Acta Orthop. Belg., 2010, **76**, 254-259

ORIGINAL STUDY

Empirical antibiotic therapy in prosthetic joint infections

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When dealing with prosthetic joint infections (PJI) there is often the need to start antibiotic therapy without having identified the underlying pathogen. Under these circumstances there is no consensus regarding which antibiotic to use. We aimed to produce local recommendations for empirical antibiotic treatment of PJI by describing the microbiological spectrum involved and respective antibiotic susceptibility profile. We examined the records of 75 consecutive patients that underwent surgery for prosthetic joint infection from July 2001 to December 2008. There were 49 women and 26 men with an average age of 63 years. Ninety culture results were available from 41 hips and 34 knee replacements.

***Staphylococcus sp.* was present in most infections (72.8%) regardless of surgical site or classification. The prevalence of methicillin-resistance among staphylococci was 64.2% with no relevant difference between sub-groups. Vancomycin is 100% effective against most commonly isolated Gram positives. Gram negative pathogens were present in about 15% of all cases, especially in haematogenous and chronic infections. Carbapenems and aminoglycosides are the most effective antibiotics against these pathogens.**

Our results suggest that in acute post-operative infections, treatment should start with vancomycin. In chronic and haematogeneous infections, vancomycin in combination with carbapenems appears to be an effective regimen. Treatment should be adjusted as soon as preliminary or definitive microbiology results are available.

Keywords : prosthetic joint infection ; microbiology ; empirical antibiotics ; antibiotic resistance.

INTRODUCTION

The number of joint replacements procedures has increased steadily during the past few years. There is a trend towards a continuing rise particularly concerning total knee arthroplasties and revision surgery (*8*). This is especially relevant if we remember that both knee replacement and revision surgery have a higher risk of infection comparing to hip and primary surgery respectively (*5*). In our own institution the infection rates for primary total hip and knee arthroplasty (at two years follow-up) are 1.8% and 3.3% respectively and even higher for revision surgery (*17*). Subsequently, the number of infected arthroplasties is also on the rise (*7*).

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No benefits or funds were received in support of this study

Despite good results in selected patients with debridement and retention of implants for acute infections (*9,18*), two-stage revision remains the most reliable method of treatment for chronically infected prosthetic joints, consisting of an initial debridement with hardware removal, insertion of an antibiotic loaded cement spacer, a period of intravenous antibiotic therapy, and, finally, a delayed reimplantation (*3*).

After initial debridement or hardware removal and before obtaining final microbiological results, antibiotic therapy should be started immediately. If the infecting microorganism has been previously identified, the antibiotic choice is evident. However there is no consensus regarding which antibiotic to use when there is no previous isolate. Since laboratory results might take up to several days, effective empirical therapy plays an important role both medically and economically.

Our goal is to describe the microbiological spectrum of prosthetic joint infections (PJI) and respective antibiotic susceptibility profile, and so guide the choice of empirical antibiotic treatment.

MATERIALS AND METHODS

We retrospectively reviewed the clinical and laboratory records of 75 consecutive patients that underwent surgery for total hip or knee prosthetic joint infection from July 2001 to December 2008 at our institution. Recorded information included basic patient demographics, arthroplasty site, infection classification, culture results (including bacterial species when positive) and the antibiotic sensitivity profile as tested with the standard protocol of our microbiology laboratory.

The mean age was 63 years and 65% (49) of the 75 patients were women. There were 41 hips and 34 knee replacements. Ninety culture results were available from various surgical interventions : debridement procedures or excision arthroplasty. Some patients had infections at different sites and others had new or recurrent infections.

Infections were classified according to Tsukayama *et al* (*19*). Chronic infection was defined as occurring more than four weeks after the index surgery, acute infection when occurring within four weeks after the index surgery and haematogeneous infection when considered to originate from a remote site seeding. For an infection to be considered as haematogeneous, the patient had to present with acute systemic signs of infection and/or acute joint inflammation in a previously asymptomatic prosthesis more than one month after total joint arthroplasty even in the absence of a documented site of remote infection with the same organism.

All culture samples were taken from deep tissues or fluid collected during surgery. A result was considered positive when two or more specimens tested positive for the same organism(s) or a single positive specimen when clinical and intra-operative findings were consistent with prosthetic joint infection. Although Atkins *et al* (*1*) have found that three or more independent positive specimens as part of a set of five or six samples collected is an accurate and practical microbiological definition of infection, we chose to increase sensitivity by reducing the number of positive cultures necessary for diagnosis.

