EAST PRACTICE MANAGEMENT GUIDELINES WORK GROUP: UPDATE TO PRACTICE MANAGEMENT GUIDELINES FOR PROPHYLACTIC ANTIBIOTIC USE IN OPEN FRACTURES

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I. Statement of the Problem

An open fracture is defined as one in which the fracture fragments communicate 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 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.[1] In general, risk of infection and incidence of limb loss correlates with the Gustilo grade (Table 1).

II. Process

Using a search methodology similar to Luchette, et al., a MEDLINE search was performed using the key words “open fractures” and “antibiotics”.[2] This search was limited to articles published subsequent to the guidelines published by Luchette. This search yielded a total of 49 articles. Sixteen (16) articles were excluded for the following reasons: technical article (6), non-English publication (5), insufficient contribution to the project (2), involved non-extremity fractures (2), animal study (1). Thirteen (13) 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 Agency for Healthcare Policy and Research of the U.S. Department of Health and Human Services as follows:

Class I Prospective, randomized controlled study

Class II Prospective, randomized, non-blinded trials. Studies in which data was 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 (19) studies were determined to be non-relevant and were excluded from further analysis; non-relevance was based on the following: poor methodology (11), inadequate study size (6), irrelevant purpose (2).

The remaining 27 articles were used to construct an evidentiary table which was analyzed to make final recommendations.

III. Recommendations

A. Level I

- Systemic antibiotic coverage directed at gram positive organisms should be initiated as soon as possible following injury.
- Additional gram negative coverage should be added for grade 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 and may have a detrimental effect on fracture healing.

B. Level II

- Antibiotics should be discontinued 24 hours after wound closure for grade I and II fractures.
- In grade III fractures, antibiotics should be continued for 72 hours following injury or not more than 24 hours after soft tissue coverage has been achieved.
- Single-dose aminoglycoside dosing is safe and effective for grade II and III fractures.

IV. Scientific Foundation

In 1998, Dr. Fred Luchette presented the results of the EAST Practice Management Guidelines Workgroup at the Eleventh Annual Scientific Assembly.[2] These guidelines were published in 2000 on the EAST website. 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 grade III fractures. In the presence of potential clostridial contamination, penicillin should also be initiated irrespective of fracture grade.

With regard to duration of antibiotic coverage, the original guidelines recommend that antibiotics be discontinued 24 hours after successful wound closure for grade I and grade II fractures. For grade III fractures, antibiotics should be

continued for 72 hours subsequent to the injury or not more than 24 hours subsequent to successful soft tissue coverage of the wound.

In 1999, DeLong 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.[3] Ninety patients with 119 open fractures were reviewed. All patients received cefazolin plus gentamicin if severe contamination was identified. Antibiotics were discontinued 2 to 3 days following the last surgical procedure. 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 compared clindamycin with cloxacillin. Clindamycin was demonstrated to be effective in grade I and grade 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 grade I and II fractures and confirms the need for additional gram negative coverage in higher grade fractures.[4]

In a study of pediatric patients with open forearm fractures, Greenbaum reported a 3% incidence of wound infections using an antibiotic regimen similar to that recommended by the original EAST guidelines.[5] In a retrospective study by Yang, 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.[6]

Citing several advantages of fluoroquinolones (e.g, oral administration, less nephrotoxicity, etc.), Patzakis performed a prospective study of ciprofloxacin in 163 patients with 171 open fractures: grade I (65); grade II (54); grade III (52). Patients were randomized to an antibiotic regimen of ciprofloxacin or ceftazadime/gentamicin. In grade I and II fractures, the infection rate for the ciprofloxacin group and the ceftazadime/gentamicin group was 5.8% and 6.0% respectively. For grade III fractures, an unacceptably high rate of infection was demonstrated in the ciprofloxacin group (31%) compared with the ceftazadime/gentamicin group (7.7%).[7] In response to a clinical observation that delayed union and nonunion were associated with ciprofloxacin, Huddleston published a laboratory investigation of the effect of this flouroquinolone on fracture healing. Wistar rats with experimentally induced femur fractures were randomized to receive cefazolin, ciprofloxacin. A third group received no antibiotics was used as a control group. Radiographic, histologic and mechanical parameters all demonstrated inhibition of fracture healing in the ciprofloxacin group.[8] Similarly, using a murine model, Holtom demonstrated a dose dependent cytotoxic effect of fluoroquinolones.[9]

