Unexpected high prevalence of Gram-negative pathogens in fracture-related infection: is it time to consider extended Gram-negative cover antibiotic prophylaxis in open fractures?

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Abstract

Background

Gram-negative organisms are increasingly seen as causative pathogens in orthopaedic fracture surgery, which might necessitate a change in antibiotic prophylaxis protocols.

Methods

A single-centre retrospective review of antibiogram results from all patients treated for fracture-related infection (FRI) was conducted. Subgroup analysis was undertaken to identify any host, injury or treatment variables predisposed to Gram-negative infection.

Results

The bacteriological results of 267 patients who underwent surgical treatment for FRI were analysed. Pathogens were isolated in 216 cases (81%), of which 118 (55%) were Gram-negative infections. Fractures involving the tibia and femur ($p = 0.007$), the presence of soft tissue defect ($p = 0.003$) and bone defects ($p = 0.001$) were associated with an increased risk of developing a Gram-negative FRI.

Conclusion

Gram-negative fracture-related infections were associated with injuries experiencing bone loss and those requiring soft tissue reconstruction. It is, therefore, prudent to consider extended Gram-negative directed antimicrobial prophylaxis in these cases to prevent the development of fracture-related infection.

Level of evidence: Level 4

Keywords: open fracture, antibiotics, fracture-related infection, Gram-negative

Introduction

Fracture-related infection (FRI) is a dreaded complication following orthopaedic trauma.[1] Extensive pre-, intra- and postoperative care is taken to minimise the risk of infection. One of these strategies is the use of prophylactic systemic antibiotics, primarily aimed at Gram-positive organisms.[2-6]

Previous studies have reported the spectrum of causative pathogens in FRI to help guide both empirical prophylactic and therapeutic antimicrobial management.[7-15] Although *Staphylococcus aureus* remains the most frequently isolated pathogen in FRI, the prevalence of Gram-negative infections is increasing, with the reported estimates ranging from 21–76%.[7-15] It is widely accepted that Gram-negative cover should be added to prophylactic antibiotic protocols in higher-grade open fractures (Gustilo-Anderson 3),[16] but this practice has not been generally accepted for closed fractures or elective orthopaedic procedures (hip and knee arthroplasty excluded).[2-6,16-20] The inaugural British Aesthetic and Plastic Reconstructive Surgeons (BAPRAS) and British Orthopaedic Association (BOA) guidelines for the management of open fractures recommended co-amoxiclav (1.2 g 8 hourly) or a second-generation cephalosporin (e.g., cefuroxime 1.5 g 8 hourly) as antimicrobial prophylaxis before the first debridement. This is then followed by either co-amoxiclav (1.2 g) or a second-generation cephalosporin plus gentamicin (1.5 mg/kg) given at the time of surgery, and co-amoxiclav/cephalosporin continued until soft tissue closure or for a maximum of 72 hours.[16] However, the most recent iteration of these guidelines

refrains from providing specific recommendations for antimicrobial prophylaxis.[21]

A multicentre audit of major UK trauma centres revealed that 78% of prophylactic antimicrobials used in the management of open fractures provided coverage against only Gram-positive pathogens.[6] Similar results were reported in a systematic review of antimicrobial choice for prophylaxis in open fractures, which reported that approximately one-third included papers recommended only agents that covered Gram-positive organisms; just over 50% of studies did, however, recommend regimens that provided cover for both Gram-positive and Gram-negative pathogens.[22] In North America, guidelines and consensus statements recommend the use of a first- or second-generation cephalosporin (e.g., cefazolin or cefuroxime) for routine perioperative antimicrobial prophylaxis in hip and knee replacement surgery.[23,24] In a survey of North American arthroplasty surgeons, cefazolin was reported to be the antibiotic of choice for prophylaxis in 97% of respondents.[25] Similar preferences and recommendations are seen in sarcoma surgery,[18,19] foot and ankle surgery[26] and spinal surgery.[27] The exception to this rule was among UK hip and knee arthroplasty surgeons. In a survey of UK centres performing elective knee and hip arthroplasty surgery, flucloxacillin with gentamicin was the most popular prophylactic regimen, with 57/146 (39%) of surveyed trusts using it. Cefuroxime was the agent of choice in 44/146 (30%), with teicoplanin plus gentamicin being the third most popular 25/146 (17%).[28]

The study aimed to review the microbiology and antibiogram data of all patients who presented to a tertiary orthopaedic unit with FRI to generate hypotheses for future research in the role of extended spectrum antimicrobial prophylaxis in fracture management surgery. Subgroup analysis was undertaken to identify any host, injury or treatment variables predisposed to Gram-negative infection development.