Culture negative infection was defined by presence of appropriate clinical and intra-operative findings (elevated CRP and ESR, elevated synovial fluid leukocyte count with high neutrophile percentage, cutaneous sinus tract, gross purulence surrounding the prosthesis or positive histopathology) in the absence of culture growth. The antibiotic susceptibility profiles of all microorganisms were studied except *S.aureus* isolated before 2005, leaving a total of 38 *S.aureus* specimens. This reflects our belief that *S.aureus* has a rapidly evolving profile and only more recent isolates should be considered (n = 38).

Using the PASW Statistics 17.0 (SPSS Inc.), the Chi-square test was applied to compare variation of culture results, microorganisms prevalence and antibiotic resistance traits in different subgroups, with significance set at $p < 0.05$.

RESULTS

We found 55 (61%) cultures originating from chronic infections, 24 (27%) from acute infections and 11 (12%) from haematogeneous infections. Of the 90 microbiology results available, 17.8% (16/90) were culture-negative. This proportion was roughly similar regardless of infection sub-type (*chi-square = 0.028 ; $p < 0.986$*) or surgical site (*chi-square = 0.010 ; $p < 0.922$*). Polymicrobial infections were present in 7.8% (7/90) of all cases also with no significant difference between infection sub-types (*chi-square = 0.595 ; $p < 0.743$*) or surgical site (*chi-square = 0.207 ; $p < 0.649$*).

Gram-positive organisms, especially staphylococci, accounted for the majority of the infections regardless of surgical site or classification. Table I

Table I. — Frequency of isolated microorganisms by site (%)

microorganism	*overall (n = 90)*	*hip (n = 46)*	*knee (n = 44)*
Staphyloccus aureus	54.3	68.3	40.0
Coagulase-negative Staphylococci	18.5	9.8	27.5
Streptococci	6.2	7.3	5.0
Enterococci	2.5	-	5.0
Gram negative	14.8	14.6	15.0
Anaerobes	1.2	-	2.5
Fungi	2.5	-	5.0
Polymicrobial	7.8	6.5	9.1
Culture negative	17.8	17.4	18.2

Table II. — Frequency of isolated microorganisms by infection sub-type (%)

microorganism	*chronic (n = 55)*	*acute (n = 24)*	*haematogenous (n = 11)*
Staphyloccus aureus	46.0	76.2	50.0
Coagulase negative Staphylococci	22.0	9.5	20.0
Streptococci	10.0	-	
Enterococci	-	9.5	
Gram negative	16.0	4.8	30.0
Anaerobes	2.0	-	
Fungi	4.0	-	
Polymicrobial	9.1	4.2	9.1
Culture negative	18.2	16.7	18.2

reflects the overall as well as site specific culture results.

Detailed analysis of the distribution of microorganisms according to the type of infection (see table II) showed a relevant trend towards lower prevalence of Gram-negative isolates in acute postoperative infections *(chi-square = 2.380 ; p < 0.123*) and higher in haematogeneous infections *(chi-square = 2.107 ; p < 0.147*).

Based on all the coagulase-negative staphylococci and on 38 *S.aureus* isolated from 2005 forward, we calculated the prevalence of most commonly used antibiotics susceptibilities (see table III). The most important finding is the high prevalence – almost two thirds – of methicilin-resistant species. There was no difference in prevalence of methicilin-resistance between acute (68.8%), chronic (61.3%) and haematogeneous (66.7%) infections *(chi-square = 0.274 ; p < 0.872*).

Other commonly isolated Gram-positives like streptococci and enterococci had a friendlier profile. All but one were penicillin-sensitive and none was vancomycin-resistant.

The Gram-negative population consists of *Acinetobacter*, *E.coli*, *Enterobacter*, *Proteus* and *Pseudomonas* two each and one *Serratia* and *Salmonella*. Antibiotic resistance profile was studied (see table IV), revealing a high prevalence of multi-resistant species.

