Helicopter Emergency Medical Services Crew Administration of Antibiotics for Open Fractures

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Abstract

This study had 3 major aims: (1) to ascertain the degree to which helicopter emergency medical services (HEMS) administration of antibiotics (Abx) can streamline the time to Abx in open fracture patients, (2) to determine whether any clinical outcome improvements were associated with HEMS Abx therapy, and (3) to calculate the cost-effectiveness of prehospital HEMS Abx. The design of the study was a prospective, nonrandomized, nonintervention, natural study of timing and clinical outcomes for patients with suspected open extremity fracture. There were 138 scene trauma cases transported by 8 participating HEMS programs from July 2009 to June 2010. The participating HEMS programs were both urban and rural. The diagnosis of an open fracture by the HEMS crews had an accuracy rate of 97.8% (95% confidence interval, 90.8%-98.4%). The time from the incident to Abx was 30 minutes shorter ($P = .0001$) when Abx were administered by HEMS crews. There was no statistical significance ($P = 1.0$) regarding the endpoint of infection or nonunion development in HEMS- versus hospital-administered Abx. In conclusion, the administration of Abx by HEMS crews to patients diagnosed with open extremity fractures is feasible, it may decrease the time to Abx by 30 minutes, and the effect magnitude (40.3% relative risk reduction) was promising.

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Introduction

Existing literature supports a contention that, as currently deployed, helicopter emergency medical services (HEMS) improves outcomes in a variety of patient populations.[1-8] The data addressing the cost benefit of air transport are also generally favorable but more limited.[1,9-11] As more emphasis is being placed on HEMS studies assessing outcomes improvement and cost-effectiveness, the investigation of nonmortality cost-effectiveness advantages is becoming a priority.

One area of potential HEMS benefit is the provision of interventions in the field, long before those interventions could be provided upon arrival at a receiving hospital. Perhaps the best example of a field intervention that may be provided only with HEMS depending on ground EMS availability and capability is endotracheal intubation (ETI).[12] The performance of HEMS of field ETI (as compared with ground EMS ETI or even emergency department ETI) shows the possibility for substantial benefit accrued by early HEMS execution of a medical intervention.[13-15]

Interventions with less critical impact than ETI could also play a role in calculations as to HEMS' cost-effectiveness. One area in which this possibility exists is in the arena of trauma orthopedics, specifically in the treatment of open fractures with early intravenous antibiotics (Abx).

Preliminary work from a Critical Care Transport Collaborative Outcomes Research Effort pilot study presented in abstract form at the 2009 American Academy of Emergency Medicine's Annual Scientific Assembly (Phoenix, AZ, March 2-4, 2009) suggested that significant time savings could be accrued by the administration of Abx in the field by HEMS crews. The Critical Care Transport Collaborative Outcomes Research Effort pilot study's suggestion that the time savings combined with earlier Abx could improve fracture site outcome[16,17] provides the underpinning of the current study. Although a randomized controlled trial was not deemed cost-effective or feasible, the varying practices with respect to prehospital (HEMS) Abx administration for open fractures created an opportunity for a natural experiment. Because there is no standard of care regarding prehospital Abx for open fractures, this study aimed to assess outcomes associated with HEMS Abx administration by accruing subjects from HEMS programs that do and do not provide prehospital Abx.

This study, the Time Savings by Rapid EMS Antibiotic Therapy for Fractures (TREAT Fx) project, was designed with

3 major aims: (1) to ascertain the degree to which HEMS Abx therapy can streamline the time to Abx in open fracture patients, (2) to ascertain whether any outcomes improvement in clinical parameters was associated with HEMS Abx therapy for suspected open fractures, and (3) to calculate the cost-effectiveness of prehospital HEMS Abx in the event that any clinical outcomes advantages were identified.

Methods

Design

This was a prospective, nonrandomized, nonintervention cohort study of timing and clinical outcomes of patients with suspected open extremity fractures. The primary independent variable was "prehospital intravenous Abx." Thus, the study groups were defined as HEMS Abx and Hosp Abx based on whether prehospital Abx were administered. The study was in effect a natural experiment because no protocol changes were made for the project. Some programs' protocols allowed for prehospital Abx and other programs' protocols did not allow prehospital Abx.

The study design entailed a prospective collection of information on patients with HEMS crew–diagnosed open fractures using a structured data form. Data collected at the time of transport included information such as timing parameters and information on patient demographics and physiology. For all patients, follow-up information from the index hospitalization was collected to confirm whether or not the prehospital diagnosis of open fracture was correct. For some participating HEMS services, data were able to be collected 6 months after transport to ascertain clinical outcomes endpoints (eg, discharge disposition, the development of fracture site infection, and nonunion).

