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No need for broad-spectrum empirical antibiotic coverage after surgical drainage of orthopaedic implant infections

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Abstract

Purpose Empirical broad-spectrum antibiotic treatment for orthopaedic implant infections after surgical lavage is common practice while awaiting microbiological results, but lacks evidence.

Methods This was a single-centre cohort study from 1996 to 2010 with a follow-up of two years.

Results We retrieved 342 implant infections and followed them up for a median of 3.5 years (61 recurred, 18 %). Infected implants were arthroplasties ($n=186$), different plates, nails or other osteosyntheses. The main pathogens were *S. aureus* (163, 49 methicillin-resistant) and coagulase-negative staphylococci (60, 45 methicillin-resistant). Median duration of empirical antibiotic coverage after surgical drainage was three days before switching to targeted therapy. Vancomycin was the most frequent initial empirical agent (147), followed by intravenous co-amoxiclav (44). Most empirical antibiotic regimens (269, 79 %) proved sensitive to the causative pathogen, but were too broad in 111 episodes (32 %). Cephalosporins and penicillins were used only in 44 and ten cases, respectively, although they would have covered 59 % of causative pathogens identified later. Multivariate Cox regression analysis showed that neither susceptible antibiotic coverage (compared to non-susceptible; hazard ratio 0.7, 95 % confidence interval 0.4–1.2) nor broad-spectrum use (hazard ratio 1.1, 0.8–1.5) changed remission rates.

Conclusions Provided that surgical drainage is performed, broad-spectrum antibiotic coverage does not enhance remission of orthopaedic implant infections during the first three days. If empirical agents are prescribed from the first day of infection, narrow-spectrum penicillins or cephalosporins can be considered to avoid unnecessary broad-spectrum antibiotic use.

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Introduction

During debridement and/or removal of infected implants, orthopaedic surgeons perform intraoperative microbiological sampling and start empirical antibiotic therapy. Because the pathogen is often unknown at debridement and due to doubts of polymicrobial and resistant nosocomial infections, this initial coverage is usually too large in the antibiotic spectrum. Sometimes, also the local epidemiology with potentially resistant germs determines the choice of empirical antimicrobial therapy and not only the desire to cover all pathogens. However, existing recommendations and guidelines address choices and durations of targeted antibiotic therapy [1, 2], but do not propose initial empirical coverage, which is left to the discretion of the treating surgeon [3]. Many colleagues think that it would be beneficial if empirical antibiotic administration could cover all possible pathogens for arthroplasty [2] and other orthopaedic infections [4], with usual recurrence rates oscillating between 15 and 28 % [2, 5, 6], and especially in cases of implant retention. Experimentally speaking, biofilms are established within a few hours or days [7], and infections

with resistant micro-organisms may harbour more treatment failures than infections due to susceptible bacteria [5]. Therefore it is not surprising that many authors routinely administer vancomycin, alone [3] or in combination with meropenem [2, 3], or aminoglycosides [4] or other antipseudomonal drugs [4], until the pathogen is identified.

However, antibiotic excesses, even of short duration, contribute to the spread of multi-resistant pathogens [8, 9] and might harm the patient, e.g. antibiotic-related diarrhoea in its multiple forms [2]. The prolongation of antibiotic administration beyond 24 hours after surgery favours the acquisition of antibiotic resistance, particularly among Gram-negative pathogens [9], which may become responsible for epidemics in septic orthopaedic wards.

In this study, we postulate that surgical drainage is the most important therapeutic action, while the antibiotic coverage during the initial days does not influence outcome.

Methods

Geneva University Hospitals serve as a 2,000-bed tertiary teaching hospital and the only public health institution in the canton (county). The Orthopedic Service has 132 beds and has conducted an arthroplasty cohort since 1996, together with several prospective databases regarding orthopaedic infections. Patients are followed up after hospital discharge until remission of infection. Arthroplasty patients are followed up at one year and five years, even in the absence of problems.

Data collection and definitions

MS and IU retrospectively collected 61 variables of orthopaedic implant infections in adults from January 1996 to December 2010. The last day of active follow-up was 31 December 2012. We excluded recurrent episodes, paediatric cases, patients in the intensive care units and those that had been treated by antibiotics before admission [10]. The diagnosis of implant infection was based upon the presence of intraoperative pus together with clinical signs of infection (new onset of pain, fever, sinus tract, discharge) and/or radiographic signs of implant loosening. Species identification required the same pathogen to be present in at least two intraoperative samples [11]. This study is about the active spectrum of prescribed antibiotic agents. For our study, we defined what we considered as adequate and what spectrum was too broad for the individual pathogen. In the literature, there is only flawed consensus on what is regarded as "too broad" and what is not, depending on the local medical culture. Empirical antibiotic treatment was considered too broad when the applied agent exceeded the minimum applicable spectrum defined as the use of penicillin, amoxicillin, cefuroxime, cefamandole, clindamycin, co-trimoxazole, flucloxacillin and