DISCUSSION

When confronted with a prosthetic joint infection, an immediate and often prolonged period of intravenous antibiotic administration is warranted after surgery. When there is no previously isolated microorganism, the surgeon faces a difficult choice since there is no consensus concerning which antibiotic to use. A correct choice (one that proves effective against the implicated microorganism) is crucial in order to optimize and shorten in-hospital treatment while waiting for definitive microbiology

Table III. – Staphylococci resistance to antibiotics (n = 53)

Drug	*Resistance (%)*
Methicilin	64.2
Fluoroquinolones	60.4
Clindamycin	41.5
Trimethoprim-sulfamethoxazole	12.8
Fucidic acid	11.4
Rifampicin	6.8
Vancomycin	0.0
Teicoplanin	0.0
Linezolid	0.0

Table IV. — Gram negative microorganisms resistance to antibiotics (n = 12)

Drug	*Resistance (%)*
Ampicilin	75.0
Amoxicilin/clavulanate	58.3
Trimethoprim-sulfamethoxazole	41.7
Fluoroquinolones	27.3
Cephalosporins (3rd generation)	25.0
Piperacilin/tazobactam	25.0
Carbapenems	8.3
Aminoglycosides	8.3

results. Our goal was to elaborate local recommendations to help choose empirical antibiotic therapy since a search of the literature found scarce and conflicting recommendations in this clinical setting.

Our study has several limitations. First, it is a single center retrospective study with potential for selection biases. Second and perhaps the major limitation of this study, was the lack of a standardized protocol for sample gathering and processing methodology. This may have influenced sample interpretation. Third, possible confounding variables such as previous medical and/or surgical treatments, co-morbidities and even day on which the culture results were positive were not accounted for.

Regardless of natural geographic variability, the microbiological spectrum found in our series presents the same main features generally found worldwide (*4,12-14,18,20*). *Staphylococcus aureus* and coagulase-negative *Staphylococci* are the most common aetiological agents and account for over 70% of identified pathogens. Gram-negative organisms play a relevant part in our series, especially in chronic and haematogenous infections. Polymicrobial involvement was found in nearly 8% of our cases, seemingly lower than recently published series that reported 19 to 37% (*10,12*). Also, we found no increased prevalence of polymicrobial infection in the early postoperative period (acute infections) as suggested by Moran *et al* (*12*). On the other hand the number of culture-negative prosthetic joint infections in our series is higher (around 18%) than the average in the literature (*20*). The authors believe the explanation for this lies in the fact that until recently there was no dedicated protocol for sample collection and laboratory processing for prosthetic joint infections. We also detected common mistakes such as no timely antibiotic suspension before surgery or reduced number of samples collected intraoperatively. We believe as do Atkins *et al* (*1*) that a minimum of 5 to 6 samples should be collected.

Our study confirms methicilin-resistant staphylococci as a growing threat. Since Staphylococcus species account for 72.8% of all infections and 64.2% of them are methicilin-resistant, one can deduce that almost 47% of all prosthetic joint infections in our institution involve methicilin-resistant staphylococci (MRS). The rising prevalence of MRS and its subsequent negative impact on treatment outcome is well established (*15,16*). Studied staphylococci show 100% susceptibility to vancomycin (as well as teicoplanin and linezolid) as do all other commonly isolated Gram-positives (streptococci and enterococci), making it the logical choice for empirical use. Other European trials (*12,13*) also found vancomycin to be 100% effective against staphylococci, streptococci and enterococci. Nevertheless the emergence of vancomycin resistance, especially with vancomycin-resistant enterococci (VRE), is a real concern worldwide (*6*). Fulkerson *et al* (*4*) confirmed VRE and even vancomycin resistant *Staphylococcus epidermidis* as a genuine threat in total joint arthroplasty. Antibiotic resistance is a growing concern in Gram-negative microorganisms also (*6*). Fluoroquinolones, piperacilin/tazobactam and even third-generation cephalosporins (e.g. cefotaxime, ceftazidime) resistance appears in about one quarter of our isolates. This might reflect an even higher proportion