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The study plan also called for the collection of financial data concerning costs related to open fracture treatment. The a priori plan was for these cost-effectiveness data to be collected only if the initial study analysis identified statistically significant clinical outcomes benefits associated with field Abx.

Study Subjects and Time Frame

Patients were a consecutive series of 138 scene trauma cases transported by participating HEMS programs over a year (July 2009-June 2010). Patients of all ages with prehospital HEMS crew diagnosis of open fractures in any extremity were eligible for inclusion in the study.

Setting

The study comprised patients flown by 8 HEMS programs. The programs all used a base staffing model of registered nurse/emergency medical technician-paramedic; some programs occasionally flew with physicians (emergency medicine residents). Human studies approval for the study was obtained at each of the 8 participating programs' affiliated institutional review board or equivalent committee.

All participating programs operated with protocols and access to direct medical oversight as needed. For the 3 programs (in Maine, Massachusetts, and Minnesota) with the capability to administer prehospital intravenous Abx, no direct medical oversight contact was required before giving Abx. The participating programs' annual HEMS transport volumes ranged between 1,000 and 2,500. The proportion of scene runs in the participating programs ranged from 15% to 30%. Geographically, participating programs were located in urban and rural regions serving the US Northeast, Midwest, Southwest, and West and the Canadian Maritime Provinces. The participating programs and locations were AirLife Denver (Colorado), Boston MedFlight (Massachusetts), EHS LifeFlight (Nova Scotia, Canada), LifeFlight of Maine (Maine), Mayo One (Minnesota), MedFlight of Ohio (Ohio), MediFlight of Oklahoma (Oklahoma), and Tulsa Life Flight (Oklahoma).

Endpoints

The study had 2 major endpoints: clinical outcomes of prehospital Abx and the surrogate endpoint of time savings accrued by the prehospital administration of Abx. Unless specifically noted in the Results section, all endpoints were defined a priori. The primary clinical endpoint was a composite endpoint of "fracture site infection or nonunion diagnosed within 6 months post-transport." Any diagnosis of fracture site wound infection (regardless of the depth or timing of infection) was sufficient to trigger a patient meeting this endpoint. Nonunion was defined as occurring if this diagnosis was recorded during the 6-month post-transport period.

Secondary clinical endpoints (eg, the need for various types of nonoperative therapy) were initially planned for analysis. However, given the study's low numbers with regard to the main endpoints, there were insufficient data to assess these secondary endpoints.

The surrogate endpoint relating to Abx timing focused on the amount of time potentially gained by administering Abx in the prehospital setting (by HEMS crews) rather than waiting until arrival at the receiving hospital. The importance of the surrogate endpoint is based on an assumption supported but not conclusively proven by available evidence[16,17] that earlier Abx improves the chances of optimal outcome for open fractures.

Data Handling and Analysis

Most data were entered into the study database upon transport of patients with open fractures diagnosed by the HEMS crews. Other data assessing follow-up were entered into study data forms as those data became available for some endpoints (eg, discharge disposition and operations) and at 6 months after transport for the assessment of fracture site infection and/or nonunion of any fracture site wound infection or nonunion. The timing and initial clinical data were collected by all HEMS services participating in the study. Five of the 8 HEMS services were able to follow their patients and provide the outcome data.

The primary analysis for the clinical endpoints of wound site infection and/or nonunion included the generation of 95% binomial exact confidence intervals (CIs) around point estimates for the proportions of HEMS Abx and Hosp Abx patients reaching predefined clinical endpoints.

A comparison of the rates of developing the composite primary clinical endpoint of infection or nonunion among the main 2 groups (HEMS Abx and Hosp Abx) was performed with the Fisher exact test. The study's a priori plan included the generation of a multivariate logistic regression model assessing the dichotomous dependent variable of "infection or nonunion" for association with prehospital Abx while adjusting for clinical factors and other confounders (eg, comorbidities, smoking status, and age). Unfortunately, low study numbers precluded meaningful performance of this type of analysis; there were insufficient numbers of patients with the composite outcome to adjust for important covariates. Thus, analysis was limited to the calculation of the risk difference (to allow estimation of the number needed to treat) and risk ratio with attendant 95% CIs and chi-square *P* values.

