Does Timing to Operative Debridement Affect Infectious Complications in Open Long-Bone Fractures?

A Systematic Review

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Background: Existing guidelines recommend emergency surgical debridement of open fractures within six hours after injury. The aim of this study was to systematically review the association between time to operative debridement of open fractures and infection.

Methods: Searches of the MEDLINE, EMBASE, and Cochrane computerized literature databases and manual searches of bibliographies were performed. Randomized controlled trials and cohort studies (retrospective and prospective) evaluating the association between time to operative debridement and infection after open fractures were included. Descriptive and quantitative data were extracted. A meta-analysis of patient cohorts who underwent early or delayed debridement was performed with use of a random effects model.

Results: The initial search identified 885 references. Of the 173 articles inspected further on the basis of the title, sixteen (six prospective and ten retrospective cohort studies with a total of 3539 open fractures) were included. No significant difference in the infection rate was detected between open fractures debrided early or late according to any of the time thresholds used in the included studies. Sensitivity analyses demonstrated no difference in infection rate between early and late debridement in subgroups defined according to the Gustilo-Anderson classification, level of evidence, depth of infection, or anatomic location.

Conclusions: The data did not indicate an association between delayed debridement and higher infection rates when all infections were considered, when only deep infections were considered, or when only more severe open fracture injuries were considered. On the basis of this analysis, the historical “six-hour rule” has little support in the available literature. It is important to realize that additional carefully conducted studies are needed and that elective delay of treatment of patients with open fractures is not recommended.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Until 150 years ago, open fractures were synonymous with sepsis and death, necessitating immediate amputation as the definitive treatment. Advances in antimicrobial therapy, fracture stabilization, and wound management dramatically decreased mortality from open fractures although the number of open fractures and similar high-energy injuries...
has increased. Epidemiologic studies have shown that open long-bone fractures occur at a rate of 11.5 per 100,000 persons per year. The prevalence of infection following internal fixation of fractures is approximately 4% overall but may exceed 30% in open fractures. Musculoskeletal infections place a cost burden on total health care expenditures, with the reported lifetime cost of the most severe open fracture injuries being as high as $680,000. Traditional clinical guidelines suggest treatment of open fractures with an initial operative debridement within six hours after injury to reduce the risk of infection. It is believed that the “six-hour rule” originated from a study conducted on guinea pigs by Friedrich in 1898. He found that when debridement of open wounds was performed within six hours, all animals remained healthy. In 1973, Robson et al. quantified wound bacterial counts to define an “open fracture infection threshold,” characterized as a density of ≥10^5 organisms per gram of tissue, and found that this threshold was reached within a mean of 5.1 hours after injury.

Although expedient and appropriate treatment of these severe injuries should be the goal, there are circumstances in which delaying the initial debridement may benefit or at the very least not harm the patient. In a large observational study, it was noted that initial debridement of 42% of open tibial fractures was delayed for more than six hours. The consequences of this delay in treatment are unknown. The purpose of the present systematic review and meta-analysis was to evaluate the association between the time to initial operative debridement of open fractures and the development of infectious complications.

**Materials and Methods**

**Data Sources**

Two of the authors (M.L.S. and S.Y.) independently carried out a comprehensive search of the MEDLINE, EMBASE, and Cochrane computerized literature databases (through December 3, 2010) for randomized controlled trials, quasi-randomized controlled trials, and cohort studies (both prospective and retrospective) that evaluated the effect of early compared with late debridement of open fractures on infection outcomes.

