Evidence-based protocol for prophylactic antibiotics in open fractures: Improved antibiotic stewardship with no increase in infection rates

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BACKGROUND: Evidence-based guidelines for prophylactic antibiotic use in open fractures recommend short-course, narrow-spectrum antibiotics for Gustilo Grade I or II open fractures and broader gram-negative coverage for Grade III open fractures. No studies to date have assessed the impact of these guidelines on infection rates in open fractures. Infection rates before and after the new protocol implementation were examined.

METHODS: A new protocol was implemented including antibiotic prophylaxis based on grade of open fracture: Grade I/II fractures, cefazolin (clindamycin if allergy); Grade III fractures, ceftriaxone (clindamycin and aztreonam if allergy) for 48 hours. Aminoglycosides, vancomycin, and penicillin were removed from the protocol. Data for 174 femur and tibia/fibula open fractures (101 preprotocol and 73 postprotocol) were analyzed. Patients who were moribund or managed at another institution for greater than 24 hours were excluded. The National Healthcare Safety Network risk index was used to provide risk adjustment.

RESULTS: No significant differences in the study cohorts (preprotocol and postprotocol) were identified for demographics (age, 37.2 [14.8] years vs. 40.0 [17.9] years; male, 71.3% vs. 79.5%) or mechanism of injury (motor vehicle crash, 67.3% vs. 64.4%; other blunt, 28.7% vs. 32.9%; penetrating, 4.0% vs. 2.8%). After protocol implementation, the use of aminoglycoside and glycopeptide antibiotics was significantly reduced (53.5% vs. 16.4%, $p = 0.0001$). The skin and soft tissue infection rate per fracture event was 20.8% before and 24.7% after protocol implementation ($p = 0.58$). There was no statistically significant change after stratification for fracture grade, National Healthcare Safety Network risk index, or fracture site. The rate per fracture event of resistant gram-positive and gram-negative organisms (15.8% vs. 17.8%, $p = 0.84$) and methicillin-resistant *Staphylococcus aureus* (2.0% vs. 4.1%, $p = 0.65$) was not different.

CONCLUSION: Implementation of an evidence-based protocol for open fracture antibiotic prophylaxis resulted in significantly decreased use of aminoglycoside and glycopeptide antibiotics with no increase in skin and soft tissue infection rates. (*J Trauma Acute Care Surg*. 2014;77: 400–408. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic study, level IV.

KEY WORDS: Open fractures; antibiotics; prophylaxis; extremity; infection.

Open fractures constitute a major source of morbidity and mortality associated with adult trauma.[1] A serious complication associated with open fractures is the development of wound infection. To date, surgical debridement remains the priority in the treatment of open extremity fractures.[1,2] However, antibiotics are an adjunctive but important component of standard therapy. High-energy, high-grade open fractures in the lower extremities confer a higher risk of infection in comparison with open fractures of the skull, face, hands, or upper extremities.[3,4] The tibial shaft is the most commonly implicated open long bone fracture[5] and is prone to infection because of its limited soft tissue coverage and relatively poor vascularization.[1]

Overall mortality associated with open fractures has decreased given the advances in modern therapy including initial stabilization, tetanus vaccination, systemic antibiotics, prompt debridement, copious irrigation, fracture stabilization, timely wound closure, thorough rehabilitation, and adequate follow-up.[6] Wound infection prevention has been assisted by identification of independent predictors of open fracture infection as first published by Gustilo et al.[7] including (1) fracture location, (2) mechanism, (3) grade, (4) operative management, and (5) antibiotic use.

Classification of open fractures by the Gustilo grade has assisted with outcomes research and standardization of care (Table 1). The system developed by Gustilo and Anderson classifies wounds into three categories (I–III) to be determined in the operative room following debridement.[8] Further stratification of the most severe Grade III injuries permits appropriate upgrading of wounds with worsening prognosis following initial evaluation.[1] One downfall of this scoring system is its low interobserver agreement.[9]

Appropriate antibiotic prophylaxis regimen, duration, and timing for the prevention of open fracture infection are controversial (Supplemental Digital Content 1: Study review on antibiotic prophylaxis in open fractures, http://links.lww.com/TA/A459).[23–29] Recent studies using wound cultures have shown that infections of open fractures are caused by nosocomial organisms rather than contaminating organisms on presentation.[10] Most infecting organisms are gram-negative rods or gram-positive cocci.[5,8,10,11] Methicillin-resistant *Staphylococcus aureus* (MRSA) have been reported as pathogenic organisms implicated in open fracture infections in hospital outbreaks.[10,12]

Recent evidence-based guidelines provide Level I recommendation for short-course, prophylactic antibiotics with gram-positive coverage for trauma patients with Gustilo Grade I or II open fractures.[2] Broader gram-negative coverage for Grade III fractures and high-dose penicillin for possible contamination with clostridium (such as farm-related injuries) are recommended.