Methods

A single-centre retrospective review of antibiogram results from all patients treated for FRI at a tertiary level musculoskeletal infection unit was conducted. FRI was diagnosed according to the international consensus definition proposed by Metsemakers et al. and modified by Govaert et al. in 2020.[29,30] Patients of any age treated for a fracture-related infection of the appendicular skeleton were included in the study. Patients with chronic osteomyelitis not related to fracture-related infection were excluded. Patient records from January 2016 to October 2022 were reviewed. Data were collected regarding patient demographics, mechanism of injury, site of infection and causative organism, including the antibiogram.

Patient records and laboratory investigations assisted in stratifying the host into A, B or C types according to the modified Cierny and Mader (C&M) classification proposed by Marais et al.[31] Laboratory studies were used to identify causative organisms.

In all cases, intraoperatively collected deep samples of infected tissue and/or biofilm were submitted for bacterial culture. Solid media consisted of tryptose blood, boiled blood and MacConkey agar (for aerobic/CO_2-enriched conditions) and Brucella and/or tryptose blood agar (for anaerobic conditions). Liquid media used consisted of cooked meat medium or tryptic soy broth. Tissue samples were crushed, and both crushed tissue and pus samples were inoculated onto the basic solid media listed prior to incubation. Tissue and pus samples were incubated on solid media for at least 48 hours. Pus swabs were incubated on solid media in CO_2-enriched conditions for a minimum of 24 hours. Current local laboratory processing guidelines do not include the use of sonication or vortexing of the sample in the absence of submitted prosthetic material.

All pure cultures were identified. Mixed cultures were reviewed by a pathologist and followed up as appropriate. Identification and susceptibility testing was performed using the VITEK 2 automated system (bioMérieux, Marcy-l'Étoile, France) with supplemental rapid biochemical or antigen-based identification and disk or gradient diffusion antibiotic susceptibility testing, as appropriate. Antibiotic susceptibility results were interpreted according to annually published Clinical Laboratory and Standards Institute guidelines. For this paper, organisms falling within the intermediate category were categorised as resistant, as antibiotic activity at the site of infection was likely to be suboptimal.

Statistical analysis was performed using Stata 16.1 (StataCorp, College Station, Texas) and EpiCalc 2000 v1.02 (Brixton Books, UK). Parametric data are reported as mean and standard deviation (SD) with 95% confidence intervals (CI) where appropriate. Non-parametric data are described with median, interquartile range and range. Categorical data are described as frequencies and/or counts, with 95% CI where appropriate. Associations were investigated using an independent t-test or a Mann-Whitney U test, depending on the distribution. Pearson chi-squared test (or Fisher's exact test, where appropriate) was used to detect significant differences between groups.

Results

Between January 2016 and October 2022, 267 patients underwent surgical treatment for FRI. No patients were excluded. The final cohort comprised 208 males and 59 females, with a mean age of 37.7 (SD 13.8) years (range 16–84) (*Table I*). The mechanism of initial injury included 134 (50%) open fractures, 94 (35%) closed fractures, and 39 (15%) gunshot-induced fractures. The anatomical site of infection was predominated by tibias (n = 130, 49%), femurs (n = 64, 24%), humeri (n = 23, 9%) and forearms (n = 22, 8%). The distribution of affected anatomical sites is shown in *Figure 1*.

Pathogens were isolated in 216/267 cases (81%) (*Table II*). A single organism was isolated in 178/267 (67%) patients, while 38/267 (14%) patients showed polymicrobial growth, of which 12/267 (4%) showed both Gram-positive and Gram-negative bacterial growth. A total of 120 Gram-positive species and 138 Gram-negative species were isolated. While 97% of Gram-positive

