

The Effect of Treatment Delay on Infection in Open Tibia Fractures: A Retrospective Study in Ethiopia

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ABSTRACT

BACKGROUND: Infection is a devastating complication of open fractures. Historically, treatment protocols advocated that initial treatment of open fractures within six hours reduced the risk of infection. Little scientific evidence has supported this “six-hour rule” but the exact time in which the risk of infection increases remains unknown.

AIM: Assess the effect of delay in treatment greater than 6 and 24 hours on the development of infection for open tibia fractures.

METHODS: A retrospective review of all patients was conducted to identify skeletally mature patients with an open tibia fracture treated

with the Surgical Implant Generation Network (SIGN) intramedullary nail from February 2006 and June 2015. Descriptive data, time to treatment, fracture characteristics, and presence of infection were collected and analyzed.

RESULTS: Infection occurred in 19 (11%) patients (Gustilo I 1/44, 2%; Gustilo II 6/39, 15%, Gustilo IIIa 9/44, 21%; Gustilo IIIb 3/44, 7%). Sixty patients received treatment within six hours of their injury, while 93 did not. One hundred forty-four patients were treated within 24 hours from injury (mean, 8.2 hours) and 28 were treated after 24 hours (mean, 41.1 hours). There was no significant difference in the rates of infection for fractures treated before or after six hours from the time of injury (15% vs. 11%, $p = 0.621$). Infection rate was similar in patients treated within 24 hours and beyond 24 hours (10% vs. 14%, $p = 0.518$). The average time to treatment of patients with and without infectious outcome were not significantly different (15.6 vs 13.4 hours, $p = 0.700$). There was an association between more severe Gustilo types and infection, yet this did not reach significance ($p = 0.402$).

CONCLUSION: Our results show that initial treatment beyond 24 hours did not lead to a significant increase in the rate of infection. While not significant, a greater proportion of infections occurred in higher Gustilo types. Our results suggest that fracture type rather than time to treatment may be a more important predictor of infection.

Key words: Infection; Trauma; Open Fracture; Delayed Treatment

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INTRODUCTION

The most frequent complication of open fractures, with a reported incidence of 3 to 40%, is infection^[1]. The anatomy of the tibia predisposes it to higher rates of infection, with due to its limited

soft tissue coverage and marginal blood supply that, which be easily disrupted from soft tissue injury^[2]. Open tibia fractures exhibit infection rates ranging 10-20 times higher than open fractures of other bones^[3]. Infection of an open fracture can be devastating, potentially leading to osteomyelitis, systemic infection, amputation, or even death^[4]. Therefore, an open fracture is one of a few orthopaedic injuries that requires timely treatment.

Current open fracture treatment protocols aim to reduce the risk of infection through emergent intravenous (IV) antibiotics and surgical debridement^[5]. Over time, an unwritten “six-hour rule” has developed within the orthopaedic community; it is widely advocated that initiating treatment within six hours of injury reduces the rate of morbidity and mortality^[6-9]. While the literature agrees that urgent care is essential, there is little scientific evidence to support this “six-hour rule”^[1,5,6,9-13].

Soddo Christian Hospital (SCH) is a mission hospital operating in Wolaita, Soddo, Ethiopia that serves as an orthopaedic referral center for a large encatchment area. As one of the only surgical hospitals in southern Ethiopia, its location provides a unique opportunity to examine the influence of prolonged time to treatment on infection in open tibia fractures. Rugged terrain and limited means of transportation often require patients to travel long distances, sometimes requiring many hours or even days, to receive care. For example, one study examining tibia fractures at hospitals in three developing countries, including SCH, found an average time from injury to surgery of 4.1 days^[14]. In addition, SCH provides a controlled environment; relatively few surgeons operate at SCH and the majority of tibia fractures are treated with Surgical Implant Generation Network (SIGN) intramedullary nails^[15]. The purpose of this study is to retrospectively examine the effect of delayed treatment on infection rates in open tibia fractures on a scale that has not previously been examined.

METHODS

Prior to all research activities, a protocol was submitted to and approved by the University of California at Irvine Institutional Review Board. All patients 18 years or older, who presented to SCH from January 2006 to June 2015 with a unilateral open tibia fracture (AO/OTA 41A, 42A-C, 43A) and were treated with the SIGN intramedullary nail were eligible for this study (Figure 1)^[16]. Exclusion criteria included patients with bilateral tibia fractures, a concomitant femur fracture, patients that presented greater than 120 days from the time of their injury, nonunions, and pathologic fractures.