depending on the pathogen. These agents cover most of the Gram-positive pathogens, the hallmark of orthopaedic infections. By study definition, broad-spectrum antibiotic therapy covered more than necessary. Consequently, co-amoxiclav, ceftriaxone, ceftazidime, cefepime, piperacillin/tazobactam, carbapenems, quinolones, daptomycin, linezolid, tigecycline, systemic or local aminoglycosides or glycopeptides were considered too broad if the pathogen was susceptible to narrow-spectrum coverage. In contrast, it was considered adequate if the bacteria were resistant, leaving no choice for a narrower spectrum.

Statistical analyses

Group comparisons were performed using the Pearson's χ^2 or the Wilcoxon rank sum test, as appropriate. A Cox regression analysis determined association with outcome remission. Only first episodes of implant infections were included. Independent variables with a p value ≤0.2 in univariate analysis were introduced stepwise in the multivariate analysis [12]. Key variables regarding antibiotic coverage were introduced into the final model independently of univariate results. All variables were checked for confounding and interaction: the latter by interaction terms and Mantel-Haenszel estimates. A p value ≤0.05 (two-tailed) was significant. Stata™ software (9.0, StataCorp, College Station, TX, USA) was used.

Results

Patients and infections

A total of 342 infections in 342 patients (133 women) met the study criteria and were actively followed up for a median of 3.5 years (range, two to 15 years). The median age was 67 years (range 18–94 years) and 109 patients (32 %) were immunocompromised due to diabetes mellitus (n=41), active cancer (25), severe alcoholism (16), steroid medication (13), Child's class C cirrhosis (4), uncontrolled human immunodeficiency virus (HIV) disease (2), splenectomy (1), dialysis (1) and and organ transplantation (1). Six patients suffered from combinations.

The infected implants were 113 hip arthroplasties, 68 knee arthroplasties, two ankle prostheses, one shoulder prosthesis, one elbow prosthesis and one unicompartmental knee implant. The remaining 156 (46 %) infected implants were dynamic hip screws, plates, screws, nails and external fixations in various bones. Pathogens varied considerably. We found 36 different monomicrobial and 18 polymicrobial episodes [11]. Sonication was not performed. The main germ was methicillin-sensitive *Staphylococcus aureus* (114, 33 %), followed by coagulase-negative staphylococci (60, 17 %) and methicillin-resistant *S. aureus* (MRSA; 49,

14 %). Enterococci were encountered in seven infections. Gram-negative infections were a minority (51, 15 %), including 18 episodes due to *Pseudomonas* spp., 11 other non-fermenting rods and two extended-spectrum beta-lactamase producers. Strict anaerobes were detected in five cases, three of which were co-pathogens. Overall, 75 episodes were bacteraemic without haemodynamically compromising sepsis.

Antibiotic treatment

The median duration of empirical treatment was three days (range 0–18 days). Overall, single-agent use (246) was more frequent than combination therapy (67). The most frequent agent used was vancomycin ($n=147$), solely (89) or in combination. Other empirical antibiotics were co-amoxiclav (44 episodes), quinolones (23), flucloxacillin (21), aminoglycosides (18), carbapenems (15), cefepime (15), ceftriaxone (10), clindamycin (13) and piperacillin/tazobactam (2). Co-trimoxazole, daptomycin, fusidic acid, metronidazole, teicoplanin and ceftazidime were mostly co-administered with other antimicrobials in less than three cases each.

The majority of antibiotic regimens (269/342, 79 %) proved to be sensitive to the later identified pathogen, but was too broad in 111 cases (32 %). Of note, 29 patients (8 %) did not receive any empirical treatment, because infection was diagnosed only when intraoperative specimens became positive. Anaerobic coverage with mostly amoxicillin/clavulanate or clindamycin was performed in 130 episodes (38 %), although only three pathogens were real strict anaerobes, while we could not elucidate why exactly the treating physicians chose agents with concomitant anaerobic coverage. Penicillin (including amoxicillin) and first- and second-generation cephalosporins were used in ten and 44 cases, respectively, although they would have covered 59 % of all later identified pathogens. Once the pathogen was identified, the overall median duration of targeted antimicrobial therapy was 56 days (range 14–294 days), of which a median of 14 days intravenously (range 0–100 days).

Surgical treatment

Surgery was part of treatment for every episode with a mean and median number of two interventions (range 0–17). The number of surgical interventions between episodes with broad-spectrum compared to narrow-spectrum coverage was similar (median two vs two interventions, $p=0.77$). In 86 episodes (25 %), the infected implant was retained. Among the 186 arthroplasty infections, 86 (46 %) were treated with debridement and retention alone, 7 (4 %) were removed without further implantation and 91 (49 %) episodes underwent a two-stage exchange with a median interval of nine weeks between the two stages. Only two one-stage arthroplasty exchanges were performed.

