Chapter 14

A Reevaluation of the Risk of Infection Based on Time to Debridement in Open Fractures

Results of the GOLIATH Meta-Analysis of Observational Studies and Limited Trial Data

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Abstract

Background: Open fractures are one of the leading causes of disability worldwide. The threshold time to debridement that reduces the infection rate is unclear.

Methods: We searched all available databases to identify observational studies and randomized trials related to open fracture care. We then conducted an extensive meta-analysis of the observational studies, using raw and adjusted estimates, to determine if there was an association between the timing of initial debridement and infection.

Results: We identified 84 studies (18,239 patients) for the primary analysis. In unadjusted analyses comparing various "late" time thresholds for debridement versus "early" thresholds, there was an association between timing of debridement and surgical site infection (odds ratio [OR] = 1.29, 95% confidence interval [CI] = 1.11 to 1.49, $p < 0.001$, $I^2 = 30\%$, 84 studies, n = 18,239). For debridement performed between 12 and 24 hours versus earlier than 12 hours, the OR was higher in tibial fractures (OR = 1.37, 95% CI = 1.00 to 1.87, $p = 0.05$, $I^2 = 19\%$, 12 studies, n = 2,065), and even more so in Gustilo type-IIIB tibial fractures (OR = 1.46, 95% CI = 1.13 to 1.89, $p = 0.004$, $I^2 = 23\%$, 12 studies, n = 1,255). An analysis of Gustilo type-III fractures showed a progressive increase in the risk of infection with time. Critical time thresholds included 12 hours (OR = 1.51, 95% CI = 1.28 to 1.78, $p < 0.001$, $I^2 = 0\%$, 16 studies, n = 3,502) and 24 hours (OR = 2.17, 95% CI = 1.73 to 2.72, $p < 0.001$, $I^2 = 0\%$, 29 studies, n = 5,214).

Conclusions: High-grade open fractures demonstrated an increased risk of infection with progressive delay to debridement.

An epidemic rise in the number of open fractures is occurring worldwide, particularly in low and middle-income countries (LMICs)[1-4]. Because of their health and economic impact, open fractures were recognized by the *Lancet* Commission on Global Surgery in 2015 as 1 of the top 3 surgical priorities, known as the "bellwether procedures[5-7]." Approximately 6 billion people have limited access to these procedures, leading to 1.2 million potentially preventable complications each year that could be reduced with better access to surgery[8-16].
The treatment of open fractures involves removal of contamination, excision of devitalized tissue, and irrigation of the wound in an attempt to reduce the risk of subsequent infection. Investigating time to surgical debridement of open fractures as an independent risk factor in the etiology of infection is challenging[17-27]. Current reports and systematic reviews have pooled all open fracture types, leading to a potential confounding effect on reported estimates[28-30]. It is possible that the most severe fractures with the worst prognosis are debrided earlier, and less severe injuries are debrided later, leading to a disproportionately higher reported infection rate with early debridement[31]. Perhaps as a result, many available studies that aggregate all Gustilo types, including meta-analyses, have reported no effect of various time thresholds to debridement on subsequent infection[28,32-36].

This study was conducted with the intent to reduce confounding in evaluating the impact of delay to debridement on the risk of infection in open fractures [28,29,31,37-39]. To address the challenges involved in interpreting this area of the literature, we formed a research collaborative (GOLIATH—Global Open Fracture CoLlaborative to Investigate Available Evidence in THe Literature).

Materials and Methods

A systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[40-42]. An a priori analysis was constructed and registered at the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020167866, Open Science Framework doi: 10.17605/OSF.IO/QD9W4).

Data Sources

PROSPERO was initially searched to ensure that no concurrent reviews were in process. Two authors (C.J.F. and A.B.) conducted the search. Databases included in the search were PubMed, Cochrane Wounds Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE (including In-Process & Other Non-Indexed Citations), Google Scholar, Web of Science Core Collection, Ovid Embase, and EBSCO CINAHL. Additional sources searched are included in the Appendix. All databases were searched from their inception to the fourth week of August 2020.