In 1999, Sorger published a study comparing the efficacy of once-daily dosing of aminoglycosides with the traditional divided-dose regimen. Two hundred

nineteen patients with grade II or grade 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). While 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%).[10] In a preliminary study, Russel demonstrated safety and efficacy of once-daily aminoglycoside dosing in conjunction with cefazolin in the treatment of 16 patients with open tibia fractures.[11]

V. 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 grade I and grade II fractures. Broader antimicrobial coverage is recommended for grade III fractures.

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

VI. Future Investigation

The available class I literature on fluoroquinolones has several limitations. Not all studies utilized 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 utilized 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.

VII. References

1. Gustilo RB, Anderson JT. Prevention of infection in the treatment of 1025 open fractures of long bones. *JBJS*: 58A: 453-459, 1976.

2. Luchette FA, Bone LB, Born CT, et al. EAST Practice Management Guidelines Workgroup: Practice management guidelines for prophylactic antibiotic use in open fractures. Eastern Association for the Surgery of Trauma, http://www.east.org/tgp/openfrac.pdf, 2000.

3. DeLong WG, Jr., Born CT, Wei SY, et al. Aggressive treatment of 119 open fracture wounds. *J Trauma* 46: 1049-1054, 1999.

4. Vasenius J. Clindamycin versus cloxacillin in the treatment of 240 open fractures. A randomized prospective study. *Ann Chir Gynaecol* 87: 224-228, 1998.

5. Greenbaum B. Open fractures of the forearm in children. *J Orthop Trauma* 15: 111-118, 2001.

6. Yang EC. Treatment of isolated type I open fractures: is emergent operative debridement necessary? *Clin Orthop Relat Res* 410: 269-294, 2003.

7. Patzakis MJ, Bains RS, Lee J, et al. Prospective, randomized, double-blind study comparing single-agent antibiotic therapy, ciprofloxacin, to combination antibiotic therapy in open fracture wounds. *J Orthop Trauma* 14: 529-533, 2000.

8. Huddleston PM, Steckelberg JM, Hanssen AD, et al. Ciprofloxacin inhibition of experimental fracture healing. *JBJS* 82A: 161-173, 2000.

9. Holtom PD, Pavkovic SA, Bravos PD, et al. Inhibitory effects of the quinolone antibiotics trovafloxacin, ciprofloxacin, and levofloxacin on osteoblastic cells in vitro. *J Orthop Res* 18: 721-727, 2000.

10. Sorger JI, Kirk PG, Ruhnke CT, et al. Once daily, high dose versus divided low dose gentamicin for open fractures. *Clin Orthop* 366: 197-204, 1999.

11. Russel GV, Jr. Once daily high-dose gentamicin to prevent infection in open fractures of the tibial shaft: a preliminary investigation. *South Med J* 94: 1185-1191, 2001.

Grade I		< 1 cm wound due to bone protrusion or low-velocity penetrating injury
Grade II		> 1 cm wound with soft tissue avulsion or flap, minimal devitalized tissue, minimal contamination
Grade III		> 10 cm wound with extensive soft tissue injury
	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

Table 1: Open Fractures – Gustilo Classification[1]

