What is the Rate of Methicillin-resistant *Staphylococcus aureus* and Gram-negative Infections in Open Fractures?

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Abstract

Background There have been increasing reports of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the community, but it is unclear whether infectious organisms in open fracture infections have changed and if our current regimen of antibiotic prophylaxis is therefore obsolete.

Questions/Purposes We determined the recent incidence of MRSA and Gram-negative organism infections after open fractures.

Methods We performed a retrospective cohort study on 189 patients with 202 open fractures treated from 2009 to 2010. During the followup, patients were evaluated for signs of infection using the Centers for Disease Control and Prevention criteria. We determined the organisms using

routine microbiology culture. The minimum followup was 3 months (median, 47 months; range, 3–108 months).

Results Of the 202 open fractures, 20 (10%) developed infections. The most common organism was *Staphylococcus*, whereas five (25%) of those infected were positive for MRSA, and 11 (55%) of those with infection were cultured for at least one Gram-negative organism. Six (30%) open fractures had infections that grew out multiple organisms. The incidence of MRSA infections in our open fracture population was 2.5%.

Conclusions There is a high incidence of MRSA and Gram-negative infections after open fractures, which may indicate that current antibiotic regimens need to be changed.

Level of Evidence Level IV, retrospective case-series. See the Guidelines for Authors for a complete description of levels of evidence.

Each author certifies that he or she, or a member of his or her immediate family, has no funding or commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request. Each author certifies that his or her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research. This work was performed at the University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

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Introduction

Guidelines for managing open fractures were first established in 1976 by Gustilo and Anderson [9]. At that time, soft tissue injuries were classified into three types: Type I fractures were clean wounds with less than 1-cm opening with minimal soft tissue injury, Type II were moderately contaminated wounds that were longer than 1 cm and had moderate soft tissue injury, and Type III wounds were severely contaminated with extensive soft tissue injury with or without vascular damage. Gustilo et al. [11] determined that Type III open fractures needed further clarification and thus divided Type III open fractures into three additional categories. Type IIIA open fractures had extensive soft tissue injury, but soft tissue and periosteal coverage could be obtained. In contrast, Type IIIB open

fractures had extensive periosteal stripping and wound contamination that would require a flap for covering the fracture site. Finally, Type IIIC open fractures were fractures with concomitant vascular injuries that required repair. These classifications were used to dictate treatment algorithms.

The initial goals of treating open fractures are to stabilize the fracture and prevent subsequent infection. The incidence of infection reportedly correlates with the type of open fracture, in which Type I fractures have an infection rate of 0% to 2%, Type II fractures 2% to 7%, and Type III fractures 10% to 25% [10]. Specifically, Type IIIA fractures have an infection rate of 7%, Type IIIB fractures have an infection rate of 10% to 50%, and Type IIIC fractures have the highest infection rate of 25% to 50% with a rate of amputation greater than 50% [4, 5, 9–11, 18, 21].

To prevent these infections, prophylactic antibiotics are typically chosen based on reports of the prevalent infectious organisms. The initial antibiotic guidelines for infection prophylaxis for open fractures encouraged the use of penicillin and streptomycin or cefalotin, a first-generation cephalosporin, with the intention of preventing Gram-positive organism infections [17]. Later studies reported the increased prevalence of Gram-negative organisms in open fracture infections, so a treatment algorithm was established in the 1980s based on the open fracture type [8]. Gustilo and Anderson [9] recommended that 2.0 g cefamandole, a second-generation cephalosporin, or cefazolin, a first-generation cephalosporin, be used for Type I fractures, and the antibiotic should be dosed 1.0 g every 6–8 hours for 48–72 hours. For Type II or III fractures, it was recommended that an aminoglycoside such as tobramycin be added as antibiotic prophylaxis at the initial dosing of 1.5 mg/kg and then continued over 10 days [11]. Penicillin was added as another antibiotic for prophylaxis if the open fracture occurred on a farm. Since those initial studies were conducted, few studies [3, 12, 16, 23] have been performed to determine if the infectious organisms and antibiotic sensitivities have changed over time and if our current regimen of antibiotic management is efficacious. The main organisms isolated from open fracture infections included methicillin-sensitive *Staphylococcus aureus* (*S. aureus*) (23% [3]; 35% [23]), coagulase-negative *Staphylococcus* (11% [12]) and Gram-negative organisms (31% [3]; 48% [12], 17% [16]). Several recent studies [2, 20] report an increasing incidence of methicillin-resistant *S. aureus* (MRSA) in the community setting but did not specifically examine the incidence of MRSA in all open fractures.

We therefore conducted this study to confirm previous findings by determining: (1) the incidence of MRSA infections after open fractures; and (2) the incidence of Gram-negative infections after open fractures.

