East Practice Management Guidelines Work Group: Update to Practice Management Guidelines for Prophylactic Antibiotic Use in Open Fractures

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STATEMENT OF THE PROBLEM

An open fracture is defined as one in which the fracture fragments communicate with the environment through a break in the skin. The presence of an open fracture either isolated or as part of a multiple injury complex increases the risk of infection and soft tissue complications. In 1976, Gustilo and Anderson[1] described a system to classify open fractures based on the size of the associated laceration, the degree of soft issue injury, contamination, and presence of vascular compromise. In a subsequent article, Gustilo et al.[2] refined the classification of severe open fractures. In general, risk of infection and incidence of limb loss correlate with the Gustilo type (Table 1).

PROCESS

By using a search methodology similar to Luchette et al.,[3] a MEDLINE search was performed using the key words "open fractures" and "antibiotics." This search was limited to articles published subsequent to the guidelines published by Luchette et al. This search yielded a total of 49 articles. Sixteen articles were excluded for the following reasons: technical article (6), non-English publication (5), insufficient contribution to the project (2), involved nonextremity fractures (2), and animal study (1). Thirteen secondary citations were obtained from bibliographies in the initial articles yielding 46 articles, which were reviewed by the subcommittee.

Each article was reviewed and classified based on methodology described by the EAST Ad Hoc Committee on Guidelines Development and the Agency for Healthcare Policy and Research of the US Department of Health and Human Services as follows[4,5]:

Class I: prospective, randomized controlled study.
Class II: prospective, randomized, nonblinded trials. That is, studies in which data were prospectively collected and analyzed retrospectively.
Class III: studies based on retrospectively collected data, database and registry reviews, and meta-analysis.

For purposes of this practice management guideline, review articles were classified as class III. Reviewers also determined whether the respective article was relevant to the purpose of the practice management guidelines. Nineteen studies were determined to be nonrelevant and were excluded from further analysis; nonrelevance was based on the following: poor methodology (11), inadequate study size (6), and irrelevant purpose (2).

The remaining 27 articles were used to construct an evidentiary table, which was analyzed to make final recommendations. Recommendations were classified based on the quality of scientific evidence available:

Level I: recommendation is justifiable based on the available scientific evidence alone; recommendation is based on class I or a preponderance of class II evidence.
Level II: recommendation is reasonably justifiable based on the available scientific evidence and supported by expert opinion; recommendation is supported by class II evidence or a preponderance of class III evidence.
Level III: recommendation is supported by available data, but inadequate scientific data are available; recommendation is supported by class III evidence.

RECOMMENDATIONS

Level I

- Systemic antibiotic coverage directed at gram-positive organisms should be initiated as soon as possible after injury.
- Additional gram-negative coverage should be added for type III fractures.
- High-dose penicillin should be added in the presence of fecal or potential clostridial contamination (e.g., farm-related injuries).
- Fluoroquinolones offer no advantage compared with cephalosporin/aminoglycoside regimens. Moreover, these agents may have a detrimental effect on fracture healing and may result in higher infection rates in type III open fractures.

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TABLE 1. Open Fractures—Gustilo Classification[1,2]

Type I	Open fracture with a skin wound <1 cm in length and clean.
Type II	Open fracture with a laceration >1 cm in length without extensive soft tissue damage, flaps, or avulsions.
Type III	Open segmental fracture with >10 cm wound with extensive soft tissue injury or a traumatic amputation (special categories in Type III include gunshot fractures and open fractures caused by farm injuries).
III_A	Adequate soft tissue coverage.
III_B	Significant soft tissue loss with exposed bone that requires soft tissue transfer to achieve coverage.
III_C	Associated vascular injury that requires repair for limb preservation.

Level II

- In type III fractures, antibiotics should be continued for 72 hours after injury or not >24 hours after soft tissue coverage has been achieved.
- Once-daily aminoglycoside dosing is safe and effective for types II and III fractures.

