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Research Paper

Which Orthopaedic Patients Are Infected with Gram-negative Non-fermenting Rods?

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Abstract

Background: 1st and 2nd generation cephalosporins used for perioperative prophylaxis in orthopaedic surgery do not cover non-fermenting Gram-negative rods (NFR).

Methods: Epidemiological cohort study of adult patients operated for orthopedic infections between 2004 and 2014 with perioperative cefuroxim or vancomycin prophylaxis. Exclusion of polyneuropathic ischemic foot infections and septic bursitis cases.

Results: Of the total 1840 surgical procedures in the study, 430 grew Gram-negative pathogens (23%), of which 194 (11%) were due to NFR and 143 (8%) to *Pseudomonas aeruginosa*. Overall, 634 episodes (35%) involved orthopaedic implants (321 arthroplasties, 135 plates, 53 nails, and others). In multivariate analysis and group comparisons, especially preoperative antibiotic use (124/194 vs. 531/1456; $p<0.01$) was significantly associated with NFR.

Conclusions: Overall proportion of NFR oscillated between 9% and 13% among our orthopaedic infections. Variables associated with NFR were antibiotic use prior to hospitalization. The low infection rate of NFR following elective surgery and the community-based epidemiology, has led us to keep our standard perioperative prophylaxis unchanged.

Key words: Orthopaedic infections; epidemiology; Gram-negative; non-fermenting rods; *Pseudomonas aeruginosa*

Introduction

We frequently see Gram-negative non-fermenting rods (NFR), such as *Pseudomonas* or *Enterobacter spp*, in orthopedic infections [1-5], e.g. after trauma [6,7] or open fractures [8]. Simultaneously, we are witnessing a rising prevalence of extended-spectrum beta-lactamase producing-rods body carriage (ESBL) on orthopaedic wards [9]. Some authors speculate that the number of orthopaedic infections due to these Gram-negative pathogens might rise in the future, especially if we consider the increasing number of elderly, diabetic [10], organ transplant [11] and oncologic persons [12] among our orthopaedic patients. According to the United States National Healthcare Safety Network, NFR infections rank fourth among the most important pathogens for all device-associated infections in the last decade [13]. Based on expert recommendations, most centers use 1st and 2nd generation cephalosporins or vancomycin for perioperative prophylaxis [14]. However, these antibiotics do not cover NFR or ESBL.

We investigate if subgroups of orthopaedic patients or procedures are particularly at risk for Gram-negative, and more specifically, NFR, ESBL or *P. aeruginosa* infections; eventually warranting an adaptation of antibiotic prophylaxis in some specific cases. Of note, we do not investigate outcomes of

various Gram-negative infections, nor the incidence or Gram-negative nosocomial infections, which have been already described elsewhere [2,3,15-21].

Methods

We performed a retrospective cohort study of adult patients operated at Geneva University Hospitals between January 2004 and December 2014. Standard perioperative antibiotic prophylaxis was a single intravenous dose of 1.5g cefuroxim or 1g vancomycin. The infection database encompassed soft tissue, joint, bone and implant infections, including both community-acquired and nosocomial infections, and supported by the local Ethical Committee.

We defined an "orthopaedic infection" as the presence of intraoperative pus, together with other symptoms (new onset of pain, fever, redness, discharge, sinus track), and radiographic signs (implant loosening or presence of sequestrae). To avoid data clustering, we included only the first episode of the same infection and excluded recurrent episodes from further analysis. We also excluded pediatric cases, polyneuropathic or ischemic foot infections, such in diabetic patients, and septic bursitis cases, because these were considered as too different populations. We processed all specimens in the microbiology laboratory according to Clinical and Laboratory Standard's Institutes' recommendations [22] except for switching to EUCAST criteria (European Committee on Antimicrobial Susceptibility Testing) in spring 2014 [23]. The standard incubation period for cultures was 5 days.

We performed group comparisons using the Pearson χ^2-test or the Wilcoxon rank-sum test. To adjust for case-mix, we performed an unmatched logistic regression analysis (outcome: Gram-negative infection). Independent variables with a p value ≤0.20 in univariate analysis were introduced stepwise into the multivariate analysis, by avoiding interactions. P values ≤0.05 were significant. We used STATA™ software (9.0; College Station, USA).

Results

In total, 2740 infection episodes were retrieved, of which 428 were diabetic foot infections and 472 septic bursitis cases, which were excluded from further analysis. An additional 261 patients were not operated and thus not followed-up by our service. The median age of the remaining 1840 episodes in the study was 57 years (range, 18-99 years). There were 652 females and 1188 males; 598 patients (33%) were immune-compromised (diabetes mellitus, solid organ or bone marrow transplants, untreated HIV disease, immune-depressive drugs, active cancer, cirrhosis CHILD C, dialysis, pregnancy, and splenectomy). Overall, 634 episodes involved implants: 321 arthroplasties, 135 plates, 53 nails, 31 spondylodesis and others. The number of bone and joint infections (including implants) was 1023 (56%), that of soft tissue infections 817. The median duration of antibiotic use prior to intraoperative sampling was 4 days; it occurred in 790 (43%) of all cases.