Patients and Methods

We performed a retrospective cohort study that identified 198 consecutive patients with 211 open fractures treated surgically from 2009 to 2010 at two Level I trauma centers. Nine patients had multiextremity open fractures and four patients had open fractures on three extremities. We excluded patients if their open fracture was initially treated at another institution and subsequently transferred to our institution for secondary care or fracture fixation. During the study period, six patients were lost to followup and three patients died. Thus, we reviewed 189 patients with 202 open fractures. Of the patients remaining for followup, there were a total of 111 males and 78 females with an average age of 45 years and average body mass index of 30 kg/m² (Table 1). Patients were followed for a minimum of 3 months (median, 47 months; range, 3–108 months). No patients were recalled specifically for this study; all data were obtained from medical records.

There were 93 (46%) right open fractures, 105 (52%) left open fractures, and four (2%) bilateral open fractures (Table 1). The Gustilo and Anderson classification was unknown in 56 fractures (28%), Type I for 48 fractures (24%), Type II for 28 fractures (14%), Type IIIA for 32 fractures (16%), Type IIIB for 31 fractures (15%), and Type IIIC for seven fractures (3%). All patients with open fractures received antibiotics, and some patients received more than one at the time of admission. Of the patients with open fractures, 160 (79%) received cefazolin, 45 (22%) received gentamicin, nine (5%) received vancomycin, 12 (6%) received clindamycin, 12 (6%) received ampicillin-sulbactam, eight (4%) received cefoxitin, six (3%) received ciprofloxacin, three (2%) received piperacillin-tazobactam, one (1%) received cefepime, one (1%) received cefuroxime, and no patients received penicillin.

Patients who sustained infected open fractures had mostly lower extremity injuries with 10 patients (50%) with AO classification 43, four patients (20%) with AO classification 42, one patient (5%) with AO classification 41, one patient (5%) with AO classification 33, and two patients (10%) with AO classification 8. Only two patients (10%) sustained a humerus fracture (AO classification 12). In terms of initial antibiotic given at the time of admission, 17 (85%) received cefazolin, seven (35%) received gentamicin, one (5%) received vancomycin, three (15%) received ampicillin-sulbactam, one (5%) received cefoxitin, two (10%) received ciprofloxacin, and one (5%) received piperacillin-tazobactam. No patients received clindamycin, penicillin, cefepime, or cefuroxime.

With regard to operative timing, 114 (56%) patients had surgery within 6 hours of ambulance arrival, 83 (41%) had surgery within 6–24 hours after arrival, and five (3%) had surgery greater than 24 hours after admission. All patients

Table 1. Demographic, surgical, and clinical data from open fracture patients comparing those who were and were not infected

Data	All open fractures	Infected	Not infected
Number	202	20 (10%)	182 (90%)
Sex			
Male	114 (56%)	12 (60%)	102 (56%)
Female	88 (44%)	8 (40%)	80 (44%)
Age (years)	46 ± 19	49 ± 17	45 ± 19
Body mass index (kg/m ²)	30 ± 7	31 ± 8	30 ± 7
ASA class			
1	7 (4%)	1 (5%)	6 (3%)
2	96 (47%)	4 (20%)	92 (50%)
3	76 (38%)	13 (65%)	63 (35%)
4	23 (11%)	2 (10%)	21 (12%)
Gustilo and Anderson grade			
Unknown	56 (28%)	2 (10%)	54 (30%)
Type I	48 (24%)	0 (0%)	48 (26%)
Type II	28 (14%)	3 (15%)	25 (14%)
Type IIIA	32 (16%)	5 (25%)	27 (15%)
Type IIIB	31 (15%)	10 (50%)	21 (11%)
Type IIIC	7 (3%)	0 (0%)	7 (4%)
Time to first surgery (days)			
< 6 hours	114 (56%)	13 (65%)	101 (55%)
6–24 hours	83 (41%)	7 (35%)	76 (42%)
> 24 hours	5 (3%)	0 (0.0%)	5 (3%)
Length of stay	17 ± 51	26 ± 16	17 ± 55
Time to followup (days)	520 ± 371	659 ± 356	495 ± 374

ASA = American Society of Anesthesiologists.

underwent irrigation and débridement of their wounds by one of seven attending surgeons. Although there was no standardized protocol, all surgeons extended the traumatic wound to provide adequate visualization of the area, débrided the traumatic wound of any devitalized tissue, and thoroughly irrigated the wound with pulse lavage using at least 6 L of normal saline with or without antibiotics or a soap additive. The majority of patients (150 [74%]) received definitive fixation at the initial surgery, 46 fractures (23%) were treated in a staged manner, and six fractures (3%) were treated with irrigation, débridement, and reduction without internal or external fixation at any point in time. Of those who underwent staged treatment, 39 of 46 (85%) were treated with bridging external fixation and delayed internal fixation. These included AO fracture classification 44 (14 patients), AO classification 41 (eight patients), AO classification 43 (six patients), AO classification 42 (six patients), AO classification 33 (two patients), AO classification 23 (one patient), AO classification 80 (one patient), and AO classification 61 (one patient). The remaining seven patients were treated with initial irrigation