SCIENTIFIC FOUNDATION

In 1998, Luchette et al.[3] presented the results of the EAST Practice Management Guidelines Workgroup at the 11th Annual Scientific Assembly. These guidelines were published in 2000 on the EAST Web site. Based on a review of 54 articles published from 1975 to 1997, the workgroup offered three level I and two level II recommendations specific to choice of antibiotic coverage and duration of therapy. The original guidelines recommend preoperative dosing with antibiotics as soon as possible after the injury has been sustained. Antibiotics should be directed at gram-positive organisms with additional gram-negative coverage for type III fractures. In the presence of potential clostridial contamination, penicillin should also be initiated irrespective of fracture type.

With regard to duration of antibiotic coverage, the original guidelines recommend that antibiotics be discontinued 24 hours after successful wound closure for type I and type II fractures. For type III fractures, antibiotics should be continued for 72 hours subsequent to the injury or not >24 hours subsequent to successful soft tissue coverage of the wound.

In 1999, DeLong et al.[6] published a case series designed to compare rates of infection as well as delayed union and nonunion in patients with open fractures based on the type of wound closure performed. Ninety patients with 119 open fractures were reviewed. All patients received cefazolin plus gentamicin if severe contamination was identified. Antibiotics were discontinued 2 days to 3 days after the last surgical procedure. By using this antibiotic regimen, the rate of deep wound infection or osteomyelitis was 7% irrespective of the wound management technique. In a prospective study of 227 patients with open fractures, Vasenius et al. compared clindamycin with cloxacillin. Clindamycin was demonstrated to be effective in type I and type II fractures with infection rates of 3.3% and 1.8%, respectively. Unacceptably high rates of infection were reported in grade III fractures for both clindamycin (29.0%) and cloxacillin (51.8%). This study demonstrates the efficacy of gram-positive coverage for types I and II fractures and confirms the need for additional gram-negative coverage in higher Gustilo type fractures.[7]

In a study of pediatric patients with open forearm fractures, Greenbaum et al.[8] reported a 3% incidence of wound infections using an antibiotic regimen similar to that recommended by the original EAST guidelines. In a retrospective study by Yang and Eisler,[9] 91 patients with grade I open fractures received cefazolin. Initial surgical debridement was not performed on an emergent basis, and no infectious complications were documented in the study cohort.

Citing several advantages of fluoroquinolones (e.g., oral administration, less nephrotoxicity), Patzakis et al. performed a prospective study of intravenous ciprofloxacin in 163 patients with 171 open fractures: type I (65), type II (54), and type III (52). Patients were randomized to an antibiotic regimen of ciprofloxacin or ceftazadime/gentamicin. In types I and II fractures, the infection rate for the ciprofloxacin group and the ceftazadime/gentamicin group was 5.8% and 6.0%, respectively. For type III fractures, an unacceptably high rate of infection was demonstrated in the ciprofloxacin group (31%) compared with the ceftazadime/gentamicin group (7.7%).[10] In response to a clinical observation that delayed union and nonunion were associated with ciprofloxacin, Huddleston et al. published a laboratory investigation of the effect of this fluoroquinolone on fracture healing. Wistar rats with experimentally induced femur fractures were randomized to receive cefazolin and ciprofloxacin. A third group that received no antibiotics was used as a control group. Radiographic, histologic, and mechanical parameters all demonstrated inhibition of fracture healing in the ciprofloxacin group.[11] Similarly, using a murine model, Holtom et al.[12] demonstrated a dose-dependent cytotoxic effect of fluoroquinolones.

In 1999, Sorger et al. published a study comparing the efficacy of once-daily dosing of aminoglycosides with the traditional divided-dose regimen. Two hundred nineteen patients with type II or type III open fractures all received standard surgical treatment of their fractures. All patients received cefazolin but were randomized to receive gentamicin in divided-dose regimen (5 mg/kg divided twice daily) or once-daily (6 mg/kg). Although a statistical difference could not be demonstrated, infection rate in the once-daily patients was lower than in the patients receiving divided dose (6.7% vs. 13.6%).[13] In a preliminary study, Russel et al.[14] demonstrated safety and efficacy of once-daily aminoglycoside dosing in conjunction with cefazolin in the treatment of 16 patients with open tibia fractures.