The medical subject headings (MeSH terms) used were “open fracture” or “open fractures” and “debridement.” Reviewers traced the bibliographies of the retrieved articles, including review articles, for citations missed by the electronic search. The senior investigators (S.M. and J.A.) also reviewed their personal files retrieved articles, including review articles, for citations missed by the electronic search. The second sensitivity analysis evaluated only studies that described “deep infection” (defined in the parent studies as infections extending below the fascia), purulent discharge or osteomyelitis, or as clinical diagnosis of pain and/or erythema and/or discharge with positive wound cultures (see Appendix). The third sensitivity analysis evaluated the outcome of any infection according to the level of evidence of the study, to determine whether focusing on studies with a higher level of evidence could uncover any significant differences in infection rate between the early and late debridement cohorts that were not identified in the primary meta-analysis. In this secondary analysis, the Level-II studies were analyzed separately from the Level-III studies. The fourth sensitivity analysis separately evaluated the results of the studies on the basis of the severity of the injury, with Gustilo-Anderson type-I and II open fractures analyzed separately from type-III open fractures. The final sensitivity analysis compared the results of studies that included only lower-extremity fractures and those that included only tibial fractures. Forest plots were generated to qualitatively assess study heterogeneity and to provide summary estimates. A funnel plot and the Eggers intercept method were used to assess the existence of publication bias due to small-study effects. Because of the heterogeneity among the studies, which included different mixtures of patient types and injury severities, we utilized a random effects model (DerSimonian and Laird) to provide a conservative method of combining the effects of multiple studies.

**Source of Funding**

No external funding sources were utilized in this investigation.

**Results**

The initial search yielded 885 citations: 294 from MEDLINE, 576 from EMBASE, and fifteen from the Cochrane Review.
(Fig. 1). Of these, 712 articles were excluded on the basis of the title because they clearly represented a review paper, represented an editorial or contained commentary without primary data, or were unrelated to our topic. Of the remaining 173 articles, 144 were excluded on the basis of the abstract because they failed to satisfy the predetermined inclusion criteria or because they were editorial in nature or represented a review article, case report, or erratum. Nineteen of the remaining twenty-nine articles were excluded when the full article was reviewed because it failed to meet the inclusion criteria. This left ten unique studies from our initial review, and a manual reference search revealed six additional studies. Our systematic review included these sixteen articles with a total of 3539 open fractures.

The funnel plot to assess study heterogeneity was relatively symmetric, with no perceivable publication bias. The Eggers intercept was 0.85 (95% confidence interval [CI], 0.66 to 2.36; p = 0.24).

**Study Characteristics**

The Appendix summarizes the key characteristics of the included studies. Six prospective studies provided Level-II evidence\(^2,27,32-34\) and ten retrospective studies provided Level-III evidence\(^20-23,25,26,28-31\). No study was randomized on the basis of the time to debridement.

The time threshold used for the comparison between the early and late debridement groups was six hours in nine studies\(^20,22-29\), five hours in two\(^19,21\), eight hours in two\(^30,31\), twelve hours in one\(^32\), and not specifically reported in two\(^33,34\). When raw data were provided and permitted separation between early and late debridement on the basis of a six-hour time threshold, the data were extracted and incorporated into the meta-analysis according to this time threshold\(^21\).

Five studies used a cohort with upper and lower-extremity fractures\(^22,27,30,32,33\), and eleven studies were limited to lower-extremity fractures\(^19-21,23,25,26,28-29,31,34\). Seven of the latter studies evaluated only open tibial fractures\(^21-23,25,28,29,31\), one examined only femoral fractures\(^26\), and one classified the fracture types as tibial or non-tibial\(^32\). The authors of this last study reported a significantly higher infection rate for tibial compared with non-tibial fractures\(^32\). Of the studies that included both upper and lower-extremity fractures, both Harley et al. and Dellinger et al. reported that lower-extremity fractures were associated with a higher rate of deep infection\(^30,33\).

We performed a quality analysis of each study according to the method described by Zaza et al. for assessing preventive medicine studies\(^13\). The population was well described in thirteen of the sixteen studies, one study did not describe consistently which bone was involved in the open injury\(^32\), and two studies had very little demographic information regarding the cohort\(^28,31\). Thirteen of the sixteen studies described the intervention adequately; the antibiotic administration was not clear in the remaining three studies\(^19,25,28\). One study did not fully describe why patients were excluded; it was mentioned that some patients were transferred, but the reason was not specified\(^24\). Seven of the sixteen studies did not use the full population over the entire study period\(^19,21,24,26,27,31,34\). One study was performed in Nigeria, with initial and definitive care differing from that in the more developed world\(^34\). An open fracture with exposed bone was described in all studies. The performance of a reliability analysis for either the classification of bone exposure (according to the Gustilo-Anderson type) or the diagnosis of infection was not described in any study. The criteria for deep infection varied among the studies and ranged from...
osteomyelitis to cellulitis, with only a few studies using culture data to confirm the presence of infection. There was no consistent definition of superficial infection among the studies. Five studies adjusted for potential confounding factors with use of multivariate logistic regression, and one study showed no difference in multiple confounding factors between groups. No study corrected for the use of multiple tests. Three studies had <80% follow-up.