A formal treatment protocol was not in place, but patients were treated according to current community standards. Patients were emergently assessed for life-threatening injury by the emergency and surgical teams and stabilized as needed. IV antibiotic prophylaxis (cloxacillin and gentamycin) was initiated and continued at the discretion of the treatment team, generally 72 hours unless otherwise indicated. Following initial stabilization, patients were urgently irrigated and surgically debrided. Repeat surgical debridement and irrigation was performed when clinically indicated. Patients were graded according to the Gustilo and Anderson classification system by the orthopedic team at SCH^[17]. All fractures were stabilized using the SIGN intramedullary nail. The method of wound closure varied depending on soft tissue injury and was determined by the surgical team. Closure was achieved by one of the following methods: primary closure, delayed primary closure, secondary closure, skin grafting, or flap closure. Patients were encouraged to return for follow up at one month and subsequent regular intervals. All surgical

and follow up data was prospectively collected and recorded in the SIGN database.

Immediate post-operative infection, those that presented during the primary hospital stay, was not documented prospectively in the SIGN database. As such, a proxy was used to determine infection. Current treatment standards recommend 72 hours of antibiotic treatment for all open fractures, regardless of severity or level of contamination, and to continue with additional blocks of coverage for 72 hours until all signs of infection have abated^[18,19]. Therefore, during our retrospective review we considered any patient that had received

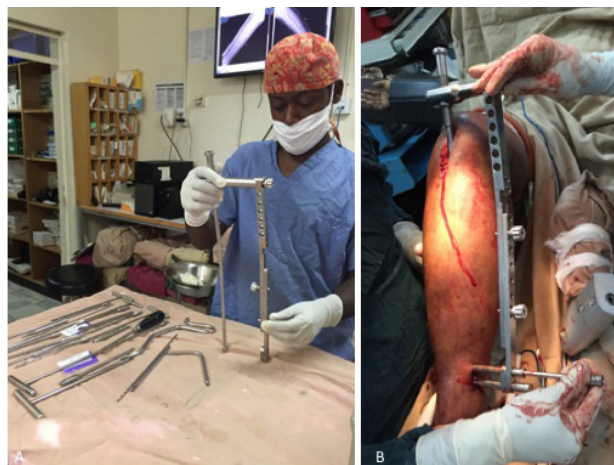


Figure 1 A: Picture of a surgical technician at Soddo Christian Hospital preparing and displaying a SIGN tibia nail. B: A picture of a SIGN tibia nail inserted into the medulla of a patient’s tibia with the aiming arm attached, showing how the distal interlocking aiming sleeves are used to place the distal interlocking bolts.

Table 1 Summary of Patient Population and Fracture Characteristics.

Characteristics	Patients and Fractures, No. (%), (n =172)
Gender	
Male	132 (77)
Female	40 (23)
AO/OTA Type	
41-A	8 (5)
42-A-C	105 (61)
43-A	55 (32)
Not Recorded	4 (2)
Gustilo Anderson Classification	
Type I	44 (26)
Type II	39 (23)
Type IIIa	44 (26)
Type IIIb	44 (26)
Type IIIc	1 (1)

Table 2 Summary of Follow Up Population and Fracture Characteristics.

Characteristics	Patients and Fractures, No. (%), (n =113)
Gender	
Male	86 (76)
Female	27 (24)
Gustilo Anderson Classification	
Type I	25 (22)
Type II	30 (27)
Type IIIa	30 (27)
Type IIIb	28 (25)
Type IIIc	0 (0)

