International Orthopaedics (SICOT) (2014) 38:2323–2327
DOI 10.1007/s00264-014-2395-x

ORIGINAL PAPER

Are there clinical variables determining antibiotic prophylaxis-susceptible versus resistant infection in open fractures?

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Received: 5 March 2014 / Accepted: 25 May 2014 / Published online: 21 June 2014

Abstract
Purpose In Gustilo grade III open fractures, it remains unknown which demographic or clinical features may be associated with an infection resistant to the administered prophylactic agent, compared to one that is susceptible.
Methods This was a retrospective case–control study on patients hospitalized from 2004 to 2009.
Results We identified 310 patients with Gustilo-III open fractures, 36 (12 %) of which became infected after a median of ten days. In 26 (72 %) of the episodes the pathogen was susceptible to the prophylactic antibiotic agent prescribed upon admission, while in the other ten it was resistant. All antibiotic prophylaxis was intravenous; the median duration of treatment was three days and the median delay between trauma and surgery was one day. In multivariate analysis adjusting for case-mix, only Gustilo-grade-IIIc fractures (vascular lesions) showed tendency to be infected with resistant pathogens (odds ratio 10; 95 % confidence interval 1.0–10; p=0.058). There were no significant differences between cases caused by antibiotic resistant and susceptible pathogen cases in patient's sex, presence of immune suppression, duration and choice of antibiotic prophylaxis, choice of surgical technique or materials, time delay until surgery, use of bone reaming, fracture localization, or presence of compartment syndrome.
Conclusion We were unable to identify any specific clinical parameters associated with infection with antibiotic resistant pathogens in Gustilo-grade III open fractures, other than the severity of the fracture itself. More research is needed to identify patients who might benefit from a broader-spectrum antibiotic prophylaxis.

Keywords Open fractures · Gustilo grade III · Antibiotic prophylaxis · Resistant infection

There are no grants, financial support, financial interests or consultancy that could lead to a conflict of interest. All authors state that they have read and approved the manuscript. It has not been published elsewhere nor is it under consideration for publication by another journal. Parts of the study have been presented as a poster at the 4th Oxford Bone and Joint Infection Meeting, 3–4 April 2014, Oxford, United Kingdom.

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Introduction

Gustilo grade III open fractures are associated with a substantial infection risk due to naturally resistant pathogens such as *Pseudomonas aeruginosa* or *Enterobacter* spp (up to 33 % in grade IIIc fractures alone; and between 10 and 15 % for the entire group of grade III fractures) [1–3]. The optimal prescription of antibiotic prophylaxis is of utmost importance, but remains largely unknown when it comes to evidence-based recommendations for duration and choice of agents. Probably, administration for more than three days does not reduce infection risk compared to shorter regimens [1], even in severe Grade-IIIc fractures with vascular injury. Regarding the choice of antibiotic agents, practice prefers second generation cephalosporins alone [1, 2, 4, 5], or combined with aminogylcosides [1, 2, 6], quinolones [1, 3] or rarely regimens for eventual anaerobic pathogens [7]. However, despite large

Table 1 Infecting pathogens of Gustilo III open fractures stratified upon antibiotic resistance to first and second generation cephalosporins and amoxicillin/clavunalate

Characteristic	Susceptible (n=26)	Resistant (n=10)	p value[a]
Gender			
Female	4	1	
Male	22	9	1.000
Psychiatric comorbidities	6	3	0.686
Age (years)			
<29 y	7	3	
30–41 y	10	4	
42–59 y	8	2	
≥60 y	1	1	0.844
Active cancer			
No	25	10	
Yes	1	0	1.000
Classifiable fracture grade			
IIIa	2	0	
IIIb	2	1	
IIIc	13	7	0.599
Type of bone[b]			
Long	2	2	
Short	24	8	0.305
Fracture localization			
Above knee	18	6	1.000
Tibia	8	4	0.700
Arm	2	1	1.000
Antibiotic prophylaxis			
1st and 2nd generation cephalosporins			
No	9	2	
Yes	17	8	0.394
More than one antibiotic agent			
No	13	3	
Yes	13	7	0.456
Carbapenem prophylaxis			
No	23	10	
Yes	3	0	0.545
Anaerobes' prophylaxis			
No	13	8	
Yes	6	2	0.675
Gram-negative prophylaxis			
No	14	8	
Yes	5	2	1.000
Prophylaxis against MRSA			
No	26	9	
Yes	0	1	0.279
Duration of antibiotic prophylaxis			
Single shot	4	1	
1–3 days	11	3	
4–5 days	4	2	
>5 days	7	4	0.819