Study Eligibility and Selection

Titles and abstracts were reviewed by 2 authors (A.B. and C.J.F.). Inclusion was agreed upon by consensus. We included observational studies and randomized trials evaluating the effect of the timing of debridement on infection in open fractures. Studies were identified that (1) included skeletally mature patients ≥17 years old, (2) described open fractures involving long bone(s), the foot, or the carpus, (3) recorded the timing of debridement from the time of injury or admission or both, and (4) reported the number of "all" infections, deep infections, or both. Fractures of the pelvis and hand were excluded (see). Studies were included in the qualitative analysis if they reported mean debridement times or regression estimates for infection; however, they were excluded from the "late" versus "early" analysis if studies did not report an infection event rate.

Data Extraction

Standardized data extraction forms were used to collect data from eligible studies. We evaluated the methodological quality, statistical analyses, and the authors' interpretation of the results. We extracted details from published and unpublished manuscripts regarding injury patterns and classifications, time to debridement, and other interventions such as antibiotic administration and the use of negative-pressure wound therapy. We contacted authors in cases where (1) stratification by Gustilo type was not provided in the manuscript, (2) we had any question about the validity of the statistical analyses, or (3) the paper did not report the details needed to calculate event rates in each group. In the majority of cases, we obtained additional analyses from authors to add data to various aspects of our systematic review. An in-depth description of the items extracted is provided in the Appendix.

Data Synthesis

Odds ratios (ORs) and 95% confidence intervals (CIs) were the measures of effect used. Pooling for the initial binary analyses that included studies with all Gustilo types was done with the random-effects Mantel-Haenszel method with a DerSimonian and Laird (DL) estimator . The remainder of the analyses used a random-effects general inverse-variance model with a DL estimator . ORs were calculated from the numbers of events or proportions provided in the study. A random-effects general inverse-variance model was also utilized to analyze tibial fractures, specifically for Gustilo type-IIIB tibial fractures and for the Gustilo type-III "time-gradient" analysis[45].

To maximize power, we initially analyzed "late" versus "early" debridement (which included mainly >6 versus ≤6 hours, >12 versus ≤12 hours, and >24 versus ≤24 hours) and assessed the association with infection. For a given study, "early" was defined as the initial time period below the cutoff (e.g., ≤6, ≤12, or ≤24 hours) and "late" was the comparator time period above the cutoff (e.g., >6, >12, or >24 hours). This analysis asked, "is delay to debridement at any cutoff associated with a change in the odds of infection?" It did not stratify for Gustilo type or fracture site, in an attempt to obtain a broad understanding of the effect of time thresholds on infection, including in low-grade injuries and those less likely to become infected, such as upper-extremity

fractures. In addition, subgroup analyses were performed for all tibial fractures (12-hour cutoff) and for Gustilo type-IIIB tibial fractures (12-hour cutoff), followed by a Gustilo type-III "time-gradient analysis." The latter used progressively later cutoff points to debridement to establish a relationship with time (i.e., do the odds of infection for type-III fractures increase as the delays to debridement increase?).

Time data were collected, organized, and aggregated into ordinal categories (i.e., ≤6 hours, 6 to ≤12 hours, >12 to ≤24 hours, and >24 hours) to produce more precise groups for analyses. Explicitly, for the tibial type-IIIB and tibial shaft analyses (12 to 24 versus ≤12 hours), we removed patients treated later than 24 hours to provide accurate estimates for this comparison. The rationale was to obtain an accurate estimate for patients treated within 24 hours by reducing the impact of substantially delayed patients. However, the latter patients were included in the type-III gradient analysis (i.e., >12 versus ≤12 and >24 versus ≤24 hours). When continuous (odds per hour) estimates were available or could be produced, we calculated the exact odds of infection for a given time point. When both continuous and dichotomous estimates were available, we used the continuous estimates to minimize the impact of patients treated long after 24 hours from injury.