Outcomes and multivariate analysis

Among all 342 episodes of implant infections, 61 (18 %) clinically recurred after a median of 5.5 months with identical pathogens. The patient populations with and without recurrences were similar with the exception of arthroplasty retention and immunosuppression (Table 1). Because of a substantial variety of pathogens, antibiotics and implants, we performed a Cox regression analysis to adjust for case mix (Table 2). In multivariate analysis, no variable was associated with recurrence. Adequate choice of empirical drugs [hazard ratio (HR) 0.7, 95 % confidence interval (CI) 0.4–1.2] [reciprocal: wrong antibiotic coverage (HR 1.1, 0.8–1.5)], broad-spectrum coverage (HR 1.1, 0.8–1.5) or duration of vancomycin use (HR 1.0, 1.0–1.0) failed to enhance remission. Of note, the receiver-operating characteristic curve value was 0.80, highlighting an acceptable accuracy of our final model.

Discussion

Among 342 adult patients with implant infections, one fifth underwent an empirical antibiotic treatment post-drainage that did not cover the later identified pathogen, and one third witnessed excessive coverage in our retrospective evaluation of daily clinical practice. However, broad-spectrum antibiotic coverage failed to enhance remission or to reduce the number of surgical interventions. Equally, empirical use of vancomycin showed no protective effect, although in our institution the MRSA endemicity among clinical *S. aureus* isolates is around 28 % [13] and 75 % of clinical coagulase-negative staphylococci are methicillin-resistant [14]. At the same time, we failed to prove any inconvenience for the episodes where empirical therapy was wrongly chosen during the first three days.

Many patients witnessed treatment against anaerobes, although finally there were only five anaerobic (co-)pathogens detected. Regarding this anaerobic coverage, we could not detect why the treating surgeons and physicians chose antimicrobial agents active against anaerobic pathogens. Retrospectively, narrow-spectrum penicillins or second-generation cephalosporins alone would have correctly covered two thirds of the pathogens.

We would discourage the use of routine empirical vancomycin coverage. Our opinion is in line with experts denying the existence of a threshold of resistant staphylococcal surgical site infections [13, 14], above which a switch to glycopeptides would be necessary in terms of prevention and empirical treatment [8, 15]. Authors from the Mayo Clinic successfully treated culture-negative prosthetic joint infections throughout the course with cefazolin alone, with no excess of treatment failure (HR 0.7, 95 % CI 0.2–3.0)

Table 1 Comparison of episodes with and without recurrence of implant infections

	Numbers, $n=342$	Recurrence, $n=61$	p^{a}	Remission, $n=281$
Female gender	133	19 (31 %)		114 (41 %)
Median age		64 years		67 years
Immunosuppression[b]	109	26 (43 %)	0.047	83 (30 %)
Arthroplasty infection	186	31 (51 %)		155 (55 %)
Retained arthroplasties	86	20 (33 %)	0.042	66 (24 %)
Two-stage exchanges	91	11 (18 %)		80 (28 %)
Bacteraemia	75	14 (23 %)		61 (22 %)
MRSA infection[c]	49	11 (18 %)		38 (14 %)
Gram-negative infection	51	10 (16 %)		41 (15 %)
Empirical vancomycin use	147	28 (46 %)		119 (42 %)
Correct empirical antibiotic coverage	269	44 (72 %)		225 (80 %)
Too broad spectrum use	111	21 (34 %)		90 (32 %)
Median duration of empirical antibiotics		3 days		3 days
Median duration of total antibiotic use		60 days		56 days
Median duration of IV antibiotics		14 days		14 days
Median no. of surgical interventions		2 interventions		2 interventions

[a] Pearson's χ^2 test. Only significant values (p value <0.05) are displayed

[b] diabetes, cancer, alcoholism, steroid medication, cirrhosis, HIV, splenectomy, dialysis

[c] Methicillin-resistant *Staphylococcus aureus*

Table 2 Cox regression analysis with outcome *remission of orthopaedic implant infections*