UPDATE TO PRACTICE MANAGEMENT GUIDELINES FOR PROPHYLACTIC ANTIBIOTIC USE IN OPEN FRACTURES: EVIDENTIARY TABLE

First Author	Year	Reference	Class	Conclusions
Patzakis MJ	2000	Prospective, randomized, double-blind study comparing single-agent antibiotic therapy, ciprofloxacin, to combination antibiotic therapy in open fracture wounds. *J Orthop Trauma 14: 529-533*	I	Ciprofloxacin compares favorably to cefazolin/gentamicin for Type I/II open fractures. No statistically significant benefit in Type III fractures. Unacceptably high failure rate for ciprofloxacin in Type III fractures.
Huddleston PM	2000	Ciprofloxacin inhibition of experimental fracture healing. *JBJS (Am) 82: 161-173*	I	Exposure to ciprofloxacin adversely affects fracture healing by altering progression of callus formation. Ciprofloxacin is chondrotoxic in experimental fracture model.
Holtom PD	2000	Inhibitory effects of the quinolone antibiotics trovafloxacin, ciprofloxacin, and levofloxacin on osteoblastic cells in vitro. *J Orthop Res 18: 721-727*	I	Exposure to quinolone antibiotics results in a dose-dependent decrease in cell number and bone mineralization.
Dirschl DR	1998	High pressure pulsatile lavage irrigation of ntraarticular fractures: effects on fracture healing. *J Orthop Trauma 12: 460-463*	I	High-pressure pulsatile lavage impairs early new bone formation, but no difference in rate of new bone formation after 7 days.
Bhandari M	1998	High pressure pulsatile lavage of contaminated human tibiae: an in vitro study. *J Orthop Trauma 12: 479-484*	I	High-pressure pulsatile lavage produces macroscopic bone destruction at the fracture site and results in intramedullary seeding of bacteria.
Benirschke SK	2004	Wound healing complications in closed and open calcaneal fractures. *J Orthop Trauma 18: 1-6*	II	Single dose of intraoperative antibiotics sufficient in open calcaneus fractures provided wound can be completely closed.
Sorger JI	1999	Once daily, high dose versus divided low dose gentamicin for open fractures. *Clin Orthop 366: 197-204*	II	Once daily dosing of gentamicin (6 mg/kg,day) is safe and effective in prevention of wound infections in Type II/II open fractures.
Vasenius J	1998	Clindamycin versus cloxacillin in the treatment	II	Clindamycin is superior to cloxacillin in Type I/II open

		of 240 open fractures. A randomized prospective study. *Ann Chir Gynaecol 87: 224-228*		fractures. Neither clindamycin or cloxacillin is effective in Type III open fractures.
Skaggs DL	2005	The effect of surgical delay on acute infection following 554 open fractures in children. *JBJS (Am) 87: 8-12*	III	In patients who receive early antibiotics, early surgical debridement (≤ 6 hours) offers no benefit compared with debridement ≤ 24 hours.
Heier KA	2003	Open fractures of the calcaneus: soft-tissue injury determines outcome. *JBJS (Am) 85: 2276-2282*	III	High rate of infection (37%) reported in open calcaneus fractures. Early surgical stabilization not recommended. Internal fixation in high-grade open fractures not recommended.
Yang EC	2003	Treatment of isolated Type I open fractures: is emergent operative debridement necessary? *Clin Orthop Relat Res 410: 269-294*	III	Patients received cefazolin within 6 hours of injury. Intravenous cefazolin continued for at least 48 hours. No infectious complications reported. Mean time to initial surgery was 5 days.
Harley BJ	2002	The effect of time to definitive treatment on the rate of nonunion and infection in open fractures. *JBJS (Am) 16: 484-490*	III	No correlation between time to initial surgery and rate of infection / nonunion in open fractures.
Ikem IC	2001	Open fractures of the lower limb in Nigeria *Int Orthop 25: 386-388*	III	High rate of wound infection (46%) and osteomyelitis (17%) despite standardized antibiotic regimen of ampicillin, cloxacillin, gentamicin for 72 hours. Average time to initial operative debridement of 6 hours implicated as etiology of infectious complications.
Russel GV	2001	Once daily high-dose gentamicin to prevent infection in open fractures of the tibial shaft: a preliminary investigation. *South Med J 94: 1185-1191*	III	Once daily high-dose gentamicin in combination with cefazolin is effective antibiotic regimen for open fractures of the tibia.
Greenbaum B	2001	Open fractures of the forearm in children. *J Orthop Trauma 15: 111-118*	III	Infection rate comparable to that documented in adult population achieved using standardized antibiotic regiment of cephalosporin and aminoglycoside. Penicillin added for