Heterogeneity was evaluated using the Cochran Q statistic and inconsistency index I . Tau was calculated using the DL method[46-47]. Funnel plots were assessed to identify publication bias. All meta-analytical calculations were made in RevMan version 5.3 (The Cochrane Collaboration, 2020).

Risk of Bias and Quality of the Evidence

The risk of bias was evaluated using the ROBINS-I (Risk of Bias in Non-Randomized Studies - of Interventions) tool[47]. The quality of the evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach[43-46]. The details of the ROBINS-I and GRADE frameworks are provided in the Appendix.

Results

Literature Search

A flow diagram and additional details are provided in the Appendix. Our search of multiple databases yielded 26,857 potential references. After extensive review, 100 different studies (102 individual references) [1,32,33,34,36,48-144], on account of duplicate publication) were identified. Of these, 7 studies only reported the mean or median times of debridement of infected and noninfected open fractures, and another 9 studies only provided adjusted estimates of the effect of delay to debridement using univariate and multivariate analyses. The remaining 84 of the 100 qualitatively analyzed studies (n = 18,239 patients) met the inclusion criteria and stratified by time to debridement for the "late" versus "early" analysis[1,32,33,34,36,48-87,89-129].

Risk of Bias

The overall summary of the percentage of studies that demonstrated bias in each domain is shown graphically in Figure 1. The details of the evaluations are provided in the Appendix.

Analysis Including All Fractures (Unstratified by Gustilo Type or Body Region)

Fifty-five of 84 studies primarily used a 6-hour cutoff (n = 12,457) [32,33,36,48,49,51,53,55,57,58,61,63-67,72-74,75,77-82,86,87,89-91,94,98-101,104,107,109-114,116,117,119-127,129]; however, some of these studies also provided data for additional cutoffs. Although our initial analysis of "late" versus "early" debridement was unstratified for severe Gustilo type or lower-extremity fracture location, it still demonstrated a significant impact of delay to debridement on infection risk (OR = 1.29, 95% CI = 1.11 to 1.49, p <0.001, I^2 = 30%, 84 studies, n = 18,239).

Unstratified Tibial Shaft Fractures and Gustilo Type-IIIB Tibial Fractures

Delay in debridement later than 12 hours (i.e., >12 versus ≤12 hours) for any type of open tibial shaft fracture was associated with an increased risk of infection (OR = 1.37, 95% = 1.00 to 1.87, p = 0.05, I^2 = 19%, 12 studies, n = 2,065, low quality). More specifically, in Gustilo type-IIIB tibial fractures, delayed debridement later than 12 hours compared with earlier than 12 hours was associated with a substantial increase in infection (OR = 1.46, 95% CI = 1.13 to 1.89, p = 0.004, I^2 = 23%, 12 studies, n = 1,255, low quality).

Evaluation of Multiple Time Points to Debridement in High-Grade Open Fractures

Infection in Gustilo type-III fractures was evaluated with respect to the most commonly reported cutoff times of 6, 12, and 24 hours. The majority of fractures that generated these estimates were in a lower extremity. A forest plot demonstrating the association between the odds of infection and delay to debridement is shown in .

When a 6-hour cutoff was used, the risk of infection with late debridement increased significantly (OR = 1.26, 95% CI = 1.13 to 1.41, p < 0.001, I^2 = 7%, 39 studies, n = 6,456, low quality,). For patients debrided later than 12 hours compared with earlier than 6 hours, the delay was associated with >1.5 times greater odds of infection (OR = 1.82, 95% CI = 1.28 to 2.59, p = 0.008, I^2 = 0%, 14 studies, n = 1,386, low quality).