Analysis of the surrogate timing endpoints included descriptive reporting of medians with interquartile ranges (IQRs) of these nonparametric data. After non-normal distribution of the data was confirmed with Shapiro-Wilk testing, nonparametric analytic approaches were used to compare time intervals between incident and Abx in the HEMS Abx and Hosp Abx groups (with the Hosp Abx group receiving no antimicrobials in the field but instead receiving Abx at the receiving hospital). Kruskal-Wallis testing was the primary approach for comparing time intervals among the 2 study groups. Because of inconsistencies in the manner and availability of documentation of the exact times of hospital-based Abx administration, the time of initial Abx therapy for all cases in which the first dose was administered in the hospital (ie, for the Hosp Abx group) was considered to be within the first 5 minutes of emergency department arrival. This allowed for more conservative results.

For all analyses in this study, the unit of analysis was the patient, not the fracture. This necessitated within-subject grouping of infection and/or nonunion in the few patients with open fractures in more than 1 extremity; there were only 11 such cases (see Results section). The advantage of using the patient as the unit of analysis was that this allowed for the reporting of appropriate standard errors and reduced the chances of calculating inappropriately low CIs. All analyses were executed with STATA 12MP (StataCorp, College Station, TX). Statistical significance was defined at the $P < .05$ level.

Results

Patient Characteristics

There were 138 study patients. The median age was 46 (range = 1-89, IQR = 27-63). Most subjects were male (99 [71.7%]), white (123 [89.1%]), and had a single extremity in which a prehospital open fracture was diagnosed (126 [91.3%]). There were 11 cases (8.0%) in which 2 extremities had suspected open fractures; in 1 case (0.7%), open fractures were suspected in 3 extremities.

The suspected site of open fracture was in an upper extremity in 41 cases (29.7%), a lower extremity in 96 cases (69.6%), and in 1 case (0.7%) there was suspected open fracture sites in upper and lower extremities. HEMS crews noted neurovascular compromise in involved extremities in 45 cases (32.6%).

The study patients' median Glasgow Coma Scale score was 15 (range = 3-15, IQR = 14-15). Twenty-three (16.7%) patients were intubated in the prehospital setting. Prehospital hypotension (systolic blood pressure < 90) was recorded at least once in 27 cases (19.6%).

HEMS Crew Open Fracture Diagnosis

Of the 138 patients in whom HEMS crews diagnosed open fractures, the ultimate diagnosis of open fracture was confirmed in 132 patients. This translates into an accuracy rate of 95.6% (95% CI, 90.8%-98.4%). For the 6 cases in which HEMS-diagnosed open fractures were not confirmed, 3 patients had closed fractures. (In the other 3 cases, there were no fractures.)

HEMS Crew Open Fracture Treatment and Time Intervals

HEMS crews administered Abx (ceftriaxone, 1 g) in 60 cases (43.5%). Thus, the number of patients in the HEMS Abx group was 60, and the number of Hosp Abx patients was 78 (56.5% of the total of 138).

When Abx were administered by HEMS crews, the time interval from the incident to Abx was 30 minutes shorter than the corresponding interval for the Hosp Abx patients. The median time from the incident to Abx therapy in the HEMS Abx group was 47 minutes (range = 27-109, IQR = 37-60). HEMS Abx patients had Abx administered a median of 33 minutes after initial HEMS crew contact (range = 1-95, IQR = 19-44). For the Hosp Abx group, the median time from the incident to initial

Abx therapy was 77 minutes (range = 33-189, IQR = 65-92). The savings of 30 minutes associated with the HEMS administration of Abx was statistically significant ($P = .0001$). There was also significance ($P < .0001$) of the univariate-calculated association between HEMS Abx status and the earlier administration of Abx.

Clinical Endpoints

Although the accuracy of prehospital open fracture diagnosis was available for all cases, the other clinical endpoints including the primary clinical composite endpoint of infection or nonunion were available from only 5 of the 8 participating HEMS programs. This yielded a subset of analysis of 83 cases for which infection and nonunion were assessed. Of the 5 programs that were able to provide 6-month follow-up data, only 1 had protocols for the administration of Abx. Two of the remaining 3 programs had protocols to administer Abx.

In these 83 cases, infection or nonunion developed in 10 cases (12.1% of 83). Low numbers translated into a lack of precision for point estimates for composite endpoint development in both study groups. For HEMS Abx cases (n = 13 with available follow-up data), the composite endpoint developed in 1 case (7.7%; 95% CI, 0.2%-36%). Of Hosp Abx patients (n = 70 with available follow-up data), the composite endpoint developed in 9 (12.9%; 95% CI, 6%-23%; Table 1). There was no statistical significance ($P = 1.0$) when comparing composite endpoint development in the HEMS Abx versus Hosp Abx groups.

