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ORIGINAL ARTICLE

Probabilistic chemotherapy in knee and hip replacement infection: the place of linezolid

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Abstract

Prosthetic joint infection (PJI) can occur with a wide range of microorganisms and clinical features. After replacement surgery of prosthetic joint, prescription of probabilistic broad-spectrum antimicrobial therapy is usual, while awaiting microbial culture results. The aim of our study was to describe the antibiotic susceptibility of microorganisms isolated from hip and knee PJI. The data were collected to determine the best alternative to the usual combination of piperacillin-tazobactam (TZP) or cefotaxime (CTX) and vancomycin (VAN). Based on a French prospective, multicenter study, we analyzed microbiological susceptibility to antibiotics of 183 strains isolated from patients with confirmed hip or knee PJI. In vitro susceptibility was evaluated: TZP+VAN, TZP+linezolid (LZD), CTX+VAN, and CTX+LZD. We also analyzed resistance to different antibiotics commonly used as oral alternatives. Among the 183 patients with PJI, 62 (34%) had a total knee prosthesis, and 121 (66%) a hip prosthesis. The main identified bacteria were *Staphylococcus aureus* (32.2% of isolates), coagulase-negative staphylococci (27.3%), *Enterobacteriaceae* (14.2%), and *Streptococcus* (13.7%). Infections were polymicrobial for 28 (15.3%) patients. All combinations were highly effective: CTX+VAN, CTX+LZD, TZP+VAN, and TZP+LZD (93.4%, 94%, 98.4%, and 98.9% of all cases respectively). Use of LZD instead of VAN in combination with a broad-spectrum beta-lactam covers almost all of the bacteria isolated in PJI. This association should be considered in probabilistic chemotherapy, as it is particularly easy to use (oral administration and no vancomycin monitoring).

Keywords Prosthetic joint infection · Probabilistic antibiotics

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Introduction

Prosthetic joint infection (PJI) is a rare but serious complication during knee and hip surgery. European monitoring reports infection incidence of 1.1% and 0.6% for hip and knee arthroplasty respectively in 2014 [1]. The consequences of incomplete empirical antibiotic coverage could be devastating in PJI, so this treatment should cover both Gram-positive and Gram-negative bacteria.

IDSA guidelines do not suggest a particular empirical chemotherapy after surgery [2], while Italian guidelines suggest an algorithm based on the risk factors of methicillin-resistant *S. aureus* (MRSA) [3]. French guidelines recommend the use of vancomycin (VAN), associated with an intravenous third-generation cephalosporin such as cefotaxime (CTX) or with piperacillin/tazobactam (TZP) [4]. This empirical treatment usually lasts 10 to 14 days, after which antimicrobial therapy can be adjusted when microbiological documentation is available. The goal of this study was to describe the antibiotic susceptibility of microorganisms found in PJI, in view of evaluating linezolid (LZD) as an alternative to VAN in probabilistic treatment of PJI. Sensitivity to antibiotics commonly used as relays was also studied.

Patients and methods

Study population

From December 2010 to March 2012, consecutive patients from seven French medical centers with suspected acute or chronic PJI were enrolled in a multicenter, prospective, observational, cross-sectional study. All patients had five surgical samples. Our study focuses on patients with microbiologically confirmed PJI.

Definition of PJI

Definition of PJI relies on clinical and microbiological features, as described in Bémer et al. [5].

Laboratory analysis

All samples were cultured as described by Bémer et al. [5]. Antimicrobial susceptibility testing was performed according to the EUCAST recommendations effective from 2010 to 2012. All strains with intermediate susceptibility were considered as resistant during the analysis. Results of susceptibility testing were pooled for polymicrobial infections. Four probabilistic antimicrobial combinations were evaluated: TZP+VAN, TZP+LZD, CTX+VAN, and CTX+LZD. Strains were categorized "S" if they were susceptible to at least one of the empirical antibiotics used. Susceptibility to antibiotics, commonly used as oral relays, was also evaluated.

Ethics

The study protocol (PHRCI API/N/041) was approved by the institutional review board and ethics committee. Informed consent was obtained from each patient before inclusion.

Results

Over a 2-year span, 183 patients with microbiologically documented PJI were included.

The clinical findings of patients and the microbiological data are shown in Table 1.

Staphylococci ($n = 135$) were the main identified organism: 39.9% ($n = 73$) of *S. aureus* and 33.9% ($n = 62$) of CoNS.