Table I: Demographics of included patients

	n = 267
Male sex (%, n)	78 (208)
Age in years (mean, SD)	37.7 ± 13.8)
Diabetes mellitus (%, n)	6 (17)
HIV positive (%, n)	9 (25)
Smoker (%, n)	52 (138)
Alcohol (%, n)	14 (37)
Drug abuse (%, n)	5 (13)
Host status (%, n)	
A	27 (72)
B_L	12 (31)
B_S	49 (132)
B_{LS}	12 (32)
Injury type (%, n)	
Open	50 (134)
Closed	35 (94)
GSW	15 (39)

Date reported as mean ± standard deviation, median (interquartile range) or as frequencies with counts in parenthesis. GSW: gunshot wounds; B_L: B-host, compromised locally; B_S: B-host, compromised systemically; B_{LS}: B-host, compromised locally and systemically

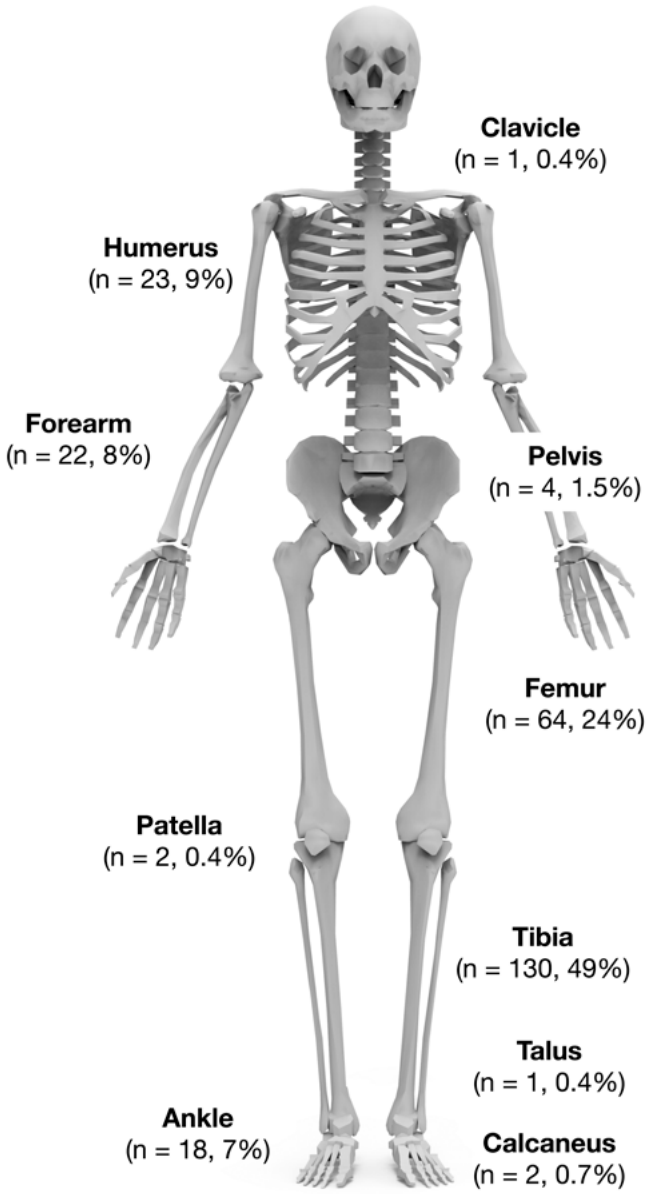

Figure 1. Distribution of affected anatomical sites

isolates comprised only two genera of pathogens (*Staphylococcus spp.* and *Streptococcus spp.*), Gram-negative cultures had a much more diverse range of isolates. Infection with at least one Gram-negative organism was found in 118/216 (55%) patients, while 98/216 (45%) patients showed infection with only Gram-positive pathogens.

No association between Gram-negative FRI and any host factor was observed (*Table III*). Fractures involving the tibia and femur (p = 0.007), the presence of soft tissue defect (p = 0.003) and bone defects (p = 0.001) were associated with an increased risk of developing a Gram-negative FRI.