Although narrow-spectrum antimicrobial prophylaxis is recommended by evidence-based guidelines, many trauma centers use broad-spectrum antibiotics. There is substantial morbidity related to the use of broad-spectrum antibiotics in the open fracture population, including potential acute kidney injury with the use of aminoglycosides, development of antimicrobial resistance, and superinfections with multidrug-resistant (MDR) organisms.

These guidelines propose preoperative prophylactic antibiotics for open fractures to be started "as soon as possible after injury." Initiating antibiotic prophylaxis within 3 hours of injury has been shown to reduce infection rates from 7.4% to 4.7%.[13,14] Regarding duration, the guidelines make a Level III recommendation for antibiotics to be discontinued 24 hours after wound closure for Grade I and II fractures. For Grade III fractures, the guidelines recommend antibiotics to be continued for the earliest of either 72 hours after the time of injury or 24 hours after soft tissue coverage of the wound. Zalavras et al.[15] recommend an initial 3-day course supplemented by additional 3-day courses at the time of any subsequent procedures.

There is a concern that narrowed spectrum of activity and decreased duration of antimicrobial prophylaxis could result in higher rates of skin and soft tissue infections after open fracture. No studies to date have assessed the impact of these guidelines on infection rates in open fractures.

TABLE 1. Gustilo Classification System for Open Fractures and Rates of Infection

Open Fracture type	Characteristics of Gustilo Grade Open Fracture	Infection Rate	Amputation Rate
Grade I	Clean wound smaller than 1 cm in diameter, simple fracture pattern, no skin crushing	0–2%	0%
Grade II	A laceration larger than 1 cm but without significant soft tissue crushing, including no flaps, degloving, or contusion. Fracture pattern may be more complex.	2–7%	0%
Grade III	An open segmental fracture or a single fracture with extensive soft tissue injury. Also included are injuries older than 8 h. Type III injuries are subdivided into three types.		
Grade IIIA	Adequate soft tissue coverage of the fracture despite high-energy trauma or extensive laceration or skin flaps.	5–10%	2.5%
Grade IIIB	Inadequate soft tissue coverage with periosteal stripping. Soft tissue reconstruction is necessary.	10–50%	5.6%
Grade IIIC	Any open fracture that is associated with an arterial injury that requires repair.	25–50%	25%

The objective of this study was to examine infection rates before and after implementation of an evidence-based protocol with decreased use of aminoglycoside and glycopeptide antibiotics for open extremity fractures. The study hypothesis was that implementation of an evidence-based narrow-spectrum antimicrobial prophylaxis protocol for open fractures would be noninferior to the broad-spectrum antimicrobial prophylaxis protocol.

PATIENTS AND METHODS

An evidence-based protocol was initiated for antibiotic prophylaxis in adults with open extremity fractures at a single American College of Surgeons–verified Level I trauma center. The protocol (Table 2, Fig. 1) implemented in June 2008 specified antibiotic prophylaxis based on grade of open fracture, early orthopedic consultation, standardized wound inspection and dressing application to limit exposure/contamination, and tetanus prophylaxis. By protocol, Grade I and II fractures were to receive cefazolin for 48 hours or clindamycin for penicillin allergy. Grade III fractures were to receive ceftriaxone for 48 hours or

TABLE 2. The University of Michigan Guidelines for Initial Antimicrobial Prophylaxis of Adult Trauma Patient With Open Extremity Fractures