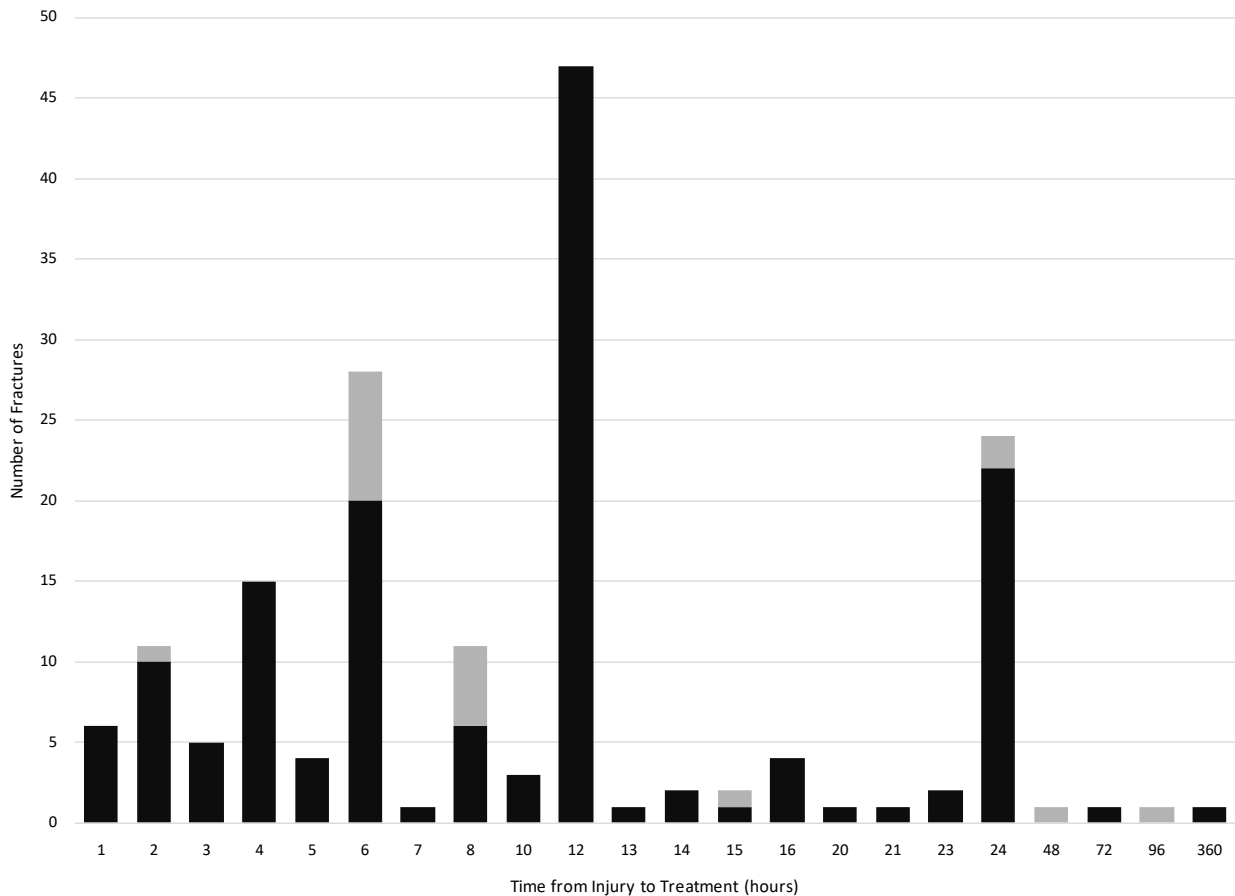


Figure 2 A histogram displaying the number of patients according to the time from injury to treatment. Black indicates the number of patients that did not develop infection, while gray signifies the number patients that went on to develop an infection at follow up.

antibiotics for greater than 72 hours as having acutely developed an infection. Deep infection was diagnosed clinically by the attending surgeon considering physical exam (fever, erythema, edema, pain), laboratory analysis (leukocytosis), or X-ray imaging (evidence of osteomyelitis or hardware loosening) at any follow-up visit greater than four weeks after treatment. Infectious complications diagnosed at follow up visits were recorded prospectively in the SIGN database, but immediate postoperative infection was determined by retrospective analysis. Both forms of infection, acute and deep, were totaled and analyzed collectively.

All data was retrospectively collected by the authors from SCH’s SIGN database and consolidated in a secure REDCap database^[20]. Time to treatment was determined by the interval from the time of injury to first antibiotic administration. Previous studies have focused on the “six-hour rule” and have not specifically examined the 24-hour cutoff. According to anecdotal recounts and previous literature, we anticipated many patients would experience significant delays in treatment and therefore chose to group patients into two groups based on presentation time: within 24 hours and 24 hours or greater^[14]. Data and statistical analysis were performed using Microsoft Excel and SPSS (IBM, Version 23). A Fisher’s exact test was used to evaluate the difference in infection rates of open fractures treated within 24 hours and those treated at 24 hours or greater. Further analysis using a χ^2 test for trend was employed to evaluate the association between Gustilo type and infection. Lastly, an unpaired *t* test was used to assess the difference in time to treatment of infected and noninfected fractures. A significance level of $p < 0.05$ was used for all statistical tests.

