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Original article

Microbiologic epidemiology depending on time to occurrence of prosthetic joint infection: a prospective cohort study

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ABSTRACT

Objectives: The high microbiologic diversity encountered in prosthetic joint infection (PJI) makes the choice of empirical antimicrobial therapies challenging, especially in cases of implant retention or one-stage exchange. Despite the risk of dysbiosis and toxicity, the combination of vancomycin with a broad-spectrum β-lactam is currently recommended in all cases, even if Gram-negative bacilli (GNB) might be less represented in late PJI. In this context, this study aimed to describe the microbiologic epidemiology of PJI according to the chronology of infection.
Methods: This prospective cohort study (2011–2016) evaluated the microbiologic aetiology of 567 PJI according to time of occurrence from prosthesis implantation—early (<3 months), delayed (3–12 months) and late (>12 months)—as well as mechanism of acquisition.
Results: Initial microbiologic documentation ($n = 511$; 90.1%) disclosed 164 (28.9%) *Staphylococcus aureus* (including 26 (16.1%) methicillin-resistant *S. aureus*), 162 (28.6%) coagulase-negative staphylococci (including 81 (59.1%) methicillin-resistant coagulase-negative staphylococci), 80 (14.1%) *Enterobacteriaceae*, 74 (13.1%) streptococci and 60 (10.6%) *Cutibacterium acnes*. Considering nonhaematogenous late PJI ($n = 182$), *Enterobacteriaceae* ($n = 7$; 3.8%) were less represented than in the first year after implantation ($n = 56$; 17.2%; $p < 0.001$), without difference regarding nonfermenting GNB (4.6% and 2.7%, respectively). The prevalence of anaerobes ($n = 40$; 21.9%; including 32 (80.0%) *C. acnes*) was higher in late PJI ($p < 0.001$). Consequently, a broad-spectrum β-lactam might be useful in 12 patients (6.6%) with late PJI only compared to 66 patients (20.3%) with early/delayed PJI ($p < 0.001$).
Conclusions: Considering the minority amount of GNB in late postoperative PJI, the empirical use of a broad-spectrum β-lactam should be reconsidered, especially when a two-stage exchange is planned.
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Introduction

Empirical antimicrobial therapy of prosthetic joint infection (PJI) is a major clinical challenge based on the emergency to introduce an efficient antimicrobial therapy, especially when a retention of prosthesis or a one-stage exchange strategy is planned, as initial therapeutic inaccuracy can have devastating consequences [1], and on the basis of the choice of an appropriate spectrum, which needs to be broad enough to target the most frequently involved pathogens while avoiding potential toxicities. Current guidelines recommend the use of a broad-spectrum β-lactam (i.e. a third-generation cephalosporin or piperacillin/tazobactam) in

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combination with vancomycin, regardless the chronology and the suspected mechanism of acquisition of infection [2,3]. This strategy allows an appropriate coverage of Gram-positive bacteria with vancomycin, including methicillin-resistant staphylococci, streptococci and most anaerobes, which are classically the most commonly encountered aetiologic agents [1,4–9]. Combination with a broad-spectrum β-lactam allows the additional targeting of Gram-negative bacilli (GNB) and other anaerobes [8–10]. However, there are several pitfalls of this combination. Many studies have reported an increased risk of renal toxicity in patients receiving vancomycin in combination with piperacillin/tazobactam [11–14], which is one of the most commonly used β-lactams in this setting. The proportion of GNB in late postoperative PJI is probably lower than in early or delayed infections, which calls into question the need of using a broad-spectrum β-lactam in all cases. Finally, the empirical use of such combination therapy in methicillin-resistant staphylococci PJI could be associated with an increased risk of treatment failure, as monotherapy had been highlighted as a predictor of unfavourable outcome in methicillin-resistant *Staphylococcus aureus* (MRSA) orthopedic device–related infections [15]. Consequently, more precise knowledge of the microbiologic epidemiology of PJI taking into consideration the chronology and route of infection may help to refine the empirical antimicrobial therapy of these difficult-to-treat infections.

In this context, we aimed to analyse the bacteriologic aetiology of PJI depending on the time to occurrence and mechanism of acquisition.

Patients and methods

Ethical statements

This study (ClinicalTrials.gov NCT03191292) received the approval of the French South-East Ethics Committee (reference QH20/2014). All patients received written information about the study. No written informed consent was required for inclusion.

Study design and inclusion/exclusion criteria

This prospective cohort study included all consecutive patients older than 18 years and treated between 2011 and 2016 for a first episode of PJI in a French regional reference centre for complex bone and joint infection. Osteosynthesis and external device–related infections were excluded.

Definitions and data collection

PJI diagnosis was based on clinical symptoms, imaging, biological inflammatory syndrome (C-reactive protein >10 mg/L and/or white blood cell count >10 000/mm^3), intraoperative findings, histopathologic examination and results of microbiologic cultures of peroperative samples.