SUMMARY

Based on a review of the literature published subsequent to their original presentation, the recommendations published in the original EAST guidelines remain valid. Antibiotics are an important adjunct to the management of

open fractures and should be initiated as soon as possible. Gram-positive coverage is recommended for type I and type II fractures. Broader antimicrobial coverage is recommended for type III fractures.

Despite the potential clinical and resource advantages of fluoroquinolones, current research does not support their use as single-agent therapy, and studies suggest these agents may impair fracture healing. When required, aminoglycosides may be prescribed in a once-daily regimen.

FUTURE INVESTIGATION

The available class I literature on fluoroquinolones has several limitations. Not all studies used an open fracture model. In addition, as these were animal studies, dosages and duration of therapy may not be equivalent to that which may be used clinically. Therefore, given the significant advantages of this class of antibiotics over aminoglycosides, research should continue in an effort to demonstrate efficacy in a clinical model. The systemic side effects of antibiotics may also be reduced through the use of local antibiotic therapy. Future research should also consider the use of this modality in the acute phase of open fracture management.

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EDITORIAL COMMENT

We congratulate and thank Drs. Hoff, Bonadies, Cachecho, and Dorlac for their review of the literature regarding prophylactic antibiotic use in open fractures, which was initially performed for the Eastern Association for the Surgery of Trauma and was posted on the Eastern Association for the Surgery of Trauma website in 2009. Their review shows that there are relatively few studies that provide meaningful data. This lack of information underscores the importance of challenging the status quo, as there is surprisingly weak scientific support for the traditions followed by many physicians in selecting prophylactic antibiotics for open fractures.

The importance of proper antibiotic selection is growing for several reasons. First, there is recognition that early antibiotic administration may be the factor that has the greatest impact on reducing infection in severe extremity injuries. This is especially important in emergency rooms that do not have orthopedists taking call, in order that appropriate antibiotics are provided before transferring the patient to a tertiary medical center.

This review correctly concludes that a first generation cephalosporin alone is appropriate prophylactic treatment for Gustilo type I and type II open fractures. However, the treating physician must be aware that there is a tendency to underestimate the severity and grade of an open fracture until the time of operative debridement, which could result in failure to administer early gram-negative coverage when appropriate.

To minimize the risk of antibiotic-related complications, judicious administration of therapeutic antibiotics for as short a period of time as possible becomes more crucial. Although there is consensus that routine use of long-term (i.e., >72 hours after surgery) prophylactic antibiotics is more likely to be harmful than beneficial, the recommendation of this report that antibiotics should be continued for "not more than 24 hours after soft tissue coverage" has little scientific foundation. Thus, some flexibility must be maintained for "surgeon judgment" to continue administration of antibiotics for 48 hours to 72 hours after coverage in select cases.

The risks of nephrotoxicity and ototoxicity with aminoglycosides are becoming more germane as the number of elderly trauma patients increases, and as many trauma patients have received, or will receive, contrast dye as part of their ongoing diagnostic and therapeutic management. This is critically important if the patient has preexisting renal compromise or if the patient has impaired renal perfusion as a consequence of systemic shock. The authors correctly report the evidence in favor of once daily dosing of aminoglycosides as an effective dosing alternative that may cause fewer side effects. The physician should alternatively consider fluoroquinolones in addition to a first generation cephalosporin for the prophylaxis of type III open fractures in elderly patients. Although there is a theoretical risk of impaired fracture healing with prophylactic administration of ciprofloxacin, the

potential morbidity from renal failure resulting from aminoglycosides is likely to be more significant.

The literature does not provide strong guidance for prophylactic antibiotic choice in penicillin-allergic patients. It is likely that vancomycin is the appropriate prophylactic antibiotic for gram-positive coverage of open fractures in these patients.

In summary, this review provides evidence-based guidelines for prophylactic antibiotics in treating open fractures. We commend the authors for their valuable contribution to physician education and patient care.

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