase in infections due to MRSA, interest in use of intrawound vancomycin powder has also increased. Vancomycin powder has already been shown to decrease surgical site infection (SSI) associated with spinal surgery.[39] A recent randomized controlled trial observed no infections in patients treated with vancomycin powder following a high-risk tibial articular fracture. The control group within the study had a 10.6% infection rate.[40]

Local antibiotics appear to decrease the risk of infection following open fracture. However, several concerns exist. First, prophylactic use of vancomycin powder in the surgical wound may accelerate the development of resistant bacterial strains. Thus far this worry appears to be unfounded. Chotai et al[41] explored the development of vancomycin-resistant organisms in spine surgery patients treated with vancomycin powder. They found significantly lower rates of infection with application of vancomycin powder, and when infection did occur, none of the responsible pathogens demonstrated resistance to vancomycin. It seems reasonable that the results would generalize to infections following open fractures.

A second concern of topical antibiotics is that high local concentrations may have direct cytotoxic effects on surrounding tissue, and thus inhibit wound healing. One study, which examined the use of local aqueous gentamicin, showed no change in the incidence of nonunion with or without application of the antibiotic.[38] On the other hand, vancomycin has been shown to interfere with fracture healing in a dose-dependent manner.[42] A second study on an

animal model showed that vancomycin powder alone slowed bone regeneration. However, a combination of tobramycin and vancomycin demonstrated no negative effect on bone regeneration.[43] Further clinical studies are required to determine the optimal dosing of vancomycin powder alone to achieve a bactericidal but not cytotoxic concentration.

Local antibiotics appear to reduce infection rates following open fracture. Antibiotic impregnated cement and direct application of antibiotic powders are both commonly used. Vancomycin powder has shown particular promise in limiting infections, though optimal dosing has yet to be established to minimize risk of direct cytotoxic effects.

Surgical Treatment

Initial surgical intervention for open fractures consists of debridement and irrigation. The goal of debridement is to removes any devitalized or contaminated tissue. Given the high contamination of open fractures, the excision of tissue should be aggressive, including bone as necessary. However, in many open fractures, it may not be obvious at the time of initial debridement which tissues are devitalized and which are viable. Many clinical scenarios may require serial debridement.

Angiosomes are specific soft-tissue areas supplied by specific arteries. During debridement, knowledge of angiosome patterns may help prevent wound-healing complications and better preserve blood supply to the wound.[44]

Irrigation with debridement helps remove contamination from open fractures and limit the risk of infection. The fluid lavage of open wounds (FLOW) trial compared various lavage fluids and irrigation pressures. They found that normal saline solution regardless of irrigation pressure appeared to minimize the reoperation rate.[45] These findings suggest that low pressure irrigation with saline offers an effective, low-cost option for irrigation of open fractures, which is corroborated in other studies.[46,47] Addition of other agents such as antiseptics, surfactants, or antibiotics to the fluid have been shown to be inferior to normal saline in reducing infection and limiting the reoperation rate.[46,47] The ideal volume of irrigant has not been determined.[47] An example of a common regimen calls for 3, 6, and 9 L of irrigant for grade I, II, and III fractures respectively.[44]

Following debridement, a dressing is applied to the surface of the open wound. Negative pressure wound therapy (NPWT) is an alternative dressing that minimizes the collection of blood and fluid in the wound and encourages the formation of granulation tissue.[48] One relatively small randomized clinical trial suggested improved outcomes with NPWT in open fractures.[49] A subsequent, larger trial failed to replicate these results, indicating no benefit to the greater cost associated with NPWT.[50] While NPWT shows no benefit when applied to open wounds, it does appear to decrease infection rates when applied to closed incisions. In a recent metanalysis, Wang et al[51] found 4.8% of patients with NPWT developed deep SSI compared to 12.7% of patients with conventional wound dressings.

Surgical management of open fractures chiefly consists of timely irrigation and debridement. The irrigation is performed with normal saline, with greater volumes used for greater degrees of contamination. Debridement consists of removing devitalized tissue and may be required more than once. The timing of wound closure remains somewhat undecided for high grade open fractures, but risk of infection appears to decrease with primary closure in Gustilo grade IIIA fractures and lower. Finally, NPWT reduces infection risk when applied to closed incisions in orthopedic trauma but is of no benefit when applied to an open wound.

Patient Factors

Multiple patient factors influence the probability of infection following open fracture, though a definitive risk assessment model has not yet been established. In a 2017 systemic review and meta-analysis, Kortram et al[4] found that diabetes mellitus, smoking, male gender, and lower extremity fracture were all associated with increased infection rates after open fracture.

Diabetes leads to numerous systemic side effects including peripheral vascular disease, peripheral neuropathy, poor immune function, and poor bone. Together, these factors decrease healing potential and increase risk of subsequent infection following open fracture. Indeed, Kortram et al found a significantly higher rate of infectious complications following open fracture in diabetic patients (25.3% versus 13.8%).

Smoking and male gender were associated with a 17.7% and 16.1% risk of infection respectively compared to the 13.8% baseline. Smoking is also associated with an increased rate of delayed union and non-union following open

fracture.[52] It decreases tissue oxygenation, attenuates the immune response, and impairs formation of granulation tissue. Cessation of smoking rapidly improves tissue oxygenation and restores inflammatory cellular function. Proliferative tissue response remains impaired however.[53] These findings are mirrored in clinical outcomes where perioperative smoking cessation reduces surgical site infection but has little influence on other healing complications.[54]

Additional risk factors may exist (malnutrition, renal disease, liver disease, etc.) though they were not encountered in the articles reviewed. Each of these conditions have been associated with impaired wound healing and increased surgical site infections.[55,56]

Summary

Minimizing the risk of infection following open fractures is a key treatment goal. The Gustillo-Anderson classification of open fractures is commonly used to guide treatment decisions. Regardless of severity of soft-tissue injury, early prophylactic systemic antibiotics have been shown to decrease the risk of infection following open fractures. Other factors for reducing infection risk include early irrigation with normal saline; aggressive debridement of contaminated and devitalized tissue; the addition of local antibiotics; and in select patients the use of negative pressure wound therapy on closed incisions.

Disclosure

The authors report no conflicts of interest in this work.

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