Table 1 Clinical and microbiological features of the 183 cases of hip or knee PJI

Variable	No. of cases	%
Characteristics of patients		
Age	71 ± 13.3	
Male sex	98/183	53.6
Total knee arthroplasty	62/183	33.9
Total hip arthroplasty	121/183	66.1
Pre-surgery punction and/or blood culture	82/183	44.8
Full match with surgery samples	69/82	84.1
Clinical features (data available for 175 patients)		
Number of anterior surgeries = 1	99/175	56.6
Number of anterior surgeries = 2	54/175	30.9
Number of anterior surgeries ≥ 3	22/175	12.6
Type of surgery		
Debridement with retention	59/175	33.7
One-stage technique	47/175	26.9
Two-stage technique	61/175	34.9
Permanent explantation of joint prosthesis	8/175	4.6
Acute infection	37/175	21
Chronic infection	128/175	73
Acute or chronic status not available	10/175	6
Microbiological features		
Polymicrobial cases	28	15.3
Causative organism (including polymicrobial data)		
Staphylococcus aureus	73	32.2
Coagulase-negative Staphylococci	62	27.3
Enterobacteriaceae	26	14.2
Streptococci	25	13.7
Anaerobic	8	4.9
Enterococci	8	4.4
Cutibacterium spp.	7	3.8
Pseudomonas aeruginosa	7	3.8
Others	11	6.0

Table 2 Antimicrobial susceptibility to probabilistic chemotherapy of microorganisms isolated from hip and knee surgery

	TZP	CTX	VAN	LZD	TZP/VAN	TZP/LZD	CTX/VAN	CTX/LZD
Isolated bacteria								
Staphylococcus aureus ($n = 73$)	82.2%	82.2%	100%	100%	100%	100%	100%	100%
Coagulase-negative Staphylococci ($n = 62$)	53.2%	53.2%	95.2%	100%	98%	100%	98%	100%
Enterobacteriaceae ($n = 26$)	88.5%	88.5%	–	–	88.5%	88.5%	88.5%	88.5%
Streptococci without Enterococci ($n = 25$)	100%	100%	100%	100%	100%	100%	100%	100%
Enterococci ($n = 8$)	100%	0%	100%	100%	100%	100%	100%	100%
Pseudomonas aeruginosa ($n = 7$)	100%	0%	–	–	100%	100%	0%	0%
All infections, polymicrobial included ($n = 183$)	73.2%	68.3%	84.2%	84.7%	98.4%	98.9%	93.4%	94.0%

TZP, piperacillin-tazobactam

CTX, cefotaxime

VAN, vancomycin

LZD, linezolid

Among the *Enterobacteriaceae* infections ($n = 26$), nine were due to *Escherichia coli*, six to *Enterobacter cloacae* complex, five to *Proteus mirabilis*, three to *Serratia marcescens*, and three to *Klebsiella spp.*

Bacterial susceptibilities to probabilistic antimicrobials isolated from hip or knee surgery are shown in Table 2. Among the 73 *S. aureus* isolates, 17.8% ($n = 13$) were methicillin-resistant, while all were susceptible to VAN and LZD. CoNS were methicillin-resistant (MRCoNS) in 46.8% of cases ($n = 29$), and three strains were resistant to VAN (one methicillin-resistant and two methicillin-susceptible). All CoNS were susceptible to LZD. *Enterobacteriaceae* were resistant to CTX and TZP with 11.5% ($n = 3$) of isolates for both molecules.

The two recommended combinations (TZP+VAN and CTX+VAN) are effective in 98.4% ($n = 180/183$) and 93.4% ($n = 171/183$) of cases respectively. LZD is as effective as VAN in combination, with 98.9% susceptibility ($n = 181/183$) for TZP+LZD and 94% ($n = 172/183$) of cases covered for CTX+LZD. Resistance to the empirical treatment was due to three *Enterobacteriaceae*, one *P. aeruginosa*, and one methicillin-resistant CoNS.

Susceptibility to standard oral relay is shown in Table 3.