Grade of Open Fracture	Recommended Antibiotic	Alternate if Penicillin Allergy
I or II	Cefazolin 1–2 g load then 1 g intravenously (IV) every 8 h for 48 h	Clindamycin 900 mg IV every 8 h for 48 h
	Preprotocol: same	Preprotocol: vancomycin 1 g IV every 12 h for 48 h
III	Ceftriaxone 1 g IV every 24 h for 48 h	Clindamycin 900 mg IV every 8 h and
	Preprotocol:	Aztreonam 1 g IV every 8 h for 48 h
	Cefazolin 1–2 g load then 1 g IV every 8 h for 48 h	Preprotocol:
	Gentamicin 1–2 g/kg (based on ideal body weight IV every 8 h for 48 h	Vancomycin 1 g IV every 12 h for 48 h instead of cefazolin
	Special open fracture conditions:	Clindamycin 900 mg IV every 8 h instead of penicillin G
	Fracture associated with a farm environment	
	Extensive severe soft tissue crush injury	
	Vascular compromise	
	Add penicillin G 4 million U IV every 4 h for 48 h	

clindamycin and aztreonam for penicillin allergy. Aminoglycosides, vancomycin, and penicillin were removed from the algorithm. All patients underwent emergent orthopedic surgical intervention for irrigation and debridement within 8 hours of injury.

A retrospective review via the trauma registry identified all adults with open femur and open tibia and/or fibula fractures (tibia/fibula) admitted from January 2006 through June 2010. Patients who were moribund or who were managed at another institution for greater than 24 hours were excluded. Additional data were then prospectively collected from the electronic medical record for microbiology, risk stratification, and compliance with antibiotic protocol. The University of Michigan Institutional

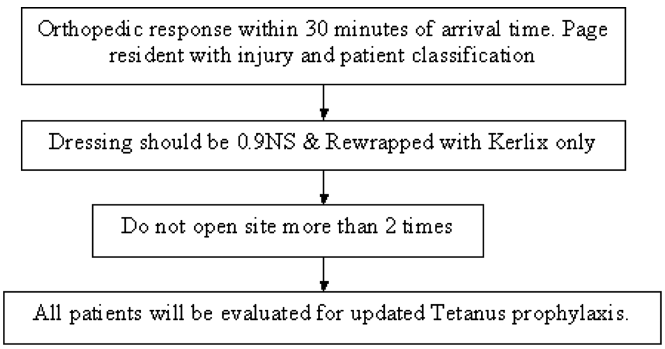

Figure 1. The University of Michigan guidelines for the initial evaluation of adult trauma patient with open extremity fractures.

Review Board approved this study (HUM00016446) with waiver of consent. A total of 174 femur and tibia/fibula open fractures (101 preprotocol and 73 postprotocol) were analyzed. Statistical analysis was performed with Excel (Microsoft Corporation, Redmond, WA) and QuickCalcs (GraphPad Software, San Diego, CA). Demographics were collected and analyzed in preprotocol and postprotocol cohorts including age, sex, mechanism of injury, and disposition. Comparisons were performed using a Fisher's exact test, with two-tailed $p < 0.05$ used to assess statistical significance between groups.

A positive surgical site infection (SSI) was defined by documentation of diagnosis of wound infection made by clinical signs and symptoms and either a positive wound culture or treatment with broad-spectrum antibiotics. Infection rate was calculated as the percentage of patients with positive SSI of all open femur or open tibia/fibula fracture events. Patients with an open tibia and open fibula fracture on the same extremity were counted as one fracture event. Patients with an open tibia/fibula fracture and an open femur fracture were counted twice given two sites at risk for SSI. Patients with both tibia/fibula and femur open fractures on the same extremity who underwent an above-the-knee amputation were counted once given the single site for SSI risk.

Infection rates were stratified by Gustilo fracture grade, National Healthcare Safety Network (NHSN) risk index, fracture site, and resistant organisms, specifically by MRSA. Infection rates with MRSA, with one or more resistant organisms, and with total resistant organisms were calculated per total fracture events and per SSI. Infection rates with at least one MDR organism were calculated per SSI.

We examined changes in MDR, extensively drug resistant (XDR), and pandrug-resistant (PDR) organisms according to standardized international terminology created by the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention (CDC).[16] Criteria for defining MDR was nonsusceptibility to one or more agents in three or more antimicrobial categories. Multidrug resistance took into account extrinsic resistance to antimicrobials; therefore, if an organism had intrinsic resistance to an antimicrobial category (for example, *Enterobacter cloacae* to non–extended-spectrum cephalosporins), this category was not counted toward the number of categories to which the bacterial isolate was nonsusceptible. Indeterminate responses to antimicrobials were counted as nonsusceptible. MRSA was considered MDR by definition. For organisms not listed in the European Centre for Disease Prevention and Control/CDC standardized terminology, MDR was defined as resistance to three or more classes of antimicrobials. Pathogens that were nonsusceptible to at least two but less than three antimicrobial classes were defined as "resistant, non-MDR." MDR organisms that were susceptible to only two or fewer antimicrobials were defined as XDR or PDR if susceptible to no antimicrobials.