Table 3 Summary of Infectious Outcomes by Time to Treatment and Gustilo Type.

Characteristics	Patients and Fractures, No. Infected/Total (%), (n =172)
Time from Injury to Treatment	
≤ 6 hours	9/60 (15)
> 6 hours	10/93 (11)
< 24 Hours	15/144 (10)
≥ 24 Hours	4/28 (14)
Gustilo Anderson Classification	
Type I	1/44 (2)
Type II	6/39 (13)
Type IIIa	9/44 (3)
Type IIIb	3/44 (4)
Type IIIc	0/1 (0)

RESULTS

One hundred and seventy-two open tibia fractures were retrospectively reviewed. The average patient age was 32 years (range, 18-70). The population consisted of 132 (77%) male and 40 (23%) female patients. There were 44 (26%) type I fractures, 39 (23%) type II fractures, 44 (26%) type IIIa fractures, 44 (26%) type IIIb fractures, and 1 (1%) type IIIc fracture (Table 1). There were 8 (5%) AO/OTA 41-A fractures, 105 (61%) AO/OTA 42-A-C fractures, and 55 (32%) AO/OTA 43-A fractures. The fracture location was not recorded for four (2%) patients (Table 1). The cause of injury was not documented for all cases.

One hundred and thirteen patients (66%), 86 (76%) males and 27 (24%) females, had sufficient follow-up. Table 2 summarizes the characteristics of the follow-up patient population. In total, 25 patients (22%) with type I fractures, 30 patients (27%) with type II fractures, 30 patients (27%) with type IIIa fractures, 28 patients (25%) with type IIIb fractures, and no patients (0%) with type IIIc fractures. The average time from surgery to the first follow-up evaluation was 12.1 weeks. The average number of follow-up visits was 1.3 with an average total follow-up duration of 18 weeks (range, 4-155 weeks).

In total, nineteen (11%) fractures were complicated by infection. Figure 2 presents infection status according to the time from injury to treatment. Thirteen (68%) infections occurred acutely in the patients' immediate post-injury hospital course and six (32%) patients presented with a deep infection at follow-up. Four (67%) of the deep infections presented at the first follow-up visit (mean, 10 weeks; range, 6-17 weeks) and two (33%) fractures were found to be infected at the second follow-up visit (mean, 45 weeks; range, 33-58 weeks). Infection occurred in one (2%) type I fracture, six (15%) type II fractures, nine (21%) type IIIa fractures, and three (7%) type IIIb fractures. The one type IIIc fracture did not become infected (Table 3). There was not a significant correlation between increasing Gustilo type and infection ($p = 0.402$).

A total of 60 patients were treated in six hours or less, nine of which developed an infection (15%). The remaining 93 patients received their initial treatment six hours after their injury with 10 complicated by post-operative infection (11%). There was no significant difference in the rate of infection among these two groups ($p = 0.621$). One hundred and forty-four (84%) patients received initial treatment within 24 hours of injury (mean, 7.0 hours; median 8.0 hours) while 28 (16%) patients did not receive initial treatment until after twenty-four hours (mean, 41.1 hours; median, 24.0 hours). Fifteen (10%) of the patients treated within 24 hours and four (14%) of the patients treated after 24 hours from the time of injury developed an infection (Table 3). The rate of infection was not significantly different ($p = 0.518$) between the two groups. The average time to treatment of the infected was greater than the noninfected fractures, 15.6 versus 13.4 hours, but this difference was not significant ($p = 0.700$).

DISCUSSION

Infection is the most important potential complication of an open tibia fracture and can lead to severe consequences. Many articles have previously examined factors that influence the development of infection in open tibia fractures and how orthopedic trauma surgeons can try to prevent this complication. Treatment protocols advocate for expedient surgical debridement and IV antibiotics to reduce the risk of infection. However, over time, a "six-hour rule" seems to have evolved based mainly on historical tradition rather than scientific evidence^[1,5,6,9-13].