Discussion

In this study, the prevalence of Gram-negative associated FRI was 55%. Previous studies have reported lower proportions of Gram-negative infections in FRI. Recent studies examining the microbiology of FRI from northern European centres estimate Gram-negative involvement in 21–28% of cases.[7-11] The results of these studies have been used to inform recommendations for the systemic antimicrobial management of FRI.[32] Furthermore,

Table II: Bacterial isolates

Culture information	% (n)
Culture result (%, n)	
No growth	19 (51)
Single organism	67 (178)
Multiple organisms	14 (38)
Gram-positive bacteria (n = 120)	
Methicillin-sensitive *S. aureus*	61 (73)
Methicillin-resistant *S. aureus*	11 (13)
Streptococcus pyogenes	16 (19)
Enterococcus faecalis	7 (8)
Staphylococcus epidermidis	2 (2)
Other*	3 (3)
Gram-negative bacteria (n = 138)	
Proteus mirabilis	22 (31)
Pseudomonas aeruginosa	22 (30)
Enterobacter cloacae	17 (23)
Klebsiella pneumonia	6 (9)
Acinetobacter baumannii	6 (9)
Escherichia coli	6 (8)
Morganella morganii	5 (7)
Serratia marcescens	3 (4)
Citrobacter fruendii/braakii	2 (3)
Other**	11 (14)

Date reported as frequencies with counts in parenthesis
* Other streptococci, *Bacillus cereus*, *Finegoldia magna,* Bifidobacterium
** *Proteus hauseri/penneri*, *Providencia stuartii*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Aeromonas hydrophila*

they reinforce the widely held belief that Gram-positive organisms should be the primary concern directing the choice of prophylactic antimicrobials.

Sagi et al. examined the causative pathogens of post-traumatic infections following open fracture in 204 patients in seven Level 1 trauma centres across the USA. While overall, *S. aureus* was the most prevalent pathogen, there were statistically significant regional variations (p < 0.001), with Gram-negative organisms the most commonly encountered pathogens in the mid-Western region (56%).[33] A small single-centre cohort study performed in Pittsburgh, USA, published in 2013, reported a similar prevalence with 11/20 cases of FRI following open fracture having Gram-negative bacteria involvement. The authors concluded that consideration should be given to a change in the choice of antimicrobial prophylaxis to allow better coverage of Gram-negative organisms. A multicentre study from northeast China found that 47% of causative microorganisms were Gram-negative pathogens in 328 FRI cases.[15] A further single-centre study from China reported a 70% prevalence of Gram-negative FRI in 535 patients.[12] Finally, Lu et al. reported that Gram-negative pathogens accounted for 76% of monomicrobial cases of FRI at a major trauma centre in the UK.[13] The cohorts reporting 47–76% Gram-negative involvement in FRI were characterised by patients experiencing more high-energy injuries (68% open injuries) of the lower limbs (68%), resulting in more high-grade open injuries (Gustilo-Anderson 3B and 3C) that required soft tissue reconstruction (22%). Similar risk factors were identified in this present study with the development of Gram-negative FRI associated with infections involving the tibia and femur (p = 0.007), the presence of soft tissue (p = 0.003) and bone defects (p = 0.001).

While there was a higher-than-expected prevalence of Gram-negative pathogens compared to previous studies, *S. aureus* remained the most commonly isolated pathogen (40%). This is comparable to the aggregate estimate of the prevalence of *S. aureus* FRI from published studies (33%).[7-12,14,15] Oxacillin resistance was identified in 18% of *S. aureus* isolates, which is

