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Enterococci in orthopaedic infections: who is at risk getting infected?

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Abstract

Summary Some orthopaedic patients might be at risk for enterococcal infections and might benefit from adapted perioperative prophylaxis.

Methods We performed a single-center cohort of adult patients with orthopaedic infections.

Results Among 2740 infection episodes, 665 surgeries (24%) involved osteosynthesis material, including total joint arthroplasties. The recommended perioperative prophylaxis was cefuroxime (or vancomycin in case of documented MRSA body carriage). Patients had received antibiotic therapy before surgery in 1167 episodes (43%); among them with potential anti-enterococcal activity (penicillins, glycopeptides, imipenem, linezolid, daptomycin, aminoglycosids, tetracyclins) in 725 (62%) cases. Overall, enterococci were identified in intraoperative samples of 100 different infections (3.6%) (*E. faecalis*, 95; *E. faecium*, 2; and other enterococci, 3). However, only 15/100 (15%) enterococcal infections were monomicrobial and 19 were nosocomial (19/2740; 0.7%), of which 15 had previous cephalosporin perioperative prophylaxis without other antibiotic exposure. This association to prior cephalosporin use was significant (Pearson-χ^2-test; 148/2640 vs. 15/100, $p<0.01$). By multivariate analysis, the presence of diabetic foot infection (odds ratio 1.9, 95% confidence interval 1.2-2.9), and polymicrobial infection (OR 6.0, 95%CI 3.9-9.4) were the main predictors of enterococcal infection, while sex, age, and type of material were not.

Conclusions Community-acquired or nosocomial enterococcal infections in orthopaedic surgery are mostly polymicrobial, rare and very seldom attributed to a nosocomial origin. Thus, even if they are formally associated with prior cephalosporin use, we do not see a rational for changing our antibiotic prophylaxis.

Introduction

The predominant infective organisms in orthopaedic surgery is *Staphylococcus aureus* [1]. Accordingly, guidelines and experts recommend the use of 1st and 2nd generation cephalosporins for perioperative prophylaxis [2] unless the patient is known to be colonized with methicillin-resistant *S. aureus* (MRSA) and thus vancomycin is recommended [3]. However, cephalosporins lack activity against enterococci [4,5]. For abdominal surgery there is ongoing controversy whether a subset of multimorbid patients might benefit from enlarged antibiotic prophylaxis including enterococcal coverage [6] and the relationship between cephalosporin use and enhanced *E. faecalis* bacteraemia incidence has been published [4]. The literature is sparse regarding orthoapedic infections and enterococci. For example, a PubMed search on 15 October 2016 with the MeSH terms ”enterococci”, “orthopaedic”, and “surgery” only identified 26 publications. Some authors think that the overall prevalence of enterococcal surgical site infections [1] might rise in the future [5,7] and have epidemiologically linked the increased cephalosporin use in perioperative antibiotic prophylaxis to the increasing incidences of enterococcal implant-infection [5].

The objective of the current study was to investigate whether some orthopaedic patients / types of procedures are at risk for enterococcal infection. Of note, we do not address prevention [1], pathophysiology [8], therapy and outcomes of orthopaedic due to enterococci, for which a broader literature is available [9-18].

Methods

We performed a single-centre, retrospective cohort study of adult patients operated at our tertiary Orthopaedic Referral Centre at the University of Geneva Hospitals between January 2004 and December 2014. Our Orthopaedic Centre also manages all trauma-related infections and soft-tissue infections requiring surgery (e.g. abscesses, septic bursitis, myositis, or fasciitis). The proportion of MRSA among all clinical *S. aureus* isolates ranged between 15%