Table 3 Antimicrobial susceptibility to standard oral relay chemotherapy of microorganisms isolated from hip and knee surgery

	FQ	SXT	Clindamycin	Rifampicin	Tetracycline
Staphylococcus aureus ($n = 73$)	80.8%	97.3%	95.8%	93.1%	96.4%
MSSA ($n = 60$)	95.0%	96.7%	98.3%	94.9%	95.6%
MRSA ($n = 13$)	15.4%	100.0%	84.6%	84.6%	100.0%
Coagulase-negative Staphylococci ($n = 62$)	57.4%	82.3%	75.4%	91.9%	73.3%
MSCoNS ($n = 33$)	96.6%	96.6%	89.7%	96.6%	89.5%
MRCoNS ($n = 29$)	21.9%	69.7%	62.5%	87.9%	61.5%
Enterobacteriaceae ($n = 26$)	73.1%	84.6%	–	–	–
Streptococci without Enterococci ($n = 25$)	85%	100%	81.3%	91.3%	73.3%
Pseudomonas aeruginosa ($n = 7$)	100%	0%	–	–	–

FQ, fluoroquinolones

SXT, trimethoprim-sulfamethoxazole

MSSA, methicillin-sensible Staphylococcus aureus

MSCoNS, methicillin-sensible coagulase-negative Staphylococci

MRSA, methicillin-resistant Staphylococcus aureus

MRCoNS, methicillin-resistant coagulase-negative Staphylococci

Discussion

In this study, we have shown that standard probabilistic antibiotic recommendations for PJI are efficient in more than 93% of cases. Intravenous VAN can be replaced by LZD with the same in vitro results. Some centers have reported use of LZD in their local probabilistic chemotherapy protocol [6].

VAN is a well-known antibiotic but has drawbacks, including kidney toxicity (increased when associated with TZP), vein irritation, and narrow therapeutic index [7–9]. CoNS with decreased susceptibility to glycopeptides are also slowly emerging in bone and joint infection [10, 11].

LZD has bioavailability of 100%, allowing for immediate oral administration or a rapid oral relay [12]. LZD is bacteriostatic on staphylococci and enterococci. As reported by Wald-Dickler et al. [13], there is no evidence of a difference in efficacy between bacteriostatic and bactericidal treatments. While the most common adverse effects of LZD are hematologic and peripheral nerve toxicities, they are closely bounded to therapy duration [14]. Indeed, studies have shown that treatment duration longer than 10 days is a predictor of thrombocytopenia induced by LZD [15]. Probabilistic treatment in the case of PJI should not last longer than 10 to 14 days (time needed to retrieve bacterial culture and antibiotic susceptibility testing).

Intrinsically, LZD is more expensive than VAN, but no central venous line is needed, and therapeutic monitoring is unnecessary [16, 17]. No resistance to LZD was detected in our cohort. More recently, the LEADER (USA, 2015) and ZAAPS (non-USA, 2016) surveillance programs showed a very low rate of resistance [18, 19]. Both studies reported 99.9% LZD-susceptibility for *S. aureus* and 98.7–99.2% for CoNS. The described mechanisms involved in Staphylococci are mutation of the 23S rRNA binding site, mutation of the ribosomal protein L3/L4, and acquisition of a plasmid-borne gene (*cfr*, *optrA*, *poxtA*) [20–23]. Outbreaks of LZD-resistant CoNS have been linked with LZD consumption [24–27]. These epidemics are related to intensive care units, with strong selection pressure. Restriction of LZD prescription, associated with isolation procedures, seems able to jugulate emergence of an outbreak. These data suggest that despite the increasing use of LZD and the discovery of new resistance mechanisms in the last years, LZD can be used probabilistically in prosthetic joint infection.

Particular attention should be paid to the results of pre-surgery documentation (blood cultures and/or joint aspiration). In 15.9% of cases ($n = 13$) of our study, one or more bacteria were missing in comparison with per-operative samples. Therefore, probabilistic treatment should be adapted in the event of an uncommon bacteria or resistance mechanism, but without dropping a broad-spectrum chemotherapy in case of polymicrobial infection.

Conclusion

LZD offers clear advantages over VAN in the empirical treatment of PJI. It shows the same in vitro susceptibility, is easier to use than VAN, and is almost free of adverse effects when applied during a short time. However, careful monitoring of the microbiological ecology in each center must be carried out, since several mechanisms of resistance exist and are linked to LZD consumption. An alternative treatment should be considered in patients with prior exposure to oxazolidinones, which is the main risk factor of resistance. Alternative antibiotics, such as daptomycin or tedizolid, should be considered in case of resistance to LZD. Their relevance in probabilistic chemotherapy during PJI could be evaluated in further studies.

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Compliance with ethical standards The study protocol (PHRCI API/N/041) was approved by the institutional review board and ethics committee. Informed consent was obtained from each patient before inclusion.

Conflict of interest The authors declare that they have no conflict of interest.

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