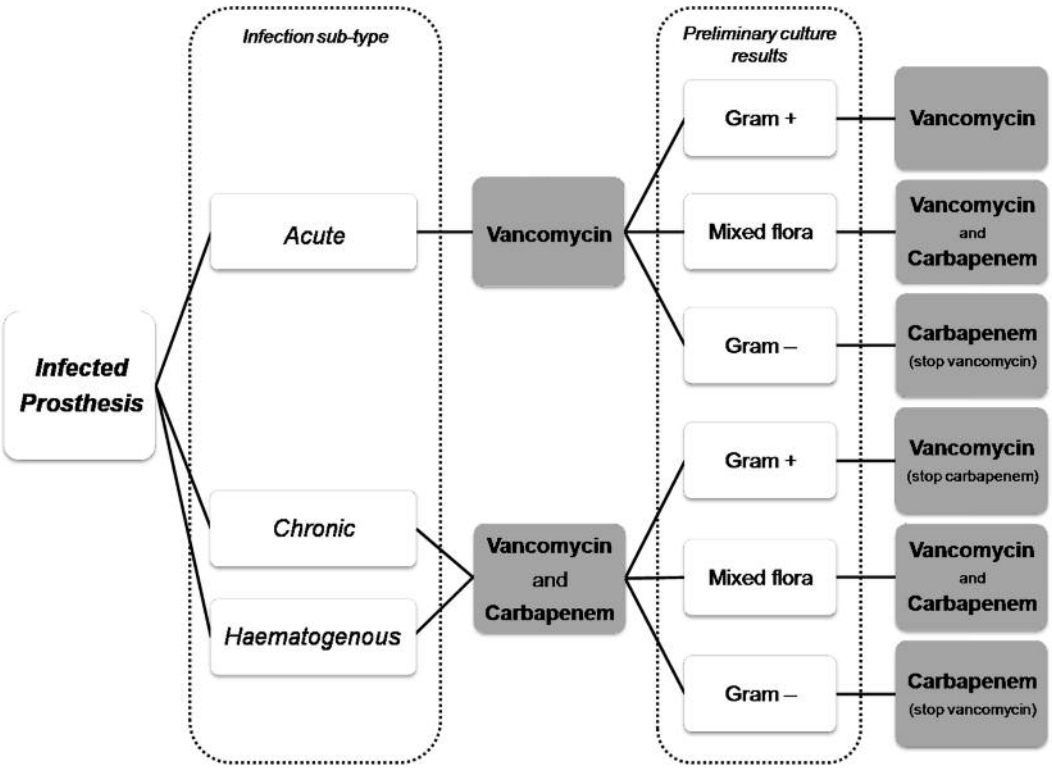

Fig. 1. — Proposed empirical antibiotic therapy fluxogram according to infection classification and preliminary culture results

of *in vivo* resistance since we are not aware of the ESBL status. ESBL are extremely broad spectrum ß-Lactamase enzymes that may emerge as response to environmental pressures, such as exposure to third-generation cephalosporins, thus compromising clinical outcome despite laboratory sensitivity (*6*). This makes carbapenems or aminoglycosides the possible choices for empirical Gram-negative coverage. While combined parenteral administration of aminoglycosides and vancomycin has potentially serious nephrotoxic side-effects, they can be safely added to bone cement. Therefore, although we use tobramycin (together with vancomycin) in spacer manufacturing, we choose carbapenems as empirical parenteral therapy much like Moran *et al* (*12*).

These results also raise a major issue relating to prophylactic antibiotics. Although we have been using cephazolin preoperatively and for a 24-hour period during the study period, the high prevalence of methicilin resistant staphylococci in our series raises the question whether or not to add a preoperative dose of vancomycin as Meehan *et al* recently suggested (*11*).

It is of course of great importance to be aware of local antibiotic resistance patterns when producing guidelines for empirical treatment. Although other centers experience and concerns might justify a narrower spectrum regimen (*4*) we advocate broad spectrum cover despite the potential complications : patient side-effects and encouraging bacterial resistance (*12,13*). Since Gram-positive microorganisms were those most commonly found, regardless of surgery site or infection sub-type and there was no difference in methicilin resistance prevalence, we found the need for vancomycin coverage in all scenarios. Albeit not statistically significant ($p < 0.123$) we found a trend towards reduced Gram-negative prevalence (only 1/24) in acute infections. This explains our choice not to use carbapenem in the acute setting. Figure 1 summarizes our approach. Antibiotic regimens should be rationalized as soon

as preliminary culture results are available, even before final results allow a narrower and more selective drug choice.

Ackowledgments

The authors wish to thank the Microbiology Department for all the help given in this and other ongoing studies.

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