When debridement was later than 12 hours compared with earlier than 12 hours, the odds of infection were significantly greater (OR = 1.51, 95% CI = 1.28 to 1.78, p < 0.001, I^2 = 0%, 16 studies, n = 3,502, low quality,). Those treated later than 24 hours had a significant twofold higher infection rate than those treated earlier than 24 hours (OR = 2.17, 95% CI = 1.73 to 2.72, p ≤ 0.001, I^2 = 0%, 29 studies, n = 5,214, moderate quality,).

Discussion

While most surgeons would agree that timely debridement in a patient with an open fracture is advantageous, other factors cannot be ignored[1,140]. The patient must be physiologically stable, the trauma system must be able to support an urgent procedure, and a surgeon with the requisite experience must be available. The lack of consensus in the role of timing to debridement in open fractures is primarily related to the tremendous confounding by Gustilo type, time to coverage, antibiotic timing and choice, location of injury, and fixation type. Additionally, further confounding stems from the fact that high-grade fractures are often treated earlier, causing substantial bias when studies aggregate all Gustilo types in their analysis. In other studies that have stratified for the severity of open fractures, the analysis typically utilized early cutoff points (i.e., 6 or 12 hours), and frequently, the majority of the data were clustered adjacent to either side of the cutoff[36]. These studies can have difficulty showing an association because there are only small differences in delay between groups on either side of the 6 or 12-hour cutoff thresholds . Many authors have attempted to define the appropriate time threshold to debridement, after which infection risk increases. However, to gain power, these studies have typically not been stratified by the severity of the open wound or the body region affected. The purpose of this study was to obtain all available manuscripts, and when possible, more detailed analyses from the source authors, to further elucidate the potential risk of incrementally longer cutoff points for the time to the initial debridement. We evaluated the most commonly reported time points of 6, 12, and 24 hours. Additionally, we separately assessed high-energy (Gustilo type-III) and open tibial shaft fractures.

The current literature reflects the difficulty with interpretation and aggregation of observational studies. Previous narrative reviews, systematic reviews, and meta-analyses have been methodologically and analytically compromised. For example, a recent narrative review[145] reported that only a single study had shown an association between delay and infection risk . As shown in our analyses, they did not identify dozens of positive studies in the literature and even more that were underpowered but showed a trend [1,48,50,52,61,65,68,73,76,79,81,90,92-95,98,99,101,103,104,106,117,119-122,125,127]. Identification of some of these studies required a "gray literature" search, which identified several Orthopaedic Trauma Association (OTA) conference-presented multicenter studies that have not been published [73,119-121]. Other reviews have reported no impact even though extraction by Gustilo type from papers was feasible and demonstrated the effect of debridement.

We can state, with moderate-quality evidence, that debridement within 24 hours for all Gustilo type-III fractures in general reduces the risk of infection versus further delays. Specifically, debridement later than 24 hours from the time of injury was associated with a twofold increase in the odds of infection ($p < 0.001$, moderate-quality evidence). More importantly, when considering high-grade open fractures, delays of >12 hours may have a harmful effect. Additionally, when looking at the highest-risk group, Gustilo type-IIIB open tibial fractures, a

separate analysis identified estimated increased odds of infection with delay of >12 hours (OR = 1.46, p = 0.004, low quality).

This study has many strengths, including a comprehensive search that captured a number of unpublished studies. Such studies include several multicenter studies identified from OTA abstracts [73,119-121]. We obtained supplemental information and manuscripts from the authors of these studies. We also (1) contacted authors to obtain additional analyses, (2) accessed entire data sets where the manuscript or access allowed, (3) stratified for Gustilo type to mitigate confounding, and (4) unified and refined results using the GRADE system for evaluating and reporting evidence.