Variable	Univariate analysis HR, 95 % CI	Multivariate analysis HR, 95 % CI
Female gender	1.0, 0.8–1.3	n.a.
Age	1.0, 1.0–1.0	n.a.
Age 65 years compared to < 65 years	1.1, 0.9–1.4	n.a.
Arthroplasty infection	1.0, 0.8–1.3	n.a.
Arthroplasty retention	1.2, 0.8–1.7	n.a.
Two-stage exchanges	0.8, 0.5–1.04	n.a.
All implant retentions	1.2, 0.9–1.6	1.4, 0.8–2.3
Immunosuppression[a]	1.1, 0.8–1.4	1.4, 0.9–2.2
MRSA infection[b]	1.1, 0.8–1.5	n.a.
Gram-negative infection	1.3, 0.9–1.8	n.a.
Due to *Pseudomonas* spp.	1.3, 0.8–2.2	n.a.
Polymicrobial infection	1.2, 0.7–2.3	n.a.
No. of surgical interventions	1.0, 0.9–1.1	1.0, 0.9–1.1
Antibiotic-related parameters		
Empirical vancomycin use	1.2, 0.9–1.5	n.a.
Duration of vancomycin use	1.0, 1.0–1.0	1.0, 1.0–1.0
Correct empirical coverage	0.8, 0.6–1.1	0.7, 0.4–1.2
(Wrong empirical coverage)	*1.2, 0.9–1.6*	*1.1, 0.8–1.5)*
Too broad spectrum use	1.2, 0.9–1.5	1.1, 0.8–1.5
Duration of empirical antibiotics	1.0, 0.9–1.1	1.0, 0.9–1.1
Duration of total antibiotic use	1.0, 1.0–1.0	n.a.
6–12 weeks compared to < 6 weeks	1.1, 0.9–1.5	1.1, 0.7–1.7
>12 weeks compared to < 6 weeks	1.1, 0.8–1.5	1.1, 0.7–2.0

n.a. omitted from final model because of interaction or limited number of variables

[a] Diabetes, cancer, alcoholism, steroid medication, cirrhosis, HIV, splenectomy, dialysis

[b] Methicillin-resistant *Staphylococcus aureus*

[17]. Despite widespread practice and recommendations, few studies scientifically advocate universal empirical vancomycin use after lavage. However, they may stem from institutions where the proportion of MRSA infections was 64 %, compared to 14 % in our study [3].

One theoretical concern of our study relates to retained implants, especially retained arthroplasties. Biofilm formation starts within a very short period of time [7]. If an implant is removed (and therefore the biofilm is removed with the implant), it is conceivable that potentially incorrect antibiotic therapy has no influence on the outcome. In contrast, it might be difficult to understand why an inadequate empirical antibiotic therapy has no influence on treatment failure when the attached implant has not been removed, as we show in this study.

For us, this discrepancy between theoretical concern and practice is not surprising for various reasons. First, empirical antibiotic coverage only lasted for the first three days (e.g. 7 % of the total duration), and not the rest of the antibiotic prescription (93 %). Second, even if the prosthesis was retained, the patient underwent at least one thorough debridement, which is more important in mechanically removing the biofilm than the chemical effect of antibiotic drugs, which combat bacteria but not the matrix of the biofilm per se. Finally, biofilm formation within hours is supported by in vitro data, but no one knows the time delay above which this biofilm becomes clinically decisive. In the literature, some groups of expert researchers advocate that, in vitro, biofilms are established rapidly, but in vivo, they still allow clinicians to retain the prosthesis up to three weeks after the onset of infection [1, 17].

In conclusion, we think the most important part in the treatment of orthopaedic implant infections is surgical drainage, long before antibiotics show benefit. The effect of this initial lavage is substantial, reducing microbial inoculum and removing pus, independently of whether or not the implant has been retained. Penicillins or cephalosporins might be sufficient to bridge the short time until availability of microbiological results, even if this narrow spectrum does not cover the pathogen. We therefore discourage the use of routine empirical vancomycin or other broad-spectrum coverage, unless the local epidemiology is unusual or there is currently an outbreak situation due to resistant pathogens. If future prospective trials confirm our findings, there is space for antibiotic stewardship, cost savings and reduction of potential spread of antibiotic resistance in orthopaedic wards [9].

Our study has biases: (1) It is a single-centre retrospective study, limiting the general application of the results. Although including 342 episodes, this number might be too small to detect differences in the outcome. Concerning substrata of implant infections, only 86 implants were retained, and only two witnessed a one-stage arthroplasty exchange, further limiting the generalisability of our data. (2) Our patients had no haemodynamic compromises. For patients in intensive care, adequate initial empirical antibiotic coverage is crucial and may be lifesaving. (3) Patients may have been followed elsewhere. However, because Geneva University Hospitals are the only public hospital in the area, and most arthroplasty patients participate in our register, we estimate this bias as minimal. (4) With only 29 episodes without any empirical antibiotics at all, we cannot pronounce on the question of whether antibiotic coverage per se would be necessary. This question needs a much larger study population. (5) The duration of empirical therapy peaked around three days, which should not be confounded with culture-negative therapy throughout the course. The literature is divided on whether a culture-negative therapy would [6] or would not be [10, 16] associated with higher failure risk.

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