Gram-negative infections

Overall, 430 (24%) samples grew Gram-negative pathogens (Table 1), of which 194 (11%) were due to NFR (Table 2), 143 (8%) to *P. aeruginosa* (Table 3), and six (0.01%) to ESBL-producing gram-negative rods. The proportion of NFR among Gram-negative pathogens was 45% (258/568). We could not detect Gram-negative infection outbreaks throughout the entire study period [24]. In multivariate analysis adjusting for case-mix, polymicrobial infections and prior antibiotic use were the only significant predictors (Table 4). These associations were similar for NFR and *P. aeruginosa*, without major differences between them (Tables 1-3).

Table 1. Comparison of orthopedic infections due to Gram-negative versus other pathogens at Geneva University Hospitals, 2004-2014.

	Other pathogens n=1410 (77%)	*p value*	Gram-negative pathogens n=430 (23%)
Patient characteristics			
F:M (percentage of female)	491:919 (35%)	ns	161:269 (37%)
Median age	54 years	<0.01	61 years
- Age < 51 years	615 (44%)	<0.01	150 (35%)
- Age 51 to 80 years	638 (45%)	<0.01	226 (53%)
- Age > 80 years	157 (11%)	ns	54 (13%)
Median serum C-reactive protein level	81 mg/L	ns	88 mg/L
- CRP < 51mg/L	427 (30%)	<0.05	108 (25%)
- CRP 51 to 200mg/L	432 (31%)		139 (32%)
- CRP > 200mg/L	551 (39%)		183 (43%)
Prior antibiotic use	561 (40%)	<0.01	229 (53%)
Median duration of prior antibiotic use	4 days	ns	5 days
Immune compromised[+]	439 (31%)	0.02	159 (37%)
- Diabetes mellitus	230 (16%)	<0.01	101 (24%)
Type of infection			
Osteoarticular infections	808 (57%)	<0.01	215 (50%)
All implant-associated infections	488 (35%)	ns	146 (34%)
- Prosthetic joint infections	251 (18%)	ns	70 (16%)
- Spondylodesis infections	20 (1%)	<0.05	11 (2%)
- Nail infections	40 (3%)	ns	13 (3%)
- Plate infections	107 (8%)	ns	28 (7%)
Soft tissue abscess	396 (28%)	ns	102 (24%)
Shoulder infections	82 (6%)	<0.01	10 (2%)
Spine infections	20 (1%)	ns	11 (3%)
Polymicrobial infections	188 (15%)	<0.01	207 (48%)

ns = not significant

[+] = diabetes, immune-suppressive medication, dialysis, active cancer, untreated HIV disease, cirrhosis CHILD C, pregnancy, splenectomy.

Table 2. Comparison of orthopedic infections due to Gram-negative non-fermenting rods versus other pathogens.

	Other than non-fermenting rods n=1646 (89%)	*p value*	Non-fermenting rods n=194 (11%)
Patient characteristics			
F:M (percentage of female)	497:957 (31%)	ns	69:125 (36%)
Median age	56 years	ns	61 years
- Age ≤ 50	615 (42%)		70 (36%)
- Age 51 to 80	668 (46%)		100 (52%)
- Age > 80	173 (12%)		24 (12%)
Median serum C-reactive protein level	87 mg/L	ns	86 mg/L
- CRP < 51mg/L	417 (29%)	ns	47 (24%)
- CRP 51 to 200mg/L	455 (31%)		61 (31%)
- CRP > 200mg/L	584 (40%)		86 (44%)
Prior antibiotic use	531 (36%)	<0.01	124 (64%)
Median duration of prior antibiotic use	3 days	<0.01	7 days
Immune-compromised[+]	471 (32%)	ns	68 (35%)
- Diabetes mellitus	259 (18%)	ns	43 (22%)
Type of infection			
Osteoarticular infections	824 (57%)	ns	104 (54%)
All implant-associated infections	514 (35%)	ns	82 (42%)
- Prosthetic joint infections	270 (19%)	ns	31 (16%)
- Spondylodesis infections	23 (2%)	0.05	7 (4%)
- Nail infections	44 (3%)	ns	8 (4%)
- Plate infections	109 (7%)	ns	22 (11%)
Soft tissue abscess	396 (27%)	ns	43 (22%)
Shoulder infections	77 (5%)	0.02	3 (2%)
Spine infections	68 (5%)	ns	5 (3%)
Polymicrobial infections	305 (21%)	<0.01	90 (46%)

ns = not significant

[+] = diabetes, immune suppressive medication, dialysis, active cancer, untreated HIV disease, cirrhosis CHILD C, pregnancy, splenectomy

Table 3. Comparison of orthopedic infections due to *Pseudomonas spp* versus other pathogens.