Effect of Delayed Debridement on Overall Infection Rates
Fourteen studies provided early and late debridement times and infection rates; these studies included 3217 open fractures and a total of 396 infections suitable for meta-analysis. On further review, one study provided data for a large number of patients but did not adequately define the fracture population. No study corrected for the use of multiple tests. Three studies had <80% follow-up. Six studies either did not report the time to follow-up or had inaccuracies in their reporting.

The overall infection rates ranged from 4% to 63%. No significant difference in the overall infection rate between early and late debridement was detected (Fig. 2). The weighted cumulative odds ratio (OR) of developing an infection after late compared with early debridement was 0.91 (95% CI, 0.70 to 1.18). The risk difference between the early and late groups was −1% (95% CI, −4% to 2%) in favor of late debridement, although this difference was not significant (p = 0.46). The odds ratio was unchanged with inclusion of the single article with the heterogeneous fracture population (OR, 0.93; 95% CI, 0.74 to 1.17). Two studies indicated that the time to debridement was a significant factor in increasing infection outcomes; however, one of these articles provided insufficient data for inclusion in the meta-analysis, and further analysis of the other article with use of six rather than five hours as the threshold between early and late debridement yielded an odds ratio for infection of 3.68 (95% CI, 0.96 to 14.06), which did not reach significance.

When the studies were analyzed according to the time thresholds for early and late debridement used by the primary authors, no significant difference in infection rates was detected with use of any of the following cutoffs: five hours (OR, 0.96; 95% CI, 0.54 to 1.71; p = 0.88), six hours (OR, 0.81; 95% CI, 0.53 to 1.24; p = 0.34), eight hours (OR, 1.15; 95% CI, 0.51 to 2.59; p = 0.73), or twelve hours (OR, 1.04; 95% CI, 0.62 to 1.73; p = 0.789).

Effect of Depth of Infection
When only deep infections were considered, no significant difference in the infection rate between early and late debridement was detected (Fig. 3). The weighted cumulative odds ratio of infection was 1.07 (95% CI, 0.74 to 1.54). The risk difference between the early and delayed groups was 1% (95% CI, −2% to 4%); this difference was not significant (p = 0.69).
Effect of Injury Severity and Delayed Debridement

Five studies reported injury severity according to the Gustilo-Anderson classification\(^1\) and evaluated the effects of delayed debridement on infection rates. For Gustilo-Anderson type-I and II fractures, 310 patients with an overall infection rate of 8% in four of these studies were available for analysis. The infection rate was 12% in the early debridement group and 5% in the late debridement group. The risk difference between the early and delayed groups was \(2\)\% (95% CI, \(-10\%\) to \(2\%\)) in favor of late debridement, although this difference was not significant (\(p = 0.25\)) (Fig. 4). The weighted cumulative odds ratio of developing an infection after late debridement was 0.58 (95% CI, 0.25 to 1.33).

For Gustilo-Anderson type-III fractures, 276 patients with an overall infection rate of 12.7% were available for analysis. The infection rate was 15% in the early debridement group and 11% in the late debridement group. The risk difference between the early and delayed groups was \(-4\%\) (95% CI, \(-12\%\) to \(5\%\)) in favor of late debridement, although this difference was not significant (\(p = 0.44\)) (Fig. 5). The weighted cumulative odds ratio of developing an infection after late debridement was 0.84 (95% CI, 0.31 to 2.31).