The study followed an a *priori* plan for analysis in case there was a lack of clinical endpoints significantly associated with HEMS Abx status. A risk difference and its 95% CI were calculated. The risk difference calculation showed a statistically insignificant 5.2% absolute reduction in infection and/or nonunion ($P = .60$). The 95% CI ranged from –2% to 11%, showing the possibility for a small increase to a slight decrease in the risk of infection and/or nonunion. The main usefulness of the risk difference calculation is that its inverse (1 divided by the absolute risk reduction) is the number needed to treat (NNT, the number of patients needing an intervention in order to achieve benefit in one case). Using this study's data, the (nonsignificant) point estimate for NNT is 19.2. Further explanation on the nonsignificant NNT calculations is provided in the Discussion section.

Table 1. Endpoint Occurrences in the HEMS Abx Versus Hosp Abx Groups

	n	Endpoint (%)
HEMS Abx	13	1 (7.7)
Hosp Abx	70	9 (12.9)
Total	83	10 (12.1%)

Discussion

The clinical importance of TREAT Fx stems from the desirability of early Abx for open fractures. Although a cutoff time for the institution of Abx is not precisely characterized, it is known that early Abx plays an important role in optimizing outcomes from open fractures.[16,17] In fact, the need for early Abx therapy to treat inevitable contamination has been identified as a major contributor to optimal outcome since the 1970s.[17,18] As stated by the American Academy of Orthopedic Surgeons, "To prevent a clinical infection, immediate antibiotic administration" is necessary.[17] The same source indicating Abx "should be given as soon as possible" points out that the time to Abx therapy but not the duration of Abx therapy or the type of wound closure is a "significant variable" in determining open fracture outcome.[17,19,20] A Cochrane review confirms the usefulness of early Abx therapy for the treatment of open fractures.[21] Other authoritative sources agree that "available evidence suggests that antibiotic treatment should be initiated as soon as possible following injury."[22]

Existing data clearly show that a delay of Abx by 3 or more hours worsens outcome.[19] In the vast majority of cases, delays on the order of 3 hours were not related to (or solvable by) prehospital personnel. In only a single case in this series was there a delay beyond 3 hours from the incident time to initial Abx therapy. The fact that HEMS intervention is not likely needed to meet a 3-hour window does not mean that there is no potential role for flight crew administration of Abx. The limited (experimental animal) data there are show that the earliest possible Abx (ie, pretreatment) is associated with the lowest risk of infectious complication.[23]

The "bottom line" of the preceding discussion is that there is certainly a time savings level at which earlier Abx treatment of open fractures improves outcome. This study attempted to ask the question of whether the particular streamlining of Abx times as could be executed by HEMS crews falls within the therapeutic window of outcomes improvement. The study's major findings are as follows: (1) HEMS crews have a high "true-positive" rate for the diagnosis of open fractures of an extremity, (2) HEMS crews can administer antibiotics approximately 30 minutes sooner than waiting for hospital administration, and (3) the 5.2% absolute reduction in open fracture site infection or nonunion was not statistically significant.

With respect to the first major finding regarding HEMS crew diagnosis of open fractures, there are important advantages and limitations. The main limitations deal with the Hawthorne effect potential of HEMS crews' participation in an open fracture study. Those cases in which open fractures were diagnosed with certainty were reported. Borderline cases may have been excluded from the study by participating HEMS crews, thus potentially inflating the diagnostic accuracy of prehospital open fracture diagnosis. Furthermore, the lack of information on all trauma patients (including those with missed open fractures) translates into an inability to truly calculate the full accuracy of prehospital HEMS crew diagnosis of open fractures.

Although there are limitations, there are potential advantages suggested by the very high "true-positive" rate of HEMS crews' diagnosis of open fractures. The advantages include the clinical, research, and cost-effectiveness arenas. A clinical

advantage is this finding supports the clinical capabilities of flight crews. Both the clinical and research arenas benefit from the HEMS crews' accuracy in that open fracture treatments, including those with risks, can be accurately targeted in the field.