Table 2. Organisms present in infected open fractures

Classification	Organism(s)	Number of open fractures
Staphylococcus	Methicillin-resistant <i>Staphylococcus aureus</i>	5
	Coagulase-negative <i>Staphylococcus</i> (CNS)	6
	CNS	2
	CNS and <i>Pseudomonas</i>	1
	CNS, <i>Enterobacter cloacae</i> , and <i>Enterococcus faecalis</i>	2
Gram-negative	CNS, <i>Klebsiella pneumoniae</i> , and <i>Enterobacter cloacae</i>	1
	<i>Serratia marcescens</i>	2
	<i>Pseudomonas</i>	1
	<i>E. cloacae</i>	1
	<i>Enterobacter aerogenes</i>	1
	<i>E. cloacae</i> and <i>Candida</i>	1
	<i>E. faecalis</i> , <i>Pseudomonas</i> , <i>Morganella morganii</i> , and <i>Aeromonas hydrophila</i>	1
Gram-positive	<i>Clostridium</i>	1
Fungus	<i>Candida</i>	1

and débridement alone and were subsequently treated with internal fixation at a later stage. The fracture classifications that were treated with initial irrigation and débridement alone were AO classification 13 (three patients), AO classification 11 (two patients), AO classification 14 (one patient), and AO classification 72 (one patient).

During postoperative followup, patients were seen in the clinic 2 weeks after discharge, at 6 weeks, 3 months, 6 months, and at 1 year. Radiographs (AP and lateral) of the surgical location were obtained at each postoperative visit; additional imaging studies depended on the location of surgery. Patients were evaluated for signs of infection using the Centers for Disease Control and Prevention criteria [6], in which patients were evaluated for a positive organism cultured from the wound, elevated laboratory values (elevated erythrocyte sedimentation rate, C-reactive protein, and white blood count), and the presence of purulence from the wound. The only data missing from patients were the Gustilo and Anderson type classification, and unknown status was appropriately designated and analyzed as a separate category.

Results

During the study period, 20 of 202 (10%) open fractures had infections. When comparing those who had infections with those who did not, the populations differed with

Table 3. Increasing incidence of methicillin-resistant *Staphylococcus aureus* in open fracture infections

Year	Author	Fracture type	Incidence of MRSA from infected open fractures
1986	Johnson and Johnston [13]	Type III open fractures	6% (32/508)
1995	Yokoyama et al. [23]	Type III open tibia fractures	12% (2/17)
1999	Carsenti-Etesse et al. [3]	Type I and II open tibia fractures	10% (5/48)
2002	Ong et al. [16]	Open tibia fractures	21% (6/29)
2007	Johnson et al. [12]	Type III open diaphyseal tibia fractures from combat	4% (1/27)
2011	Glass et al. [7]	Type IIIB open tibia fractures	11% (1/9)
2012	Present study	All open fractures	25% (5/20)

regard to Gustilo and Anderson type of open fracture and American Society of Anesthesiologists (ASA) class in which patients who developed infections had more severe open fractures (more Type III fractures) and had more patients who were ASA Class 3, indicating medically higher risk patients. The age, sex, body mass index, timing to first surgery, length of hospital stay, and time of followup were similar (Table 1).

The most common organism of infection was *Staphylococcus*, in which five patients were cultured positive for MRSA (25% of those infected) and six patients were culture-positive for coagulase-negative *Staphylococcus* (CNS, 30% of those infected). Of the six open fractures infected with CNS, four patients were infected with multiple species of organisms (one patient with CNS and *Pseudomonas*; two patients with CNS, *Enterobacter cloacae*, and *Enterococcus faecalis*; and one patient with CNS, *Klebsiella pneumoniae*, and *E. cloacae*). The incidence of MRSA infections in our open fracture population was 2.5%.

Five patients exclusively developed a Gram-negative organism infection, including two open fractures with *Serratia marcescens*, one with *Pseudomonas*, one with *E. cloacae*, and one with *Enterobacter aerogenes*. Two additional patients developed multispecies infections with one patient developing a *Candida* and *E. cloacae* infection and another patient developing an *E. faecalis*, *Pseudomonas*, *Morganella morganii*, and *Aeromonas hydrophila* infection. Finally, one patient developed *Clostridium* and another patient developed *Candida*. In total, 11 (55%) open fractures infections developed at least one Gram-negative organism (Table 2).