The NHSN risk index was used to provide risk adjustment of SSI rates.[17] The NHSN risk index is composed of three variables as follows: the American Society of Anesthesiologists score as a subjective assessment of preoperative health of the patient (scores 3, 4, or 5 indicating severe systemic disease that is not incapacitating, incapacitating disease that is a constant threat to life, or a moribund patient who is not expected to live 24 hours with or without surgery, respectively); wound classification (contaminated/dirty); and open reduction procedure duration (>75th percentile or >137 minutes). Each factor represents 1 point with a risk index range of 0 (low risk) to 3 (high risk). Patients with open fractures who did not undergo open reduction, such as those with closed reductions or with amputations, were excluded from the NHSN risk index calculations.

Compliance with the open fracture antibiotic protocol was determined by chart review for type and duration of antibiotic regimen. The use of aminoglycosides and glycopeptides (including vancomycin, gentamicin, tobramycin, and amikacin) was noncompliant and calculated per fracture event before and after protocol implementation.

TABLE 3. Demographic and Baseline Characteristics of Study Population

	Preprotocol	Postprotocol	*p*
N	101	73	
Age, mean (SD), y	37.2 (14.8)	40.0 (17.9)	0.58
Sex, male, n (%)	72 (71.3)	58 (79.5)	0.29
Mechanism of injury			
Motor vehicle crash	68 (67.3%)	47 (64.4%)	0.75
Automobile	42	29	
Motorcycle	20	17	
Other motor vehicles*	6	1	
Other blunt trauma	29 (28.7%)	24 (32.9%)	0.62
Fall	15	11	
Motor vehicle crash vs. pedestrian	6	7	
Blunt assault	2	0	
Otherwise specified blunt**	4	6	
Bicycle	2	0	
Penetrating trauma	4 (4.0%)	2 (2.7%)	1.00
Gunshot wound	4	0	
Other penetrating	0	2	
Site of injury			
Tibia/fibula	76 (75.2%)	48 (65.8%)	0.18
Fibula only	7 (5.9%)	4 (5.5%)	0.76
Femur	19 (18.8%)	21 (2.9%)	0.15
Gustilo grade, n (%)			
I	27 (21.8)	15 (20.5)	0.47
II	17 (16.8)	20 (27.4)	0.27
III	37 (36.6)	20 (27.4)	0.26
IIIA	13 (35.1)	5 (25.0)	0.56
IIIB	11 (29.7)	6 (30.0)	1.00
IIIC	9 (24.3)	6 (30.0)	0.76
III-unspecified	4 (10.8)	3 (15.0)	0.69
Unspecified	22 (21.8)	18 (24.7)	0.72
Disposition			
Home	46.0	45.2	
Care facility	49.5	50.7	
Transfer	2.0	1.4	
Death	2.0	2.7	

*Other motor vehicles include all-terrain vehicle, plane, boat, snowmobile, tractor, golf cart.
**Otherwise specified blunt trauma includes struck by falling object and horse accidents.

Statistical Analysis

Differences in baseline characteristics and SSI rates were examined. Continuous data were analyzed using the Wilcoxon nonparametric rank-sum test. Categorical data were analyzed using χ^2 tests of association or the Fisher's exact test where appropriate. Normality was assessed by the Kolmogorov-Smirnov test to ensure that the sample distribution was normal. The baseline characteristics of the patients were not different, so propensity matching and regression analyses were not used. A $p < 0.05$ was considered statically significant. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

No significant differences in the study cohorts (preprotocol and postprotocol) were identified for baseline characteristics, including demographics (age, 37.2 [14.8] years vs. 40.0 [17.9] years; male, 71.3% vs. 79.5%), mechanism of injury (motor vehicle crash, 67.3% vs. 64.4%; other blunt, 28.7% vs. 32.9%; penetrating, 4.0% vs. 2.8%), or disposition (home, 46.0% vs. 45.2%; care facility, 49.5% vs. 50.7%; transfer, 2.0% vs. 1.4%; death, 2.0% vs. 2.7%) (Table 3).