and 25% during the study period [19]. Hospital-wide, the proportion of penicillin-resistance was 1% for *E. faecalis* and 87% for *E. faecium*. We defined infection clinically as the presence of intraoperative pus, together with other signs or symptoms (new onset of pain, fever, warmth, redness, discharge), or radiographic signs of implant loosening or the presence of sequestrae. The detailed definitions for prosthetic joint, nosocomial and diabetic foot infections stem from the Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection [20], the Diabetic Foot Infection Guidelines of the Infectious Diseases Society of America [21], and the Center of Disease Control (CDC) definitions of healthcare-associated infections [2]. For this study, we considered early-onset open fracture infections as community-acquired, since they were usually acquired on the road [22]. To avoid data clustering, we included only the first episode of the same infection and excluded recurrent episodes (and pediatric cases) from further analysis, unless there would be improbable situation that the recurrent pathogen of the infection would be an *Enterocccous* sp (as the new pathogen). The composite database was in line with the local Ethical Committee requirements.

Microbiological samples

Surgeons obtained all microbiological specimens (tissue and swabs) intraoperatively. Collaborators carried them in aerobic and anaerobic transport media to the microbiology laboratory in the same building, which normally takes 0.5-3 hours. During opening hours of the laboratory, the specimens were manually Gram stained and then cultured on sheep blood, chocolate, MacConkey, colistin-nalidixic acid and/or 'CDC anaerobe' agars. We lacked sonication or specific enterococcal polymerase-chain reaction (PCR) facilities and performed all antimicrobial susceptibility testings according to CLSI (Clinical and Laboratory Standard's Institute) recommendations [23]. These recommendations evolved using the current criteria of each year, except for switching to EUCAST criteria (European Committee on Antimicrobial Susceptibility Testing) in spring 2014 [24]. The standard incubation period for cultures was

five days unless the Infectious Diseases physician demanded for longer incubation basing of previous results, the patient's history and the presentation of the individual case.

Statistical analysis

Group comparisons were performed using the Pearson-χ^2-test, Fisher-exact-test or the Wilcoxon-ranksum-test, as appropriate. To adjust for case-mix, we performed an unmatched logistic regression analysis (outcome enterococcal infection). Independent variables with a *p* value ≤0.20 in univariate analysis were introduced stepwise into the multivariate analysis [25]. *P* values ≤0.05 (two-tailed) were significant. We used STATA™ software (9.0; Texas, USA).

Results

The median age of patients was 57 years (range, 18-99 y). Among 2740 infection episodes, 1021 (37%) were among immune-compromised patients (diabetes mellitus (n=659), solid organ or bone marrow transplants (15), untreated HIV disease (22), immune-depressive drugs (77), active cancer (139), cirrhosis CHILD C (28), dialysis (32), pregnancy (1), and splenectomy (2)). Many had multiple immune suppressions. A total of 665 surgeries (24%) involved osteosynthesis material (implants), which included: total joint arthroplasties (n=321); intramedullar nails (n=54), and plates (n=150). The rest were wires, screws, external fixation pins and cerclages. Among the soft tissue surgeries, 1070 were related to abscesses, 472 were septic bursitis cases, 20 were necrotizing fasciitis, and 429 episodes were related to foot surgery.

The recommended perioperative prophylaxis was cefuroxime (or vancomycin in case of documented MRSA body carriage). Overall, in 1167 episodes (42%), patients received antibiotic therapy before surgery. Among them two third (725/1167; 62%) with agents harbouring potential anti-enterococcal activity (penicillins, glycopeptides, imipenem, linezolid,

daptomycin, aminoglycosides, tetracyclins). For this study purposes, we classified meropenem and ertapenem as not active against enterococci.

Enterococci

Enterococci were identified from intraoperative samples in 100 different patients (3.6%) (*E. faecalis*, 95; *E. faecium*, 2; and other enterococci, 3). All enteroccoci were present at the index infection, and did not emerge as the new causative pathogen of recurrent or persistent infection. Of these, 1 *E. faecalis* and both *E. faecium* were resistant to penicillin, and 26 *E. faecalis* and 1 *E. faecium* resistant to tetracyclines. None yielded resistance to vancomycin or teicoplanin. Only 15/100 (15%) enterococcal infections were monomicrobial. The majority (85/100; 85%) revealed a co-infection resuming 34 different microbiological combinations. Enterococci were the primary pathogen in 28 cases according to quantitative interpretation of the microbiology technician. These groups of co-pathogens were *Staphylococcus aureus* (n=14; of which 2 due to MRSA), Gram-negatives (n=32; of which 15 non-fermenting rods, including 8 cases with *Pseudomonas* spp), streptococci (n=3), skin commensals (corynebacteria, micrococci, coagulase-negative staphylococci; n=13). We could not detect co-infection with propionibacteria or anaerobes. Throughout the entire study period, we failed to detect an outbreak of enterococcal infections (more than two cases on a ward) in our service.