Table 1 (continued)

Characteristic	Susceptible (n=26)	Resistant (n=10)	p value[a]
Surgical treatment			
Reaming when osteosynthesis			
No	20	8	
Yes	2	2	0.572
Plate osteosynthesis			
No	23	9	
Yes	3	1	1.000
Vascular repair			
No	13	2	
Yes	13	8	0.142
Fasciotomy (compartment syndrome)			
No	19	6	
Yes	7	4	0.454
Primary closure (no second look)			
No	19	7	
Yes	7	3	1.000
Time delay trauma to surgery			
0 days	13	9	
1 day	2	0	
>2 days	11	1	0.199

[a] Group comparisons per Pearson-chi² or Fisher's exact test, as appropriate

[b] Long bones=humerus, radius, ulna, femur, tibia, and fibula

antibiotic coverage, infection still occurs and it remains unknown why some infections are resistant to the administered prophylactic agents, while others are not.

Methods

In this single-centre study from 2004 to 2009 at Geneva University Hospitals, we assessed clinical variables associated with resistant pathogens in Gustilo-III open fractures. Formally, resistance was defined as antibiotic resistance of the later pathogen towards the prior administered antimicrobial agent(s), but practically it was equivalent with resistance to aminopenicillins and generation I-II cephalosprins. The classification of open fractures was based on the original papers of Gustilo and Anderson [2]. Infection was defined when pus was present also when surgical and antibiotic care was considered necessary for the treatment of the infection. Patients aged <18 years and those with a follow-up shorter than 60 days were excluded. Furthermore, patients were also excluded with infections occurring after two months of the first surgical treatment or during a subsequent hospitalization, because they were arbitrarily considered as hospital-acquired (and potentially unrelated to the traumatic contamination). For open fracture treated in our institution, priority is given to damage control, vascular repair, skeletal stabilization, irrigation with at least 9 L of normal saline and administration of antibiotic prophylaxis using cefuroxime (1.5 g tid) or amoxicillin-clavulanate (1.2 g tid). Second look surgery is often performed after 48 h, and definitive osteosynthesis is performed later. Nevertheless, despite written recommendations, treating physicians and anaesthetists are free to choose the agent of initial prophylaxis. Especially during the early study period, many surgeons stem from different countries with a variety of personal experiences in the management of open fractures. This was part of an internal quality assessment project supported by studies approved by the local Ethical Committee [1].

Results

We identified 310 patients (median age 39 years; five females; one immune-suppressed patient due to active cancer) with Gustilo-III open fractures (63 grade IIIa, 53 grade IIIb, 63 grade IIIc, and 131 episodes without clear subgradification into a or b in surgical files). Only 36 episodes (12 %) became infected after a median of ten days after admission. Patients were followed through 31 December 2011, e.g. until two years after the inclusion of the last patient [1]. All patients were treated surgically with a median number of two interventions (range, 1–9) and a median delay between trauma and first

Table 2 Clinical variables associated with susceptible infection in open fractures Gustilo grade III (unmatched logistic regression analysis)