The Effect of Study Level of Evidence

When only deep infections were evaluated according to the level of evidence, the weighted cumulative odds ratio of infection after late compared with early debridement did not differ significantly between the studies that provided Level-II evidence\(^19,24\) and Level-III\(^21,23,25,26,29-31\) evidence. For studies with Level-II evidence, the weighted cumulative odds ratio of infection was 1.13 (95% CI, 0.63 to 2.03) for late debridement. For studies with Level-III evidence, the weighted cumulative odds ratio of infection was 1.04 (95% CI, 0.65 to 1.65) for late debridement.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>Exposed n(e)[E=1]n[e]</th>
<th>Control n[c][E=1]n[c]</th>
<th>Favors Late Debridement</th>
<th>Favors Early Debridement</th>
<th>Weight (%)</th>
<th>Association measure with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kindsfater</td>
<td>1995</td>
<td>8/18</td>
<td>5/28</td>
<td></td>
<td></td>
<td>7.00%</td>
<td>3.68 (0.96 to 14.08)</td>
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<tr>
<td>Harley</td>
<td>2002</td>
<td>10/100</td>
<td>9/115</td>
<td></td>
<td></td>
<td>15.00%</td>
<td>1.31 (0.51 to 3.36)</td>
</tr>
<tr>
<td>Ashford</td>
<td>2004</td>
<td>4/36</td>
<td>2/12</td>
<td></td>
<td></td>
<td>4.00%</td>
<td>0.63 (0.1 to 3.93)</td>
</tr>
<tr>
<td>Spencer</td>
<td>2004</td>
<td>5/46</td>
<td>7/69</td>
<td></td>
<td></td>
<td>9.00%</td>
<td>1.08 (0.32 to 3.64)</td>
</tr>
<tr>
<td>Charalambous</td>
<td>2005</td>
<td>8/199</td>
<td>8/184</td>
<td></td>
<td></td>
<td>13.00%</td>
<td>0.52 (0.34 to 2.51)</td>
</tr>
<tr>
<td>Nouni</td>
<td>2005</td>
<td>1/35</td>
<td>4/76</td>
<td></td>
<td></td>
<td>3.00%</td>
<td>0.53 (0.06 to 4.92)</td>
</tr>
<tr>
<td>Reuss</td>
<td>2007</td>
<td>4/50</td>
<td>3/31</td>
<td></td>
<td></td>
<td>5.00%</td>
<td>0.81 (0.17 to 3.9)</td>
</tr>
<tr>
<td>Tripuraneni</td>
<td>2008</td>
<td>11/150</td>
<td>7/65</td>
<td></td>
<td></td>
<td>13.00%</td>
<td>0.66 (0.24 to 1.78)</td>
</tr>
<tr>
<td>Potak</td>
<td>2010</td>
<td>36/214</td>
<td>14/93</td>
<td></td>
<td></td>
<td>30.00%</td>
<td>1.14 (0.58 to 2.23)</td>
</tr>
<tr>
<td>META-ANALYSIS</td>
<td></td>
<td>87/848</td>
<td>59/673</td>
<td></td>
<td></td>
<td>100%</td>
<td>1.07 (0.74 to 1.54)</td>
</tr>
</tbody>
</table>

Fig. 3
Random effects meta-analysis comparing the relative risk of deep infection after late debridement (“exposed” group) and early debridement (“control” group) of open fractures. The association measure is the odds ratio for infection after late compared with early debridement. CI = confidence interval, and OR = odds ratio.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>Exposed n(e)[E=1]n[e]</th>
<th>Control n[c][E=1]n[c]</th>
<th>Favors Late Debridement</th>
<th>Favors Early Debridement</th>
<th>Weight (%)</th>
<th>Association measure with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kindsfater</td>
<td>1995</td>
<td>3.5/16.5</td>
<td>3.5/9.5</td>
<td></td>
<td></td>
<td>22.00%</td>
<td>0.46 (0.08 to 2.71)</td>
</tr>
<tr>
<td>Khotod</td>
<td>2003</td>
<td>2.5/13.5</td>
<td>7.5/49.5</td>
<td></td>
<td></td>
<td>28.00%</td>
<td>1.27 (0.26 to 6.17)</td>
</tr>
<tr>
<td>Sungaran</td>
<td>2007</td>
<td>0.5/36.5</td>
<td>0.5/17.5</td>
<td></td>
<td></td>
<td>4.00%</td>
<td>0.37 (0.01 to 19.37)</td>
</tr>
<tr>
<td>Tripuraneni</td>
<td>2008</td>
<td>5.5/111.5</td>
<td>5.5/49.5</td>
<td></td>
<td></td>
<td>46.00%</td>
<td>0.42 (0.12 to 1.42)</td>
</tr>
<tr>
<td>META-ANALYSIS</td>
<td></td>
<td>12/188</td>
<td>17/126</td>
<td></td>
<td></td>
<td>100%</td>
<td>0.58 (0.25 to 1.33)</td>
</tr>
</tbody>
</table>