Perioperative antibiotic prophylaxis during index surgery

Nineteen episodes (19/2740; 0.7%) were classified as nosocomial according to the CDC criteria. According to these criteria the index surgery occurred within 30 days prior to the onset of infection for implant-free surgery, and within 1 year for implant-related surgery [2]. Among these 19 cases, 17 had received a prior perioperative prophylaxis which was not active against enterococci: cephalosporins (n=15), and lack of prophylaxis (n=2). Only two nosocomial

104 enterococcal infections developed under correct prophylaxis, of which one was monomicrobial
105 and the other due to a co-infection with *Bacillus* sp.
106
107 *Prior systemic therapeutic antibiotic use for infection*
108 Among all 100 infection episodes involving enterococci, 56 had received systemic antibiotic
109 drugs within two weeks prior to intraoperative sampling for infection. Among these 56 cases,
110 48 (48/56; 86%) witnessed ongoing antibiotic exposure until the day of intraoperative
111 sampling. In three cases, the antibiotic was stopped ("antibiotic-free window") seven days
112 before. This "antibiotic-free window" was one day, two days, three days, six days, and eight
113 days in the remaining six cases (Table 1). Regarding antibiotic drugs, we detected 25 different
114 preoperative therapeutic regimens: cephalosporins (n=15), quinolones (n=4), clindamycin
115 (n=2), fluoxacillin (n=1), amoxicillin/clavulanate (n=18), imipenem (n=9), glycopeptides
116 (n=7), or a mix of various classes. There was no prior meropenem, ertapenem, aminoglycoside
117 or piperacillin use. Overall, 31 previous antibiotic regimens (31/56; 55%) had no potential anti-
118 enterococcal activity. Overall, prior antibiotic use was associated with the occurrence of
119 enterococci in later infections (Table 1), but not when prior cephalosporin administration was
120 excluded from the analyses. Prior antibiotic administration involved the 42 cases with
121 cephalosporin exposure (15 as therapy and 17 episodes as prophylaxis). This prior
122 cephalosporin exposure was particularly associated with enterococcal (co)infection (Tables 1
123 and 2) albeit it did not reach significance in the multivariate results (Table 2).
124
125 *Non-antibiotic associations with enterococcal infection*
126 The proportion of enterococci among all pathogens in diabetic foot infections was 7%. In
127 contrast, enterococci were almost never identified in septic bursitis, soft tissue abscesses and
128 native bone or joint infections. By multivariate analysis, the presence of diabetic foot infection
129 (odds ratio 1.9, 95% confidence interval 1.2-2.9), implant-related infection (OR 2.0, 95%CI

1.2-3.3) and polymicrobial infection (OR 6.0, 95%CI 3.9-9.4) were strong associations with enterococci, while sex, age, and type of implant were not (Table 2).

Discussion

In this 11-year retrospective, single referral-centre cohort study, we addressed the question which type of orthopaedic patients gets infected with enterococci. We found that enterococcal infections were rare. They contributed only to 3.6% of all infections. The nosocomial or monomicrobial parts were even smaller with corresponding total incidences of 0.7% and 0.7%, respectively. With a proportion of 85%, we encountered enterococci mostly as co-pathogens in polymicrobial and implant-related infections, and in the ulcerating diabetic foot.