There are several limitations to this review related to the challenges in conducting high-quality observational studies. These challenges include the overuse of dichotomization, which is associated with several issues. Dichotomization can produce groups that are very similar or hugely discrepant. We addressed the discrepancy (i.e., outlier) issue by obtaining continuous estimates from authors, when available, instead of using dichotomized data. These conversions led to more modest estimates of the effect of delay in our Gustilo type-III and IIIB tibial fracture analyses. Also, the predominant observational study design was retrospective, which reduces data quality. Confounding related to factors associated with later surgical care (e.g., time to closure/coverage for Gustilo type-IIIB fractures) is a substantial source of bias in open fracture studies. Many studies attempted to address some causes of confounding with regression, while others excluded diabetics and other high-risk groups. Prophylactic antibiotic reporting in time-to-debridement studies has been devoid of assessment despite being a considerable potential confounder. We provide a thorough assessment of antibiotic reporting in the Appendix. Deep infection was not well defined in 58 studies; however, we found no subgroup effect among the 23 studies that reported deep infection only (see). Also, 34 studies did not effectively specify the time origin used in the study (i.e., admission or injury). In addition, we include suggestions for future research to mitigate the impact of effect modification, confounding, and outliers (and other data-distribution issues) in the Appendix.

Progressive delays generated a risk gradient that may be established well before 24 hours from injury in Gustilo type-III and IIIB fractures. Although a gradient or “time-dose” response is a potent tool to support causation, there are several considerations to acknowledge. The time from injury to the hospital (i.e., secondary delays) is associated with the time from injury to debridement. In most studies, not all of these time measures were reported. Thirty-four studies had poor descriptions of the time origin of the study, a situation that must improve. Therefore, we are uncertain to what degree secondary delays are driving the effect estimates. This consideration is important because, even with this large collection of data, we cannot provide precise guidance (i.e., effect estimates) to clarify the impact of a delay to surgery once the patient arrives at the hospital (i.e., receives primary open fracture care).

In addition, our primary analyses focused on confirmed Gustilo type-III fractures. Although lower Gustilo types are included in the “early” versus “late” analysis, we are unable to make

specific recommendations for these injuries, regarding optimal time of debridement (i.e. the safe window), from the analyses presented in this study.

Conclusions

Gustilo type-III open fractures are at higher risk for infection with delays to debridement, with a 1.5-fold increase in the relative odds of infection after 12 hours (low-quality evidence) and a twofold increase after 24 hours post-injury (moderate-quality evidence). Our results should only be applied to high-grade fractures, as the relationship between delay and infection follows a different temporal association in low-grade fractures. To our knowledge, this is the first study that has strategically attempted to minimize confounding in this area of research that is confined to investigation with observational studies.

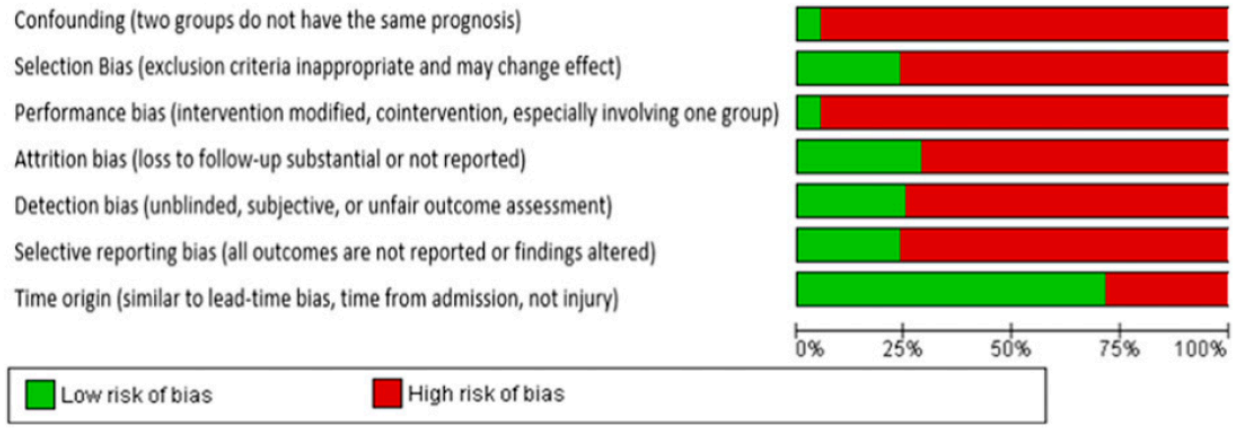

Fig. 1 Summary of risk of bias according to an adapted ROBINS-I tool for assessment of observational studies.