Table III: Distribution of Gram-positive and Gram-negative infections

	Gram-positive (n = 98)	Gram-negative (n = 118)	Culture-negative (n = 51)	
Sex				
Male (%, n)	84 (83)	75 (88)	73 (37)	p = 0.067
Female (%, n)	15 (15)	25 (30)	27 (14)	
Age in years (median, IQR)	33 (26–45)	34 (27–50)	36 (30–49)	
Diabetes (%, n)	6 (6)	8 (9)	4 (2)	p = 0.790
HIV (%, n)	7 (7)	11 (13)	10 (5)	p = 0.355
Smoking (%, n)	59 (58)	47 (56)	47 (24)	p = 0.078
Alcohol (%, n)	21 (21)	11 (13)	6 (3)	**p = 0.027**
Drug abuse (%, n)	5 (5)	4 (5)	6 (3)	p = 1.000
Host status				
A (%, n)	21 (21)	28 (33)	35 (18)	
B_L (%, n)	11 (11)	12 (14)	12 (6)	p = 0.281
B_S (%, n)	57 (56)	45 (53)	45 (23)	
B_{LS} (%, n)	10 (10)	15 (18)	8 (4)	
Anatomy				
Tibia (%, n)	43 (42)	54 (64)	47 (24)	
Femur (%, n)	17 (17)	27 (32)	29 (15)	
Humerus (%, n)	12 (12)	4 (5)	12 (6)	
Forearm (%, n)	14 (14)	4 (5)	6 (3)	
Ankle (%, n)	5 (5)	8 (10)	6 (3)	**p = 0.007**
Pelvis (%, n)	3 (3)	1 (1)	0 (0)	
Calcaneus (%, n)	2 (2)	0 (0)	0 (0)	
Patella (%, n)	2 (2)	0 (0)	0 (0)	
Clavicle (%, n)	1 (1)	0 (0)	0 (0)	
Talus (%, n)	0 (0)	1 (1)	0 (0)	
Fracture				
Open (%, n)	44 (43)	55 (65)	51 (26)	p = 0.187
Closed (%, n)	38 (37)	33 (39)	35 (18)	
GSW (%, n)	18 (18)	12 (14)	14 (7)	
Soft tissue defect				
Yes (%, n)	20 (20)	39 (46)	20 (10)	**p = 0.003**
No (%, n)	80 (78)	61 (72)	80 (41)	
Bone defect				
Yes (%, n)	6 (6)	23 (27)	16 (8)	**p = 0.001**
No (%, n)	94 (92)	77 (91)	84 (43)	

Date reported as mean, standard deviation, median (interquartile range) or as frequencies with counts in parenthesis. GSW: gunshot wounds; B_L: B-host, compromised locally; B_S: B-host, compromised systemically; B_{LS}: B-host, compromised locally and systemically

lower than reports from China (25%), Brazil (35%) and the Middle East (60%).[15,34,35] This could be ascribed to the fact that many patients are antibiotic naïve at the time of presentation to our limb reconstruction unit.

From the published literature, polymicrobial infections are estimated to affect 22% of FRI cases,[7-12,14,15] which was greater than the estimate from this present study (14%). It has been previously postulated that adherence to a structured tissue sampling protocol and stricter diagnostic criteria, such as that implemented in this study, may reduce the prevalence of polymicrobial culture results due to reduced cross-contamination with skin flora and the requirement for isolates to be present in more than one culture.[36] As a single-centre cohort, it is more likely that the patients in this current study received a more consistent and homogenous treatment, including intraoperative sampling, which may have resulted in a lower prevalence of polymicrobial infection for the reasons described above.

The call for extended Gram-negative coverage has been raised by various other orthopaedic disciplines. A 2021 review of 989 spinal fusion procedures showed a 54% incidence of Gram-negative infection, and the authors proposed Gram-negative prophylactic antibiotic coverage for a specific subset of patients undergoing spinal fusion.[37] Bosco et al. identified that Gram-negative bacilli caused 30% of their periprosthetic joint infections and that the introduction of an extended Gram-negative antimicrobial prophylaxis protocol resulted in a statistically significant reduction in periprosthetic joint infections in their hip arthroplasty patients.[38] Previous publications,[17,39] as well as guidance from the National Institute of Clinical Excellence in the UK,[40] have recommended tailoring both therapeutic and prophylactic antimicrobial choices on local microbiology data.

Several factors limit the generalisability of this study. These include the single-centre cohort and the retrospective nature of the study design. We also acknowledge that contemporary antibiotic prophylaxis is primarily aimed at Gram-positive organisms, which could explain a relative decrease in Gram-positive infections. It is, however, prudent to recognise that Gram-negative FRI is a significant problem in this population and warrants further investigation and discussion.

Conclusion

There is a rising prevalence of Gram-negative fracture-related infection, which is associated with injuries experiencing bone loss and those requiring soft tissue reconstruction. It is, therefore,

prudent to investigate whether extended Gram-negative directed antimicrobial prophylaxis in these cases can prevent the development of fracture-related infection.

Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

Ethical approval for this study was obtained before the commencement of data collection from the Health Research Ethics Committee (HREC) of Stellenbosch University: N22/01/007. This retrospective review received a waiver of informed consent from the Stellenbosch University Health Research Ethics Committee.

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

NF: study conceptualisation, data collection, manuscript preparation, approval of final manuscript
SJT: manuscript preparation, approval of final manuscript
AJvR: data collection, approval of final manuscript
RV: data collection, approval of final manuscript
GZE: study conceptualisation, data collection, approval of final manuscript

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