In the literature, enterococci might accompany other pathogens 10% [16], 18% [26], 19% [7], 22% [5], 32% [18], 33% [17] or 54% [29] of orthopaedic infections, but their overall incidence is still less than four percents [9-11,17,27,28]. Moreover, monomicrobial enterococcal bone and joint infections are very often hematogenous [30], stemming from a remote origin, e.g. endocarditis [27,28] or prostate [15], whereas implant-free, native joint community-acquired arthritis, septic bursitis or osteomyelitis due to enterococci are very seldom [7,18,31,32]. In contrast, enterococcal diabetic foot infections are a well-known clinical entity [21,33,34].

In our analysis, enteroccocal infections were strongly related to prior cephalosporin exposure, mostly administered as prophylaxis. Cephalosporins inherently lack anti-enterococcal activity [4]. Our finding is in line with a large observational study involving more than thousand patients from Denmark [5]. Siesing et al. investigated wound and bone infections in orthopaedic patients from 1990 to 2009 and determined whether there was a correlation between the incidence of enterococci in tissue samples from orthopaedic patients and the consumption of cefuroxime in the orthopaedic department. In their hospital, cefuroxime use

156 increased from 40 defined daily doses (DDD) per 1000 bed-days in 2002 to 212 DDD in 2009,
157 while total cephalosporin use increased three-fold in whole Denmark. In the same period, the
158 incidence of patients with enterococci in tissue samples increased steadily from 1.03% to 5.9%.
159 Moreover, the proportion of (penicillin-resistant) *E. faecium* increased from 7% in the first 3-
160 year period to 15% in the last 3-year. The association was impressive [5].
161
162 Our study has major limitations. i) This retrospective, single-center cohort study does not
163 consider epidemiological changes over time. The small number of enterococcal infections does
164 not allow for such trend analysis. ii) The standard incubation time for microbiological
165 specimens was 5 days. While a prolongation beyond 5 days is less likely to raise the number of
166 enterococcal species, it may raise the proportion of co-pathogens such as *Propionibacterium*
167 *acnes* [35] or skin commensals. In our orthopaedic database, there were zero enterococcal co-
168 infections with *P. acnes* and only 13 with skin commensals. iii) Our perioperative antibiotic
169 regimens are in line with several Western European and US recommendations. However, these
170 might not be ubiquitous. For example, many centres facing major *Clostridium difficile*
171 problems might not use cephalosporins and might have switched to alternative prophylaxis
172 regimens such as teicoplanin, or flucloxacillin plus gentamicin with anti-enterococcal activity;
173 or many other combinations. Thus, our findings could be different in these settings. iv) We
174 summarized imipenem as an agent with anti-enterococcal activity. Like other institutions, we
175 cannot directly test enterococcal isolates for imipenem susceptibility [36,37] due to lack of
176 guidance. Many microbiologists would not consider imipenem having relevant activity against
177 *E. faecium*. However, according to sparse literature available on this topic, the *in vitro* activity
178 of penicillin and ampicillin versus *E. faecalis* and *E. faecium* might accurately predict that of
179 imipenem [36,37]; at least for *E. faecalis* or if the *E. faecium* is susceptible to penicillins.
180 Therefore, we believe that the assumption of imipenem susceptibility based on penicillin
181 testing is accurate. Of note, in our study, only 3 enterococcal isolates were resistant to

182 penicillin (3/100; 3%), and all prior carbapenem use concerned imipenem, and not meropenem
183 or ertapenem.
184
185 In conclusion, enterococcal infections in orthopaedic surgery were mostly community-
186 acquired, co-pathogens in diabetic foot infections and associated to prior cephalosporin
187 exposure. Because of their absolute rarity, and the even smaller proportion of the nosocomial
188 part, we did not change our antibiotic policy.
189

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202 IU had full access to all of the data in the study and take responsibility for the integrity of the
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Table 1 - Comparison of orthopedic infections due to enterococci versus other pathogens