Fig. 4
Random effects meta-analysis comparing the relative risk of infection after late debridement (“exposed” group) and early debridement (“control” group) of Gustilo-Anderson type-I and II fractures. The association measure is the odds ratio for infection after late compared with early debridement. CI = confidence interval, and OR = odds ratio.
Random effects meta-analysis comparing the relative risk of infection after late debridement ("exposed" group) and early debridement ("control" group) of Gustilo-Anderson type-III fractures. The association measure is the odds ratio for infection after late compared with early debridement. **OR** = odds ratio.

**Discussion**

In this review, we present the aggregation and analysis of sixteen systematically identified studies on the effect of late debridement of open fractures on the infection rate. The meta-analysis revealed no association between later debridement times and higher infection rates when all infections were considered, when only deep infections were considered, or when only more severe open fracture injuries were considered.

**Strengths and Weaknesses of This Review**

In this review, we attempted to extract as much data as possible from the individual studies and we performed a systematic analysis of study quality with use of a previously described methodological tool. Fourteen studies (3217 fractures) that included the time to operative debridement as a recorded metric were available for the meta-analysis. Furthermore, the study data were amenable to subgroup analysis according to fracture severity (Gustilo-Anderson type), infection depth, study level of evidence, and anatomic location.

Inclusion of retrospective cohort studies has inherent risks of bias, confounding, and associations that are not improved by aggregating studies. However, despite their limitations in methodology, such studies included a substantial number of patients, and ignoring them might have affected the external validity of the findings of the meta-analysis. Furthermore, differing infection definitions, wound handling, irrigation practices, antibiotic administration, patient comorbidities, virulence of potential contaminants, injury characteristics, and skeletal instability could not be controlled for in this analysis, and these will require further study.

In addition, the details of antibiotic administration were not well described in most of the studies (see Appendix). As antibiotic use is likely a major factor in reducing infection rates, it is an important factor to consider when designing future studies. Two studies reported neither the type nor the timing of antibiotic administration. Nine additional studies reported the type of antibiotic administered but did not describe the timing after injury. Dellinger et al. reported a mean time to antibiotic administration of 2.1 hours (range, 0.2 to nine hours) but did not make any associations between delayed antibiotic administration and the infection rate. Spencer et al. reported that all patients received antibiotics within four hours of injury. Patzakis and Wilkins noted a higher infection rate in patients who received antibiotics more than three hours after injury (7.4% compared with 4.7%). Similarly, Pollak et al. noted that a prolonged time between injury and hospitalization (more than two hours)—which served as a proxy for the timing of antibiotic administration—was associated with a higher rate of infection. Finally, Al-Arabi et al. did not find an association between the timing of antibiotic administration and the infection rate, but they did note that two patients who had delays in both operative debridement and antibiotic administration developed infections.

**Other Studies—Clinical Data**

Two studies included in the systematic review did not provide extractable data for the meta-analysis. Dellinger et al. performed a prospective study that evaluated the development of deep and superficial infections in a cohort of 263 upper and lower-extremity fractures. The authors determined that the mean time to debridement was 5.7 hours for patients who did not develop infections compared with 5.0 hours for patients without infection; this difference was not significant. Ikem et al. prospectively evaluated a series of sixty-three consecutive open fractures and noted that patients who developed infections had a significantly longer...