After protocol implementation, the use of aminoglycoside and glycopeptide antibiotics was significantly reduced (53.5% vs. 16.4%, $p = 0.0001$). The SSI rate per fracture event of 20.8% for the preprotocol and 24.7% for the postprotocol cohort was not significantly different ($p = 0.58$). There was no statistically significant difference in SSI rates after stratification for fracture grade or fracture site (Table 4). Furthermore, no significant differences in SSI were identified with risk stratification based on NHSN risk index (Table 5). No difference in the SSI rate due to MRSA or other resistant pathogens was identified.

The SSI rate per fracture event related to resistant gram-positive and gram-negative organisms (defined by culture and antibiotic use) was not different (15.8% vs. 17.8%, $p = 0.84$) after protocol implementation (Table 6). There was no difference in the MRSA rate per fracture event after protocol implementation (3.0% vs. 2.7%, $p = 1.0$). Our institutional MRSA SSI rates are low related to a number of infection control strategies aimed at prevention of MRSA hospital-acquired infections. Bacterial organisms cultured from fracture sites in SSI patients were not different comparing before with after protocol implementation (Table 6). We did not identify any increase in specific pathogens with the new protocol.

Resistant pathogens constituted a significant portion of the causative pathogens of SSIs (16 of 21, 76.2% preprotocol; 13 of 18, 72.2% postprotocol; $p = 1.0$); however, there was no difference in SSI with one or more resistant pathogens in the preprotocol and postprotocol cohorts (8 of 21, 38.1%; 6 of 18, 33.3%; $p = 1.0$). Further stratification for multidrug resistance in SSI was not different (4 of 21, 19.0%; 4 of 18, 22.2%; $p = 1.0$). MRSA was the most represented causative pathogen and was not different in occurrence among MDR SSI before and after protocol implementation (3 of 4 vs. 2 of 4, $p = 0.52$). The second most common pathogen in MDR infections was methicillin-resistant coagulase-negative staphylococci, with other pathogens

TABLE 4. Results of Aminoglycoside/Glycopeptide Use and SSI Rate Stratified by Gustilo Grade and by Fracture Site

	Preprotocol Rate (per Fracture Event)	Postprotocol Rate (per Fracture Event)	*p*
Aminoglycoside/ glycopeptide use	53.5% (54/101)	16.4% (12/73)	0.0001
SSI Rate	20.8% (21/101)	24.7% (18/73)	0.58
By Gustilo Grade			
Gustilo Grade I	29.4% (5/17)	6.7% (1/15)	0.09
Gustilo Grade II	8% (2/25)	20% (4/20)	0.24
Gustilo Grade III	29.7% (11/37)	40% (8/20)	0.62
Not graded	13.6% (3/22)	27.8% (5/18)	0.09
By site			
Tibia/fibula	22.0% (18/82)	25% (13/52)	0.68
Femur	15.8% (3/19)	23.8% (5/21)	0.53

TABLE 5. Results of Aminoglycoside/Glycopeptide Use and SSI Rate Stratified by NHSN Risk Index; Resistant Organism Infection Rates

	Preprotocol Rate (per Fracture Event)	Postprotocol Rate (per Fracture Event)	*p*
Aminoglycoside/glycopeptide use	53.5% (54/101)	16.4% (12/73)	0.0001
SSI rate per total fracture events	20.8% (21/101)	24.7% (18/73)	0.58
SSI rate per 100 operations	20.8% (21/100)	24.6% (25/100)	0.61
By NHSN risk index			
NHSN risk index 0	0% (0/0)	0% (0/0)	n/a
NHSN risk index 1	0% (0/1)	0% (0/3)	1.0
NHSN risk index 2	13.3% (8/60)	28.2% (11/39)	0.07
NHSN risk index 3	21.7% (5/23)	11.8% (2/15)	0.68
Not scored	47.1% (8/17)	35.7% (5/9)	0.72
Resistant organisms*			
Patients with resistant organism(s) SSI per total fracture events	7.92% (8/101)	8.21% (6/73)	1.0
Resistant organisms total/ total fracture events	15.8% (16/101)	17.8% (13/73)	0.84
Resistant organism(s) (≥1)/SSI	38.1% (8/21)	33.3% (6/18)	1.0
Resistant organisms (total number)/SSI	76.2% (16/21)	72.2% (13/18)	1.0
MDR organisms/SSI	19.0% (4/21)	22.2% (4/18)	1.0
MRSA			
Patients with MRSA SSI per total fracture events	2.97% (3/101)	2.74% (2/73)	1.0
MRSA/SSI	14.2% (3/21)	11.1% (2/18)	1.0

*Resistant organisms include both MDR and "resistant, non-MDR" pathogens. MDR is defined as resistance to three or more classes of antimicrobials per standardized terminology.[16] MRSA is MDR by definition. Resistant organisms are defined as nonsensitivity to at least two antimicrobial classes. Pathogens that are nonsusceptible to at least two but less than three antimicrobial classes are defined as "resistant, non-MDR."