Characteristic	Univariate analysis		Multivariate analysis	
Variable	Odds ratio (95 % CI)	*p*-value	Odds ratio (95 % CI)	*p*-value
Female gender	1.6 (0.2–16.7)	0.678	n.a.	
Psychiatric comorbidities	0.7 (0.1–3.6)	0.668	n.a.	
Age (continuous variables)				
>29 years and ≤42 years	1.1 (0.2–6.4)	0.939	n.a.	
>42 years and ≤60 years	1.7 (0.2–13.4)	0.608	n.a.	
>60 years	0.4 (0.0–9.4)	0.590	n.a	
Summer period	2.4 (0.5–10.7)	0.250	0.57 (0.1–10.1)	0.670
Grade IIIc fracture	0.1 (0.1–1.2)	0.145	0.1 (0.0–1.1)	0.058
Compartment syndrome	0.6 (0.1–2.9)	0.540	0.4 (0.1–13.3)	0.606
Vascular repair	0.3 (0.1–1.9)	0.209	n.a	
Long bone fracture[a]	3 (0.3–24.9)	0.309	n.a.	
Fracture below knee	1.0 (0.2–4.7)	0.960	n.a.	
Tibia fracture	1.5 (0.3–6.8)	0.600	1.5 (0.1–24.9)	0.774
Arm fracture	0.8 (0.1–9.3)	0.823	n.a.	
Cephalosporin prophylaxis	3.9 (0.6–23.8)	0.142	n.a.	
Prophylaxis targeting anaerobes	3.7 (0.4–36.5)	0.264	n.a.	
Prophylaxis against Gram-negative rods	1.3 (0.2–8.1)	0.815	n.a.	
Prophylaxis with two agents	1.6 (0.3–10.2)	0.610	n.a.	
Prophylaxis duration				
2–3 days compared to 1 day	0.9 (0.1–11.6)	0.946	2.2 (0.1–72.7)	0.667
≥5 days compared to 1 day	0.4 (0.4–5.4)	0.519	0.7 (0.1–21.7)	0.859
Reaming	0.4 (0.1–3.5)	0.425	n.a.	
Primary closure	2.3 (0.2–25.2)	0.487	n.a.	
Plate osteosynthesis	1.4 (0.1–15.6)	0.774	n.a.	

[a] Long bones=humerus, radius, ulna, femur, tibia, and fibula

n.a. not available

surgery of 0 days (interquartile range (IQR), 0–1). All patients received systemic prophylactic parenteral antibiotics for a median duration of three days (IQR, 3–6). No antibiotic-loaded beads or other devices allowing local antibiotic therapy were used, and there was no targeted therapy, e.g. identification of potential future pathogens during the first surgical access with consequent pre-emptive therapy [1]. Cefuroxime alone was the most frequently prescribed regimen (n=215; 69 %). Empirical carbapenems were involved in three cases. Among 54 combined prophylactic regimens, seven were planned to cover non-fermenting rods, seven were designed for potential anaerobes, and one episode covered potential methicillin-resistant *S. aureus*.

In 26 (72 %) episodes, the pathogen was susceptible to the prophylactic antibiotic agent prescribed upon admission. Susceptible pathogens were mostly *Enterobacter cloacae* (n=8), and *Pseudomona*s spp (n=8), followed by *Bacillus* spp (n=6). In contrast, the infecting pathogen was resistant to prior antibiotic treatment in the other ten cases [*Pseudomonas aeruginosa* (n=4), *Enterococcus faecalis* (n=4), *Enterobacter cloacae* (n=4), and others (Table 1)]. In the multivariate model [8] adjusting for case-mix (Table 2; accuracy with a receiver-operating curve (ROC) value of 0.82), only Gustilo-IIIc fractures (vascular lesions) showed tendency to be infected with resistant pathogens (odds ratio 10; 95 % confidence interval 1.0–10.0; p=0.058). There were no significant differences between cases caused by antibiotic resistant and susceptible pathogen cases in: patient's gender, presence of immune suppression, duration and choice of antibiotic prophylaxis, choice of surgical technique or materials, primary surgical closure, time delay until surgery, use of bone reaming, fracture localization, or presence of compartment syndrome.

Discussion

We were unable to identify any specific clinical parameter associated with infection due to resistant or susceptible

pathogens in Gustilo-grade-III open fractures, with the noteworthy exception of the severity of the fracture itself. In our retrospective study cited in the beginning of the manuscript [1], 71 % of infections with grade III fractures were due to pathogens presumably selected by the antibiotic agents used. However, a combination of cephalosporins with aminoglycosides, quinolones, metronidazole, vancomycin or carbapenems equally failed to reveal a protective effect in all univariate analyses, underlining that the use of a larger antibiotic coverage is not a guarantee for absence of subsequent infection. Open fractures are contaminated by a large variety of antibiotic-susceptible pathogens, including *P. aeruginosa* and *S. aureus* [1]. Thus, it seems unpredictable which pathogen will be selected by ongoing antibiotic prophylaxis. A hypothetical large antibiotic coverage including glycopeptides and carbapenems is not feasible and would be very costly [1] for every grade III open fracture. Additionally, it is not granted that even maximal antibiotic coverage would prevent infection, especially in tissues with debris and reduced blood circulation. As the consequence of our internal evaluation, we therefore renounce to change our empirical antibiotic recommendations until future randomized trials might identify patients who could benefit from a broader-spectrum prophylaxis [9].

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