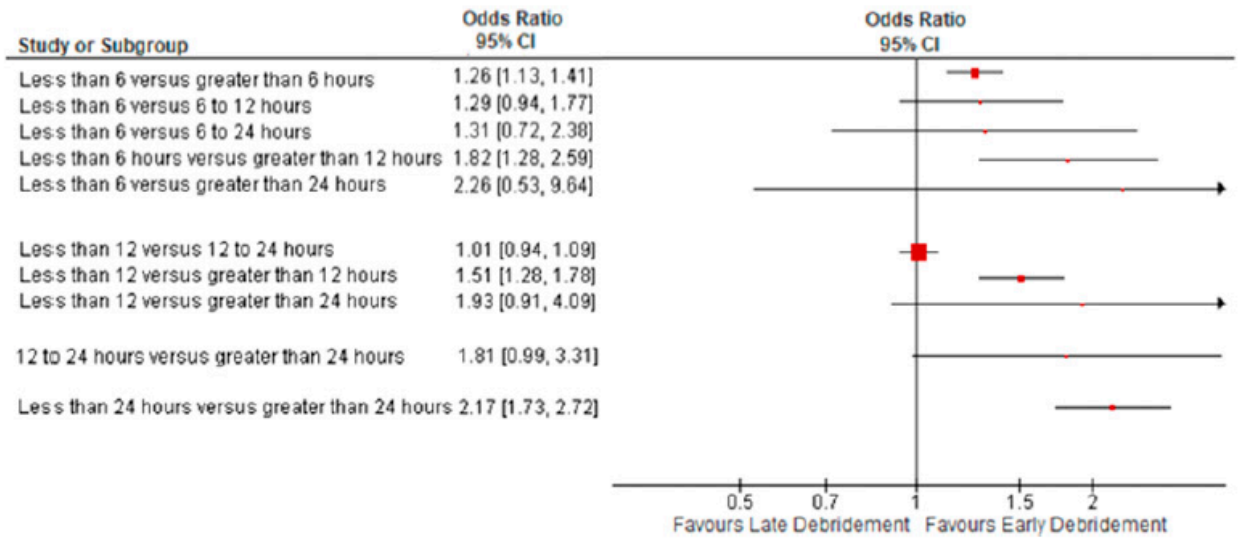

Fig. 2 Forest plot showing the effect estimates for the odds of infection with progressive delay in high-grade open fractures (reference = least delay). The majority of fractures generating these estimates involved the lower extremity.

TABLE I The Aggregate Effect of "Late" Versus "Early" Debridement Along with Subgroup Analyses for Gustilo Type-IIIB and Tibial Shaft Fractures

		Certainty Assessment					No. of Patients with Infection		Effect			
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Late	Early	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Infection, all late vs. early												
84	Observational studies	Very serious	Not serious	Serious	Not serious	All plausible residual confounding would reduce the demonstrated effect	1,274/ 9,762 (13.1%)	883/ 8,477 (10.4%)	OR, 1.29 (1.11 to 1.49)	26 more per 1,000 (from 10 more to 44 more)	Low	Critical
Infection, Gustilo IIIB open fractures												
14	Observational studies	Serious	Not serious	Serious	Not serious	Dose-response gradient	185/727 (25.4%)	107/563 (19.0%)	OR, 1.46 (1.13 to 1.89)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	Low	Critical
Infection, tibial shaft fractures												
12	Observational studies	Serious	Not serious	Serious	Serious		166/971 (17.1%)	111/ 1,094 (10.1%)	OR, 1.37 (1.00 to 1.87)	1 fewer per 1,000 (from 2 fewer to 0 fewer)	Low	Critical

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