Discussion

The initial guidelines for antibiotic prophylaxis of open fracture infections were developed in the 1970s, in which patients with open fracture were administered first-generation cephalosporins such as cephalothin or penicillin and

streptomycin [9, 17]. Since then, aminoglycosides had been added to the treatment of more severe open fractures to prevent Gram-negative organism infections [8, 11]. However, since the initial antibiotic prophylaxis guidelines for open fracture management were established in 1976 [9] when methicillin resistance was not a commonly used phrase, the incidence of MRSA in open fractures has increased [1]. If the incidence of MRSA has increased in open fractures, our current prophylactic antibiotic management regimens may not be effective for prophylaxis against MRSA infections. Thus, the goals of our study were (1) to determine the incidence of MRSA infections after open fractures; and (2) to evaluate the incidence of Gram-negative infections after open fractures.

There are a few limitations to our study. First, because this study was conducted at two Level I trauma centers, the study population may consist of patients with more Type III open fractures than would be commonly found in a community setting, which could make the findings less generalizable to all hospitals treating orthopaedic patients [15]. Second, we found a large variation in followup times (Table 1) as a result of the nature of our patient population: trauma patients frequently do not come for followup appointments once their fracture is healed unless a problem like an infection develops. Because the followup time for noninfected trauma patients was shorter, complications that developed after the last followup may not have been captured. Finally, our study included a relatively small sample size. With a larger sample size of patients, we may have performed more in-depth analysis. It is also possible that with a larger sample size, we could have conducted a multivariate logistic regression to determine what factors were more likely to contribute to developing an infection after open fracture.

Our data suggest the incidence of MRSA in open fracture infections is still high and confirm findings reported by other authors (Table 3). MRSA infections in fractures were first addressed in 1986, when it was noted that 32 patients with Type III open fractures developed MRSA infections

out of 508 MRSA-positive patients, and these patients only received a first-generation cephalosporin as prophylaxis [13]. Interim studies noted that there was an increased rate of MRSA infections (range, 10.4%–20.7%) [3, 16, 23], except in combat-related injuries, in which the MRSA rate in Type III open tibia fractures was 3.7% [12]. A subsequent study conducted by Glass et al. [7] demonstrated that of nine Type IIIB open tibial fracture infections, one patient developed MRSA (11.1%). In our open fracture population, we reported a high rate of MRSA (25%) and Gram-negative organisms (55%) in infected open fractures. Additionally, the incidence of MRSA infections in our open fracture population was 2.5%. Our study agrees with findings in previous studies, because most of our infected patients had Type III open fractures and our patients with infected open fractures were medically compromised, as measured by the ASA classification. Interestingly, development of an infection was not associated with the timing of initial surgery, because the majority of the infected patients did undergo surgery within 6 hours of arrival, or the length of stay, which emphasizes the necessity of using prophylactic antibiotics as a critical adjunct to the surgical procedure [22].

Based on the results of this study, the current antibiotic regimen of prophylactic treatment developed in the 1980s with treatment by first-generation cephalosporins such as cefazolin may not be adequate for preventing MRSA or Gram-negative organism infections in open fractures. In our infected open fracture patient population, 85% of these patients received cefazolin as a first-line antimicrobial agent, and only 5% of these patients received vancomycin, which covers MRSA. These patients often received multiple antibiotics for infection prophylaxis, but only seven of 20 (35%) patients received antibiotics for Gram-negative coverage (gentamicin, cefoxitin, ampicillin-sulbactam, ciprofloxacin, and piperacillin-tazobactam). Because the rate of MRSA and Gram-negative infections was high in our open fracture patient population, using cefazolin as the first-line agent for most of our patients with open fractures may not be the most efficacious method of infection prevention. Substituting or augmenting cefazolin with an antibiotic with improved MRSA and Gram-negative organism coverage may be helpful for preventing infections after open fractures, especially in institutions that have increased incidence of MRSA. Medications such as oral trimethoprim and sulfamethoxazole or intravenous vancomycin are effective for treating MRSA infections and may be helpful for prophylaxis. Other new medications such as newer-generation cephalosporins (ceftaroline fosamil) may deserve further study, because they cover a broader spectrum of organisms with the added benefit of covering MRSA. Thus far, this antibiotic has been

approved for acute bacterial skin and skin structure infection and community-acquired pneumonia [14, 19].

Open fracture management involves a complex and integrated approach, including preoperative prophylactic antibiotics, timing of surgery, method of thorough irrigation and débridement, type of fracture stabilization performed, subsequent débridement, and postoperative antibiotic management. Although surgical débridement and fixation are of utmost importance for preventing open fracture infections, the use of antibiotics to prevent infection is a topic of interest. Given the high incidence of MRSA and Gram-negative rods in open fracture infections, future consideration for changing antibiotic prophylaxis to cover MRSA and Gram-negative organisms may be effective for reducing the rate of infection in open fractures.

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