Finally, the high "true-positive" rate of HEMS crew diagnosis means that even if the actual clinical benefit from HEMS Abx therapy is small, the cost-effectiveness of HEMS Abx administration is likely to be favorable because there are low costs or risks associated with HEMS Abx therapy. In fact, because the Abx are going to be administered in the receiving hospital anyway, increasing the pharmacy of the aircraft would be the main real "cost" associated with moving that therapy to the field (if such early administration proves to accrue benefit). However, there are 2 issues other than cost associated with moving the administration of Abx to HEMS. The first being HEMS Abx may take away time from other necessary tasks. The second is the transport crew may have limited knowledge of allergies and may inadvertently administer an antibiotic to which an unconscious patient is allergic.

The study's second major finding was the savings of significant time when prehospital Abx are administered by HEMS crews. Given the previously discussed evidence base that supports arguments that earlier Abx administration is better, the finding of a time savings of a half hour is both noteworthy and potentially of clinical significance.

The third major conclusion of the study was that there was no statistically significant demonstration of benefit associated with the time savings in Abx administration. There are 3 issues to consider in regards to the negative results in the TREAT Fx data. The first issue is that they may be correct. This would mean the time savings of a half hour simply does not translate into clinical benefit. However, it appears premature to definitively conclude that there are no benefits associated with HEMS crew Abx administration for open fractures.

The second issue with respect to the negative clinical results of TREAT Fx lies with endpoint definitions. The endpoints in this study, infection and nonunion, were defined a priori based on a review of the literature and discussion with trauma orthopedists. It is a possibility (not addressed with our data) that some other endpoints may be impacted by the earlier administration of Abx. Further study, especially if larger datasets are collected in the future, may attempt to define additional endpoints such as the depth of infection or days of Abx or hospitalization.

The third and most important issue to consider regarding the negative clinical results of this study is related to the study's low number of patients developing the primary clinical endpoint of infection and/or nonunion. The study was powered to accrue 320 subjects, which would enable 80% power for detection of a 50% relative reduction in composite outcome occurrence. The CIs surrounding point estimates for infection/nonunion were wide; the imprecision of these point estimates leaves room for possibilities of outcome improvement with early Abx administration. Low study numbers prevented regression model building incorporating known confounders of a possible relationship between Abx timing and outcome. There simply were insufficient "outcomes" (infections or nonunion cases) to incorporate more than 1 or 2 independent variables. Adjustment for these confounders (eg, the degree of injury, smoking status, age, and comorbidities) in a larger study could more definitively address the question of whether early Abx improves outcomes in open fracture patients.

Despite the negative results with respect to the statistical significance of the development of infection and/or nonunion, the (nonrobust) point estimate for absolute risk difference of about 5% supports attempts at further investigation. This is because of the fact that if there is a true 5% reduction in infection/nonunion risk with field Abx, the substantial lost work and medical/surgical cost savings of these complications would render HEMS Abx quite cost-effective. The 5.2% risk difference that was the point estimate from these data translates into a 40.3% relative risk reduction; the number is not statistically significant, but the wide 95% CIs leave much room for further studies to identify a clinical benefit. If there were even marginal effectiveness (ie, outcomes improvement) accrued by the earlier administration of drugs that are already going to be given anyway (upon hospital arrival), the cost-effectiveness of field Abx would be high.

HEMS administration of Abx does incur "costs" that weigh against the routine administration of antimicrobials. No reactions or problems were identified in this study, but carrying antibiotics may add to the prehospital drug formulary or otherwise increase complexity of care in the resource-strained prehospital setting. Thus, although some HEMS programs are obviously already administering Abx for suspected open fractures in the field, the data in this study do not support any calls for increasing the frequency of this practice. However, the substantial time savings associated with earlier Abx therapy could be interpreted as supporting the decisions of those HEMS programs that have chosen to adopt this protocol. In effect, the positive finding in the surrogate (timing) outcome with the negative finding in the clinical outcome could be argued to create equipoise for a randomized controlled trial. Given the point estimates in this study, such a trial would require roughly 1,150 patients.

This study showed the feasibility of HEMS crews' administration of Abx therapy to patients with a prehospital diagnosis of open extremity fracture. The study data also showed the significant degree of time savings that may be expected from HEMS crew Abx administration. The results of the study were not statistically significant with respect to clinical endpoints of infection and/or nonunion, but the precision of the point estimate for risk reduction was low and the effect magnitude (40.3% relative risk reduction) was promising. Based on suggestive evidence regarding early Abx administration and the demonstration in this study that approximately a half hour can be gained by the HEMS crew administering Abx, it appears reasonable for HEMS crews to

provide Abx for patients identified in the field as having open fractures; however, this should not be the standard of care. The study results support equipoise to conduct a randomized controlled trial for the administration of Abx to patients with suspected open fractures.