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**Table 1**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>Exposed n</th>
<th>Control n</th>
<th>OR (log scale)</th>
<th>Weight (%)</th>
<th>Association measure with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bednar</td>
<td>1993</td>
<td>2/43</td>
<td>2/20</td>
<td>1.80</td>
<td>0.44</td>
<td>(0.06 to 3.37)</td>
</tr>
<tr>
<td>Kindsfater</td>
<td>1995</td>
<td>5/10</td>
<td>2/12</td>
<td>1.90</td>
<td>0.5</td>
<td>(0.7 to 35.5)</td>
</tr>
<tr>
<td>Khatod</td>
<td>2003</td>
<td>3/14</td>
<td>7/24</td>
<td>2.50</td>
<td>0.66</td>
<td>(0.14 to 3.12)</td>
</tr>
<tr>
<td>Sungaran</td>
<td>2007</td>
<td>1/50</td>
<td>5/48</td>
<td>1.60</td>
<td>0.18</td>
<td>(0.02 to 1.56)</td>
</tr>
<tr>
<td>Tripuraneni</td>
<td>2008</td>
<td>6/99</td>
<td>2/16</td>
<td>2.20</td>
<td>1.27</td>
<td>(0.23 to 7.09)</td>
</tr>
<tr>
<td>META-ANALYSIS:</td>
<td></td>
<td>17/156</td>
<td>18/120</td>
<td>100%</td>
<td>0.84</td>
<td>(0.31 to 2.31)</td>
</tr>
</tbody>
</table>

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**Fig. 5**

Random effects meta-analysis comparing the relative risk of infection after late debridement ("exposed" group) and early debridement ("control" group) of Gustilo-Anderson type-III fractures. The association measure is the odds ratio for infection after late compared with early debridement. **CI** = confidence interval, and **OR** = odds ratio. **THE JOURNAL OF BONE & JOINT SURGERY** VOLUME 94-A NUMBER 12 JUNE 20, 2012 JBJS.ORG 1062
delay to initial debridement. Of note, the clinical practice of orthopaedics in Nigeria differs to a substantial extent compared with that in more developed nations. In that series, fracture stabilization was achieved with skeletal traction, Steinmann pins, external fixation, and plaster casting with a cast window cut out for wound care.

Two additional retrospective case series were excluded from the systematic review and meta-analysis on the basis of the inclusion criterion involving the minimum level of evidence. Furthermore, two Level-III studies of pediatric patients were excluded from the systematic review and meta-analysis on the basis of the inclusion criterion involving patient adulthood. Nonetheless, the results of these additional clinical studies were consistent with the findings of our meta-analysis, suggesting that early initial debridement may not be a critical factor in reducing infection rates following open fractures.

Other Studies—Experimental Data
In a 1961 study involving subcutaneous inoculation of guinea pigs, Burke concluded that prevention of infection was best achieved when antibiotics were administered prior to bacterial inoculation and that the effect of systemic antibiotics decreased as the time interval after inoculation increased, reaching a threshold of no effect after three hours. In another study involving administration of cephadrine to prevent tibial osteomyelitis in a rabbit model, administration of the antibiotic prior to inoculation was shown to be significantly more effective than administration after inoculation; however, administration up to four hours after injury still had a dramatic effect on the prevention of infection. There is also substantial clinical evidence to support early antibiotic administration as a critical factor in preventing infection after open fractures.

Implications of Our Review
Although initial expedient and appropriate irrigation and debridement of open fracture injuries should be the goal, there are circumstances in which early debridement may not be possible. For example, hospital facilities in a rural setting or in a remote military theater may not have the resources to accommodate this. Furthermore, two Level-III studies of pediatric patients were excluded from the systematic review and meta-analysis on the basis of the inclusion criterion involving patient adulthood. Nonetheless, the results of these additional clinical studies were consistent with the findings of our meta-analysis, suggesting that early initial debridement may not be a critical factor in reducing infection rates following open fractures.

Unanswered Questions and Future Directions
Our study cannot be considered to conclusively invalidate the “six-hour rule.” However, it provides sufficient equipoise to justify prospective investigations into the timing of initial debridement of open fractures. Clearly, open fractures can lead to substantial infectious morbidity. The identification and analysis of modifiable risk factors (including the previously suggested factors of time between injury and admission to a trauma center, quality of debridement, timing of antibiotic administration, substantial bone loss, fracture location, patient comorbidities, and smoking status) in well-designed prospective trials will allow us to decrease the morbidity associated with open fractures.

References