To our knowledge, no studies have examined delays in treatment of the magnitude studied in this paper. This is most likely due to the ethical implications of withholding treatment for the benefit of assessing the point at which infection becomes a greater risk. Our study utilized the naturally delaying factors of the Ethiopian geography and limited access to care to help further elucidate the relationship between treatment delay and infection in open fractures. Our results show that treatment delay beyond twenty-four hours does not lead to a significantly increased risk of infection. Current literature further supports this argument.

Several studies have directly challenged the idea that reduced time to treatment leads to fewer infections. A retrospective study of 191 open tibia fractures showed no significant increase in infection with respect to time from injury to initial operative management^[1]. Similarly, Bednar and Parikh showed no significant increase in infection rate with late irrigation and debridement^[6]. More recently, a prospective 5-year study examining infection in open long bone fractures did not find statistical evidence of an increased infection rate in fractures debrided greater than six hours from the time of injury^[11]. Conversely, one investigation did show a significant increase in the occurrence of infection debrided more than five hours after the initial injury^[7]. However, it is important to note that this study only examined patients with the more severe Gustilo type II and III tibia fractures, which may have led to biased results^[8].

Although our results did not show a statistically significant association between increased fracture severity and increased rate of infection, our results do suggest that a trend may exist; a greater proportion of infections occurred in the more severe, higher Gustilo types. In fact, all but one infection occurred in type II and III fractures. This trend is further supported in the literature. A recent study created a multivariate model to evaluate the influence of several factors on infection rates and Gustilo type was found to be the greatest predictor of nonunion and infection^[13]. This suggests that management of open tibia fractures should be guided by Gustilo type rather than time from injury^[13]. Our trend did not show statistical significance, possibly because the limitations of our study, which may have hidden an association between Gustilo type and infection.

Our study is not without limitations. Loss to follow up, with only 66% of patients returning for follow up evaluation, prevented SCH's orthopedic team from fully evaluating all subjects for deep infection. However, our follow up rate is similar to those of other SIGN database studies in developing countries^[21,22]. Furthermore, the retrospective design limited the amount and type of data that could be collected. For example, infection during the immediate post-operative hospital stay was not documented necessitating that we use duration of antibiotic coverage as a proxy for the presence of infection. In addition, a community standard protocol supervised by two attending orthopedic surgeons was used to guide treatment but no formal protocol for surgical debridement or wound management was employed. But, it is important to note that all patients were treated similarly with expedient debridement, antibiotic prophylaxis, and fixation with the SIGN intramedullary nail creating a relatively controlled study environment. Moreover, it was difficult to control for confounding variables such as previous medical conditions, trauma history, tobacco use, and mechanism of injury. Despite these limitations, our study does provide valuable information on the effects of treatment delay beyond 24 hours.

CONCLUSION

Ethiopia, with its rugged terrain and difficult transportation, provided a unique environment that allowed analysis of treatment delays that, for ethical reasons, would not be possible in a developed nation. The findings of the study suggest that significant delays in time to treatment of open tibia fractures is not associated with an increased risk of post-operative infection. While factors may limit the significance of this study, our results are consistent with current literature. The trend seen with our data, while not significant, is consistent with current literature suggesting that Gustilo type may be the best predictor of infection risk. Further research is needed to determine if Gustilo type is in fact the best management guide and

what other factors can help guide management of open tibia fractures, both in the developed and developing worlds. It is our belief that expedient treatment should be employed in all cases, but we contend that growing evidence does not support the idea that early treatment reduces the risk of infection.