The NHSN risk index (three variables, 1 point each: American Society of Anesthesiologists score (3, 4, or 5); wound classification (contaminated, dirty); and procedure duration (>75th percentile, minutes); risk index rage of 0 [low risk] to 3 [high risk]) was used to provide risk adjustment of SSI rates.

n/a, not applicable.

TABLE 6. Bacterial Isolates Cultured From Fracture sites

Species	Total Positive Cultures by Species	
	Preprotocol (42 Isolates)	Postprotocol (40 Isolates)
Gram-positive bacteria	28/42 (66.7%)	24/40 (60.0%)
Staphylococci species		
MSSA	1	1
MRSA	3 (MDR)	2 (MDR)
MSCNS	2 (1 resistant, non-MDR)	2
Methicillin-resistant coagulase-negative staphylococci	3 (2 MDR)	2 (MDR)
Nongroupable *staphylococci*	3	1
Streptococci species		
G streptococci	1	1
Unspecified *streptococci*	0	1
Enterococcus species		
Enterococcus, not VRE	4	5
Enterococcus, VRE	1	2 (resistant, non-MDR)
Bacillus species	4	1
Clostridium species	2 (1 resistant, non-MDR)	1
Diphtheriae species	2	0
Unspecified anaerobic GPC	1	4
Unspecified GPR	1	1
Gram-negative bacteria	14/42 (33.3%)	16/40 (40.0%)
Pseudomonas species	3	5 (2 resistant, non-MDR)
Enterobacter species	2 (1 resistant, non-MDR)	3 (1 resistant, non-MDR)
Proteus mirabilis	2 (1 MDR)	0
Serratia species	1 (resistant, non-MDR)	0
Alcaligenes faecalis	0	2 (1 MDR; 1 resistant, non-MDR
Escherichia coli	1	1
Stenotrophomonas maltophilia	1	1
Klebsiella species	1	0
Providencia stuartii	1	0
Acinetobacter species	0	1
Achromobacter xylosoxidans	0	1 (MDR)
Unspecified GN bacteria	2	2
Yeast/fungus		
Candida species	0	1
Fusarium species	0	1
Unspecified yeast	0	1

MSSA, Methicillin-sensitive staphylococcus aureus; MSCNS, Methicillin-sensitive coagulase-negative staphylococci; VRE, Vancomycin-resistant enterococcus; GPC, gram-positive cocci; GPR, gram-positive rod; GN, gram-negative.

being present in only one case. No XDR or PDR organisms were identified.

DISCUSSION

The optimal antibiotic regimen in the prevention of infection in open fractures is still controversial. Implementation of an evidence-based open fracture antibiotic protocol (including a short course of narrow-spectrum antibiotics and excluding glycopeptides or aminoglycosides) for open fractures antibiotic prophylaxis initiated by the trauma team at the time of injury identification resulted in significantly decreased use of aminoglycoside and glycopeptides antibiotics. There was no increase in skin and soft tissue infection rates. This finding held true after risk stratification for fracture grade, fracture site, and NHSN risk index.

Importantly, there was no increase in SSIs caused by gram-negative bacteria or resistant pathogens, including MDR pathogens or MRSA. In this context, improved antibiotic stewardship was demonstrated considering risks such as nephrotoxocity and the emergence of antimicrobial resistance with glycopeptide and aminoglycoside use.[18,19]

The most significant limitations of this study are consistent with a single-institution, retrospective analysis. This study may be limited by sample size and by several possible confounders. These include patient comorbidities, time admitted to hospital after injury, time to and extent of debridement, use of internal reduction techniques (such as nail reaming), time to wound closure, type of wound closure, vascular or other concomitant injuries, and trauma injury severity. The weakness of the microbial culture data may be caused by time to culture or technique. This study also does not

take into account the effect of antibiotic beads, which were used occasionally in our study population. The effect of their use was not measured given the small sample size.