				contamination with soil.
Folk JW	1999	Early wound complications of operative treatment of calcaneus fractures: analysis of 190 fractures. *J Orthop Trauma 13: 369-372*	III	Wound complications in patients with calcaneus fractures increased in the presence of smoking, diabetes and the presence of open fractures despite standard antibiotic regimen.
Sirkin M	1999	A staged protocol for soft tissue management in the treatment of complex pilon fractures. *J Orthop Trauma 13: 78-84*	III	Open reduction and internal fixation of complex pilon fractures in the immediate post-injury period is associated with high rate of wound infection. Recommend staged protocol to allow for more favorable soft tissue status.
DeLong WG	1999	Aggressive treatment of 119 open fracture wounds. *J Trauma 46: 1049-1054*	III	Immediate primary closure of open fracture wounds is not associated with significant increase in wound infection, delayed union or nonunion
Ikem IC	2004	The bacteriology of open fractures in Ile-Ile, Nigeria. Niger J Med 13: 359-365	III	Staphylococcus aureus is the most common wound organism isolated. Proteus and pseudomonas were the most common gram negative organisms isolated. Commonly isolated organisms demonstrated high sensitivities to commonly recommended antibiotics.
Zalvaras CG	2005	Management of open fractures. *Infectious Dis Clin NA 19: 915-929*	III (R)	Recommend early, broad-spectrum antibiotics to cover gram positive and gram negative organisms. Describes common regimen as three-day course of first generation cephalosporin and aminoglycoside. Ampicillin or penicillin should be added for anaerobic coverage in selected injuries.
Zalvaras CG	2004	Local antibiotic therapy in the treatment of open fractures and osteomyelitis. *Clin Orthop Relat Res 427: 86-93*	III (R)	Reported advantages of local antibiotic therapy include (1) high local antibiotic concentration, (2) decreased toxic effects of systemic antibiotics, (3) mechanical filler in the presence of bone loss.
Gosselin RA	2004	Antibiotics for preventing infection in open limb fractures. Cochrane Database Sys Rev, 2004	III (R)	The use of antibiotics is an effective intervention in the management of open fractures of the extremities. Specific antibiotic choice should reflect the local infectious agents.

Zalvaras CG	2003	Open fractures: evaluation and management. *J Am Acad Orthop Surg 11: 212-219*	III (R)	Recommend early initiation of broad-spectrum systemic antibiotics to cover gram negative and gram positive organisms. Describe a 3-day regimen of a first generation cephalosporin and an aminoglycoside. Supplement coverage with penicillin or ampicillin in the presence of soil contamination or associated vascular injury.
Anglen JO	2001	Wound irrigation in musculoskeletal injury. *J Am Acad Orthop Surg 6: 219-226*	III (R)	Irrigation of open fracture wound with soap solution improves removal of dirt and interferes with bacterial adhesion at low cost and low patient risk. However, clinical efficacy has yet to be established.
Luchette FA	2000	EAST Practice Management Guidelines Workgroup: Practice Management Guidelines for prophylactic antibiotic use in open fractures. *http://www.east.org/tgp/openfrac.pdf*	III (R)	Multiple studies have documented a reduction in wound infections with the use of antibiotics in patients with open fractures.
Holtom PD	1999	Introduction to adult posttraumatic osteomyelitis of the tibia. *Clin Orthop Relat Res 360: 6-13*	III (R)	Use of intravenous antibiotics at the time of injury is an important principle of care for open tibial fractures to reduce the incidence of osteomyelitis.
Templeman DC	1998	Update on the management of open fractures of the tibial shaft.	III (R)	Antibiotic therapy should be initiated as soon as possible. For Gustilo Type I fractures, cephalosporin is indicated. For Gustilo Type II/III fractures a cephalosporin / aminoglycoside regiment is recommended.

(R) – Review article