	Other than *Pseudomonas* n=1697 (92%)	*p value*	*Pseudomonas* spp n=194 (8%)
Patient characteristics			
F:M (percentage of female)	596:1101 (35%)	ns	56:87 (39%)
Median age	56 years	ns	56 years
- Age < 51	705 (42%)		60 (42%)
- Age 51 to 80	795 (47%)		69 (51%)
- Age > 80	197 (12%)		14 (10%)
Median serum C-reactive protein level	87 mg/L	<0.01	66 mg/L
- CRP < 51mg/L	490 (29%)		45 (31%)
- CRP 51 to 200mg/L	527 (31%)		44 (31%)
- CRP > 200mg/L	680 (40%)		54 (38%)
Prior antibiotic use	712 (42%)	<0.01	78 (55%)
Median duration of prior antibiotic use	4 days	ns	5 days
Immune-compromised[+]	556 (33%)	ns	42 (29%)
- Diabetes mellitus	306 (18%)	ns	25 (17%)
Type of infection			
Osteoarticular infections	952 (56%)	ns	71 (50%)
All implant-associated infections	588 (35%)	ns	46 (32%)
- Prosthetic joint infections	308 (18%)	<0.01	13 (9%)
- Spondylodesis infections	25 (1%)	0.02	6 (4%)
- Nail infections	49 (3%)	ns	4 (3%)
- Plate infections	123 (7%)	ns	12 (8%)
Soft tissue abscess	472 (28%)	0.01	26 (18%)
Shoulder infections	91 (5%)	0.01	1 (1%)
Spine infections	74 (4%)	ns	3 (2%)
Polymicrobial infections	324 (22%)	<0.01	71 (50%)

ns = not significant

[+] = diabetes, immune-suppressive medication, dialysis, active cancer, untreated HIV disease, cirrhosis CHILD C, pregnancy, splenectomy.

Table 4. Logistic regression analysis with outcome "Gram-negative infection".

	Univariate analysis *Odds ratio with 95% confidence intervals*	Multivariate analysis *Odds ratio with 95% confidence intervals*
Female sex	1.1, 0.9-1.4	n.a.
Median age	1.0, 1.0-1.0	1.0, 1.0-1.0
Serum C-reactive protein level at admission	1.0, 1.0-1.0	n.a.
Immune-compromised	***1.3, 1.0-1.6***	1.1, 0.9-1.5
- diabetes mellitus	***1.6, 1.2-2.1***	n.a.
Bacteraemia	0.7, 0.5-1.1	0.7, 0.5-1.1
Presence of osteosynthesis material	1.0, 0.8-1.2	1.0, 0.7-1.4
- total prosthetic joint	0.9, 0.7-1.2	1.0, 0.7-1.5
- nails	1.1, 0.6-2.0	n.a.
- plates	0.8, 0.6-1.3	n.a.
Prior antibiotic use	***1.7, 1.2-2.4***	***2.0, 1.5-2.5***
Bone and joint infection	0.7, 0.6-1.0	n.a.
Shoulder infections	***0.5, 0.2-0.9***	n.a.
Spine infections	0.8, 0.4-1.4	n.a.
Presence of abscess	0.8, 0.6-1.1	n.a.
Polymicrobial infections	***5.0, 3.8-6.4***	***4.9, 3.8-6.3***

n.a.= analysis not performed. Only results in ***bold and italic*** are statistically significant (two-sided $p<0.05$)

Discussion

In this 11-year single-centre cohort of 1840 operated orthopaedic infections, we witnessed an overall proportion of 24% for Gram-negative pathogens, 11% for NFR, and 8% for *P. aeruginosa*. ESBL infections were quasi inexistent. Of note, even if the proportion of NFR among all infections ranged around 10%, its proportion among Gram-negative pathogens was 45%. Our 45% are consistent with the literature reporting NFR proportions of 49% [17], 51% [16] or 53% [18] among Gram-negative microorganisms.

Thus, a broader antibiotic prophylaxis would make sense if Gram-negative infections were expected in elective surgery, which, however, we found only in the substrata of polymicrobial infections and those with prior antibiotic use. These situations were mainly encountered in cases of community-acquired infections that failed conservative treatment prior to hospitalization. In contrast, elective osteoarticular, prosthetic joint and implant-related infections lacked associations with Gram-negative bacteria, which

suggest a true lack of genuine Gram-negative association.

In conclusion, with a low proportion of NFR and ESBL, and their striking association with community-acquired infections with prior antibiotic intake, we have currently kept our standard perioperative prophylaxis unchanged and continue to survey.

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Competing Interests

All listed authors declare no financial support, grants, financial interests or consultancy that could lead to conflicts of interest with this work.

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