Interobserver reliability in assessing fracture class and wound infection may also affect the results. In addition, studies suggest that the reliability and reproducibility of the classification of open fractures may be improved upon from the Gustilo grade as suggested by recent literature that further assesses skin injury, muscle injury, arterial injury, contamination, and bone loss.[20]

As with any study examining clinical care protocols, compliance can be difficult to assess. There were several aspects of protocol compliance that were not measured including timing of orthopedic consultation, wound management, and tetanus prophylaxis. We were, however, able to measure the compliance with antibiotic use.

In our study, we report a significantly higher infection rate than in many previous studies, but our reported rates are similar to a recent study that reported SSI rates of 21% for Type II fractures and 29% for Type III open fractures[21] and another study that reported a 21.4% SSI rate.[22] Furthermore, most of our patients were in the high NHSN risk index group. This may also be related to our study methodology and the SSI definition that was used. We did not use a standard CDC SSI definition because it was a retrospective study, and we wanted to be certain to use the same definition over the two periods of the study. If antibiotics were started for any wound-related reason, an SSI was tallied, which could result in the overestimation of the true SSI rate. Furthermore, our analysis also used a measure of infection per fracture site. Two fracture sites on a single patient were counted as two separate fractures given the risk for SSI at each site, thus increasing the reported SSI rate in this study. This is consistent with the CDC SSI rate national calculation standard, which standardizes SSI rates per 100 operations, thus counting each open fracture site and repair as a separate site at risk for SSI. Despite this overall higher infection rate, we found no difference in the SSI rates or in the SSI microbiology comparing preprotocol and postprotocol periods. Significantly decreased use of glycopeptide and aminoglycoside antibiotics was confirmed in this study.

CONCLUSION

Implementation of an evidence-based protocol (short course of narrow spectrum antibiotics, excluding glycopeptides or aminoglycosides) for open fracture antibiotic prophylaxis resulted in significantly decreased use of aminoglycoside and glycopeptide antibiotics with no increase in skin and soft tissue infection rates. Additional large-scale studies are warranted to validate these findings and further elucidate the potential benefits of our current clinical care guidelines that are consistent with improved antimicrobial stewardship.

AUTHORSHIP

All authors have contributed significantly to the study including design, data acquisition, analysis, interpretation of data, and manuscript preparation and review.

DISCLOSURE

The authors declare no conflicts of interest.

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DISCUSSION

Dr. Hans-Christoph Pape (Pittsburgh, Pennsylvania): This manuscript is based on observations about increased risks of local and inflammatory infections associated with major fracture in a major Level I trauma center. The senior author is an internationally-renowned expert for the diagnosis and management of surgical infections and has authored and coauthored numerous publications on this topic.

In 2008, the unit changed its antibiotic management of open extremity fractures. In the revised protocol, they have relied on evidence-based protocol published by EAST. This study documents consecutively treated patients before and after implementation of this protocol. The authors include a complete literature review on the management of open fractures to improvement judgment of their findings.

A total of 174 fractures were documented retrospectively, among which 101 were pre-protocol. The authors also performed a very thorough assessment for fracture and soft tissue classification based on the Gustilo-Anderson classification.

According to their documentation, motor vehicle accidents were the cause of injury in most patients. They also elaborate on the rates of antibiotic treatments before and after implementation of the antibiotic protocol.

In summary, this is a well-conducted, Level IV evidence study. The classification of injuries appears to have been performed in a thorough fashion. The questions that I have for the author are as follows:

First, what was the protocol for prophylaxis and treatment of soft tissue infections prior to 2008?

Second, in your protocol, the orthopedic resident has to be in the ER within 30 minutes of arrival of the patient for assessment of the injury, serving as the basis for treatment. Who-resident or attending physician, ortho or general surgery-is assigned to grade the severity of the soft tissue injury? And at what stage after admission is this grading performed, ER versus OR?

Third, according to your definition of infection both clinical signs and a change to broad-spectrum antibiotics are included. How is this decision made to switch to a more aggressive antibiotic regime?

Fourth, in your results there was a 36% rate of third-degree open fracture before the change in protocol versus 27% rate of third degree open fracture afterwards. How do you think this might have affected your results in terms of a generally similar or slightly not-significantly-improved infection rate observed in your patient population?