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REFERENCES

1. Khatod M, Botte MJ, Hoyt DB, et al. Outcomes in open tibia fractures: relationship between delay in treatment and infection. *J Trauma* 2003; **55(5)**: 949-54. [DOI: 10.1097/01.TA.0000092685.80435.63]
2. Newman SDS, Mauffrey CPC, Krikler S. Distal metadiaphyseal tibial fractures. *Injury* 2011; **42(10)**: 975-84. [DOI: 10.1016/j.injury.2010.02.019]
3. Patzakis MJ, Wilkins J, Moore TM. Considerations in Reducing the Infection Rate in Open Tibial Fractures. *Clinical Orthopaedics and Related Research* 1983; &NA; **(178)**: 36-41. [DOI: 10.1097/00003086-198309000-00006]
4. Papakostidis C, Kanakaris NK, Pretel J, et al. Prevalence of complications of open tibial shaft fractures stratified as per the Gustilo-Anderson classification. *Injury*. 2011; **42**: 1408-1415.
5. Halawi MJ, Morwood MP. Acute Management of Open Fractures: An Evidence-Based Review. *Orthopedics* 2015; **38(11)**: e1025-33. [DOI: 10.3928/01477447-20151020-12]
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. *Journal of Orthopaedic Trauma* 1993; **7(6)**: 532-35. [DOI: 10.1097/00005131-199312000-00008]
7. Kindsfater K, Jonassen EA. Osteomyelitis in Grade II & Grade III Tibia Fractures with Early and Late Debridement. *Journal of Orthopaedic Trauma* 1993; **7(2)**: 167. [DOI: 10.1097/00005131-199304000-00043]
8. Pollak AN. Timing of debridement of open fractures. *J Am Acad Orthop Surg* 2006; **14(10 Spec No.)**: S48-51. [DOI: 10.5435/00124635-200600001-00011]
9. 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(7)**: 397-402. [DOI: 10.1097/BOT.0000000000000573]
10. Harley BJ, Beaupre LA, Jones CA, et al. The Effect of Time to Definitive Treatment on the Rate of Nonunion and Infection in Open Fractures. *Journal of Orthopaedic Trauma* 2002; **16(7)**: 484-90. [DOI: 10.1097/00005131-200208000-00006]
11. Spencer J, Smith A, Woods D. The effect of time delay on infection in open long-bone fractures: a 5-year prospective audit from a district general hospital. *Ann R Coll Surg Engl* 2004; **86(2)**: 108-12. [DOI: 10.1308/003588404322827491]
12. Crowley DJ, Kanakaris NK, Giannoudis PV. Debridement and wound closure of open fractures: the impact of the time factor on infection rates. *Injury* 2007; **38(8)**: 879-89. [DOI: 10.1016/j.injury.2007.01.012]
13. Thakore RV, Francois EL, Nwosu SK, et al. The Gustilo-Anderson classification system as predictor of nonunion and infection in open tibia fractures. *Eur J Trauma Emerg Surg* 2016 [DOI: 10.1007/s00068-016-0725-y]
14. Stephens KR, Shahab F, Galat D, et al. Management of Distal Tibial Metaphyseal Fractures With the SIGN Intramedullary Nail in 3 Developing Countries. *J Orthop Trauma* 2015; **29(12)**: e469-75. [DOI: 10.1097/BOT.0000000000000396]
15. SIGN Fracture Care International. SIGN Fracture Care International >> Global Programs January 1, 2017 [Available from: <https://signfracturecare.org/global-programs/> accessed February 18 2017.
16. Marsh JL, Slongo TF, Agel J, et al. Fracture and Dislocation Classification Compendium - 2007. *Journal of Orthopaedic Trauma* 2007; **21(Supplement)**: S1-S6. [DOI: 10.1097/00005131-200711101-00001]
17. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones. *The Journal of Bone & Joint Surgery* 1976; **58(4)**: 453-58. [DOI: 10.2106/00004623-197658040-00004]
18. Zalavras CG, Patzakis MJ. Open Fractures: Evaluation and Management. *Journal of the American Academy of Orthopaedic Surgeons* 2003; **11(3)**: 212-19. [DOI: 10.5435/00124635-200305000-00008]
19. Zalavras CG. Prevention of Infection in Open Fractures. *Infect Dis Clin North Am* 2017; **31(2)**: 339-52. [DOI: 10.1016/j.idc.2017.01.005]
20. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42(2)**: 377-81. [DOI: 10.1016/j.jbi.2008.08.010]
21. Sekimpi P, Okike K, Zirkle L, et al. Femoral fracture fixation in developing countries: an evaluation of the Surgical Implant Generation Network (SIGN) intramedullary nail. *J Bone Joint Surg Am* 2011; **93(19)**: 1811-8. [DOI: 10.2106/JBJS.J.01322]
22. Young S, Lie SA, Hallan G, et al. Low infection rates after 34,361 intramedullary nail operations in 55 low- and middle-income countries: validation of the Surgical Implant Generation Network (SIGN) online surgical database. *Acta Orthop* 2011; **82(6)**: 737-43. [DOI: 10.3109/17453674.2011.636680]

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