References

1. Thomas SH, Arthur AO. Helicopter EMS: research endpoints and potential benefits. Emerg Med Int 2012 (Epub 2011 Dec 1).
2. Brown B, Pogue K, Williams E, Hatfield J, Arthur A, Thomas SH. Helicopter EMS transport outcomes literature: annotated review of articles published 2007-2011. Emerg Med Int 2012 (Epub 2012 Jan 11).
3. Sullivent E, Faul M, Wald M. Reduced mortality in injured adults transported by HEMS. Prehosp Emerg Care 2011;15:295-302.
4. Brown J, Stassen N, Bankey P, Sangosanya A, Cheng J, Gestring M. Helicopters and the civilian trauma system: national utilization patterns demonstrate improved outcomes after traumatic injury. J Trauma 2010;69:1030-6.
5. Taylor CB, Stevenson M, Stephen J, Middleton PM, Fitzharris M, Myburgh JA. A systematic review of the costs and benefits of helicopter emergency medical services. Injury Int J Care Injured 2010;41:10-20.
6. Shepard M, Trethewy C, Kennedy J, Davis L. Helicopter use in rural trauma. Emerg Med Australas 2008;20:494-9.
7. Mitchell AD, Tallon JM, Sealy B. Air versus ground transport of major trauma patients to a tertiary trauma centre: a province-wide comparison using TRISS analysis. Can J Surg 2007;50:129-33.
8. Schiller J, Tarsia V, McCormack J, et al. Improvement of trauma-related mortality with implementation of helicopter transport [abstract]. J Trauma 2006;61:1572.
9. Oppe S, DeCharro F. The effect of medical care by a helicopter trauma team on the probability of survival and the quality of life of hospitalised victims. Accid Anal Prev 2001;33:129-38.
10. Nicholl J, Turner J, Stevens K, et al. A review of the costs and benefits of helicopter emergency ambulance services in England and Wales. Washington, DC: Department of Health; July 3, 2003.
11. Silbergleit R, Scott P, Lowell M, Silbergleit R. Cost-effectiveness of helicopter transport of stroke patients for thrombolysis. Acad Emerg Med 2003;10:966-72.
12. Thomas SH, Harrison T, Wedel SK. Flight crew airway management in four settings: a six-year review. Prehosp Emerg Care 1999;3:310-5.
13. Wang H, Peitzman A, Cassidy L, Adelson P, Yealy D. Out-of-hospital endotracheal intubation and outcome after traumatic brain injury. Ann Emerg Med 2004;44:439-50.
14. Zink B, Maio R. Out-of-hospital endotracheal intubation in traumatic brain injury: outcomes research provides us with an unexpected outcome. Ann Emerg Med 2004;44:451-3.
15. Cudnik MT, Newgard CD, Wang H, Bangs C, Herrington R IV. Distance impacts mortality in trauma patients with an intubation attempt. Prehosp Emerg Care 2008;12:459-66.
16. Pollak AN, Jones AL, Castillo RC, Bosse MJ, MacKenzie EJ. The relationship between time to surgical debridement and incidence of infection after open high-energy lower extremity trauma. J Bone Joint Surg Am 2010;92:7-15.
17. Zalavras CG, Marcus RE, Levin LS, Patzakis MJ. Management of open fractures and subsequent complications. J Bone Joint Surg Am 2007;89:884-95.
18. Patzakis MJ, Harvey JP Jr, Ivler D. The role of antibiotics in the management of open fractures. J Bone Joint Surg Am 1974;56:532-41.
19. Patzakis MJ, Wilkins J. Factors influencing infection rate in open fracture wounds. Clin Orthop Relat Res 1989;243:36-40.
20. Skaggs DL, Friend L, Alman B, et al. The effect of surgical delay on acute infection following 554 open fractures in children. J Bone Joint Surg Am 2005;87:8-12.
21. Gosselin RA, Roberts I, Gillespie WJ. Antibiotics for preventing infection in open limb fractures. Cochrane Database Syst Rev 2004:CD003764.
22. Okike K, Bhattacharyya T. Trends in the management of open fractures. A critical analysis. J Bone Joint Surg Am 2006;88:2739-48.
23. Worlock P, Slack R, Harvey L, Mawhinney R. The prevention of infection in open fractures. An experimental study of the effect of antibiotic therapy. J Bone Joint Surg Am 1988;70:1341-7.