I would like to thank the AAST for the opportunity to review this important manuscript.

Dr. Philip S. Barie (New York, New York): Did you perform a power calculation? I would surmise that there is not a possibility but a certainty of a Type II error in this study, particularly with the paucity of Gustilo-Anderson Type III fractures, which is where all of the risk is really concentrated.

Second, I infer from your data tables that you performed a multiplicity of two-by-two contingency table analyses and wonder whether it would have been more appropriate to have performed multi-group contingency table analyses.

You are going to degrade what little power you have by doing repetitive two-by-two analyses, it seems to me. Thank you.

Dr. Carl J. Hauser (Boston, Massachusetts): Unlike my friend Dr. Barie, I rise to support the results of this study. And I would like to thank the authors for beginning to drive a stake through the heart of aminoglycoside use in open fractures. They haven't done it completely but it's a beginning!

Aminoglycoside use in open fractures is based on a single paper done by Patzakis in 1974 and, if you actually read that study carefully, the results don't match the conclusions. In fact, the results of that prospective Level I study only support the use of first generation cephalosporins in open fractures. The study shows no benefit for gram negative coverage–none, zero. The conclusions just don't match the data.

But like Phil Barie, I am going to ask you: you used gram positive coverage only in Gustilo I's and II's and you used some gram negative coverage in Gustilo III's. Do you now plan to extend the use of gram positive coverage only to Gustilo III injuries?

Secondly, all your study has examined is fracture-related injuries. Every study in the literature on this subject examines fracture-related infections and no one has ever looked at the patients for nosocomial secondary infections. Did your study follow nosocomial infections? It looks like you could easily have studied them in this patient cohort. After all, isn't the frequency and type of nosocomial infection like resistant gram negative pneumonia and *C. difficile*-associated colitis just as critical in sick trauma patients as whether they get osteomyelitis? I think it's high time for us to recognize that antibiotic management of fractures can't be studied in a vacuum. We need to study the overall effects of fracture-related antibiotic use on more global patient outcomes in future multi-center studies if we are to make any difference at all to their care.

Very nice work. Thank you very much.

Dr. Hee Soo Jung (Ann Arbor, Michigan): Thank you very much for all your questions and comments.

To start off with Dr. Pape's questions: First, regarding the 2008 pre-protocol, antibiotic regimen specifically included clindamycin to replace cefazolin for penicillin allergies and gentamycin for Grade III fractures. There was no specific care protocol before 2008 delineating time of orthopedic surgery evaluation and care and tetanus prophylaxis.

Regarding who assesses the fracture grade... While the described Gustilo open fracture grading is in the operating room after debridement, we found divergent locations documented in the medical record. For our study it includes both grading in the operating room and if not available documentation of grading before and after debridement.

It is our usual practice to begin antibiotics based on the orthopedic resident initial assessment, in consultation with the orthopedic attending surgeon. We then to tailor further antibiotic management to operative assessment of the open fracture wound.

Regarding the third question about how the decision was made to switch antibiotics, there is no specific institutional protocol for treatment of wound infections related to open fractures. Empiric antibiotics were selected based on severity of infection and then tailored to culture data and all infections. In ICU patients MRSA and VRE surveillance is performed weekly. Patients with MRSA colonization were also administered anti-MRSA antimicrobials.

In regard to the fourth question regarding the high open fracture Grade III injury rate, while this was not statistically significant this could have led to improved post-protocol infection rates leading to a Type II error. A larger study with more power would be necessary to further elucidate this relationship.

In reply to Dr. Barie's question regarding the power analysis, again, this is a descriptive study. The power analysis for a prospective study, with our results as a pilot, predicts a need for about 1,500 patients. With historical cohort data, our sample would have to be about 3,000 patients. So this is an underpowered descriptive study of the current state of antimicrobial use in open fractures.

And thank you very much for your comments on multigrade analysis. The analysis was done with two-by-two Fisher's exact tests and we will undergo further review of this data.

Dr. Hauser, thank you, again, for your comments and questions. We have not yet considered limiting the antibiotic coverage to just Grade III Gustilo fracture rates but we will definitely take that into consideration.

We have not studied yet the other nosocomial infections related to our patients but we do have the data. You bring up a great point and we should look into that.

In conclusion, I think these types of questions raise further need for larger studies in this arena. Again, I would like to thank all of you for allowing me the privilege of speaking today.