	Other pathogens		Enterococci
n = 2740	**n = 2640**	***p* value***	**n = 100**
Female sex	845 (32%)	n.s.°	26 (26%)
Median age	56 years	n.s.”	65 years
Median C-reactive protein level	76 mg/L	n.s.”	104 mg/L
Median duration of prior antibiotic use	4 days	n.s.”	4 days
Prior antibiotic use overall	1111 (42%)	0.006	56 (56%)
- excluding overall cephalosporin use	963 (36%)	n.s.°	42 (42%)
- prior therapeutic use of cephalosporins	148 (6%)	0.001°	15 (15%)
- prior cephalosporin prophylaxis	42 (2%)	0.001°	17 (17%)
- prior therapeutic use of penicillins	680 (26%)	n.s.°	27 (27%)
- prior therapeutic use of glycopeptides	61 (2%)	0.001°	6 (6%)
Median duration of antibiotic window prior to intraoperative sampling	0 days	n.s.”	0 days
Immune suppression[+]	965 (37%)	0.001°	56 (56%)
- Diabetes mellitus	611 (23%)	0.001°	48 (48%)
Type of infection			
Osteoarticular infections	1150 (44%)	n.s.°	52 (52%)
All osteosynthesis (implant) infections	630 (24%)	0.011°	35 (35%)
- Prosthetic joint infections	304 (12%)	n.s.°	17 (17%)
- Spondylodesis infection	28 (1%)	n.s.[&]	3 (3%)

- Nail infections	52 (2%)	n.s. [&]	2 (2%)
- Plate infections	142 (5%)	n.s.°	8 (8%)
Septic bursitis	468 (18%)	0.001[&]	4 (4%)
Foot infections	400 (15%)	0.001°	29 (29%)
Shoulder infections	92 (3%)	n.s.[&]	1 (1%)
Abscess formation	1045 (40%)	0.003°	25 (25%)
Polymicrobial infection	505 (22%)	0.001°	67 (67%)

*Only significant *p* values ≤0.05 (two-tailed) are displayed.

°Pearson-χ^2-tests; “Wilcoxon-ranksum-tests; [&]Fisher-exact-tests

[+]Immunosuppressive therapy, renal dialysis, cirrhosis Child C, human immunodeficiency virus infection, active malignancy, pregnancy, splenectomy, agranulocytosis.

n.s. = not significant

Table 2 – Odds ratios of independent variables associated with enterococcal orthopaedic infections (by univariate and multivariate unmatched logistic regression analysis)*

n = 2740	Univariate analysis	Multivariate analysis
Female sex	0.7 (0.5-1.2)	0.8 (0.5-1.5)
Age (continuous variable, years)	1.0 (1.0-1.0)	n.d.
- >50 years compared to <50	1.3 (0.9-1.8)	1.1 (0.7-1.8)
C-reactive protein (continuous variable, mg/L)	1.0 (1.0-1.0)	n.d.
- >50 mg/L compared to <50	1.2 (0.9-1.5)	n.d.
Prior antibiotic use (continuous variable, days)	1.0 (0.9-1.1)	1.2 (0.7-2.0)
- Prior cephalosporin use°	***2.3 (1.3-4.2)***	1.7 (0.8-3.4)
Immune suppression[+]	***2.2 (1.5-3.3)***	1.5 (0.8-2.7)
Diabetes mellitus	***3.1 (2.0-4.6)***	***1.9 (1.2-3.0)***
Type of infection		
Native bone and joint infection	1.4 (0.4-2.1)	n.d.
Osteosynthesis (implant) infection	***1.7 (1.1-2.6)***	***2.0 (1.2-3.3)***
- Prosthetic joint infection	1.6 (0.9-2.7)	n.d.
Foot infection	***2.3 (1.5-3.6)***	***1.9 (1.2-2.9)***
Polymicrobial infection	***0.5 (3.0-10.0)***	***6.0 (3.9-9.4)***

* Results are displayed as odds ratio (95% confidence interval).

Variables in bold and *italic* are statistically significant (*p* value <0.05)

[+] Immune-suppressive therapy, dialysis, cirrhosis Child C, human immunodeficiency virus infection, active malignancy, pregnancy, splenectomy, agranulocytosis

n.d. = not done

°Cephalosporin use = for prophylactic and therapeutic purposes