For each patient, three to five intraoperative periprosthetic tissue samples were collected under sterile conditions. They were then inoculated onto a Columbia sheep's blood agar plate (with reading at days 1, 2 and 3 before being thrown away), two PolyVitex chocolate agar plates (with reading at days 1, 2 and 3 before being thrown away for the first one and with reading at days 7 and 10 for the second one), two blood agar plates for anaerobic incubation (with reading at days 3 and 5 before being thrown away for the first one and with reading at days 7 and 10 for the second one) and into a Schaedler anaerobic liquid broth for which a daily reading was performed. If not cloudy, the broth was systematically subcultured on day 10 onto chocolate and blood agar plates for anaerobic incubation, incubated for 5 days in 5% CO_2 and anaerobic atmosphere, respectively. Isolated bacteria were identified according to standard laboratory procedures (VITEK 2 system or VITEK matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; bioMérieux, Marcy l'Etoile, France). Antibiotic susceptibility profiles were determined using VITEK 2, disc diffusion methods or ATB ANA (bioMérieux) according to the guidelines of the Antibiogram Committee of the French Society for Microbiology. When several specimens were positive, the identification of each type of colony was performed for all specimens. Antimicrobial susceptibility profiles were determined at least twice for each type of bacteria after a random selection among the positive specimens. For each patient, two or more culture-positive peroperative samples were considered significant for low virulent pathogens and/or potential contaminants (i.e. coagulase-negative staphylococci (CoNS), *Corynebacterium* spp., *Cutibacterium acnes*) and at least one for the more virulent pathogens (i.e. *S. aureus,* streptococci, GNB), as recommended in the Infectious Diseases Society of America guidelines [2].

Collected data included patient characteristics (gender and age at time of diagnosis, body mass index and American Society of Anesthesiologists (ASA) score at time of surgery), details about arthroplasty (type, placement time and rank) and clinical symptoms (draining by sinus tract or wound nonunion, fever, pain and local inflammation). A sinus tract, even occurring recently, made us classify the infection as chronic. Finally, time to occurrence from prosthesis implantation, first symptoms date and surgical management date were gathered to chronologically classify PJI.

Time to occurrence allowed to describe early (i.e. first symptom appearance within 3 months after prosthesis implantation), delayed (i.e. first symptom appearance between 3 and 12 months after prosthesis implantation) and late (i.e. first symptom appearance more than a year after implantation) PJI [16]. Late PJI was also classified according to the suspected mechanism of acquisition, differentiating late acute PJI from late chronic PJI. Late acute PJI included infections with an acute clinical presentation, a delay between first symptoms to diagnosis of <4 weeks and a seeding from an obvious source, thus gathering haematogenous seeding, inoculation after infiltration or extension from a contiguous focus of infection. Late chronic PJI occurred when the suspected pathogen inoculation was per- or perioperative and without obvious source of seeding. According to clinical presentation, these late chronic PJI were subdivided into late insidious PJI (symptoms lasting >4 weeks) and late exacerbated PJI (delay between first symptoms and diagnosis of <4 weeks and acute clinical presentation).

Statistical analysis

Descriptive statistics were used to estimate frequencies of the study variables, described as count (percentage) for dichotomous values and median (interquartile range) for continuous values. For the percentage calculation of each variable, the number of missing values was excluded from the denominator. Fisher's exact test or the Mann-Whitney *U* test was used to compare the study group, as appropriate. $p < 0.05$ was considered significant. All analyses were performed by SPSS 17.0 (IBM SPSS, Chicago, IL, USA).

Results

Included population

A total of 567 PJI were analysed, occurring in 284 men (50.1%) with a median age of 70.3 (interquartile range, 59.8–78.8) years at the time of diagnosis. Most patients had comorbidities, with a median ASA score of 2 (interquartile range, 2–3). PJI mainly concerned hip (n = 285; 50.3%) and knee (n = 255; 45.0%)

arthroplasties. In 216 cases (40.3%), PJI occurred on a revision prosthesis. Concerning the chronology of infection, early, delayed and late PJI represented 232 (40.9%), 94 (16.6%) and 241 (42.5%) cases, respectively. Late infections were distributed into 59 (10.4%) late acute and 182 (32.1%) late chronic PJI, among which 44 (24.0%) were late exacerbated infections. Clinical presentation and differences according to the delay of occurrence and mechanism of acquisition are reported in Table 1.

Microbiologic aetiology

Microbiologic cultures were conducted in 511 cases (90.1%), with a higher rate of culture-negative infections in late PJI (19.7%) than in early/delayed PJI (6.2%, p <0.001). Infection was polymicrobial in 103 cases (18.2%). Multiple pathogens were more frequently found in the early/delayed PJI (22.8%) than in the late chronic (10.9%, p 0.002) and late exacerbated (6.8%, p 0.016) PJI. However, the prevalence of polymicrobial infections in the early/delayed PJI and the late acute PJI (15.3%, p 0.231) was not statistically different. In this last group, the nine polymicrobial infections all resulted from an inoculation or contiguous mechanism. All microbiologic findings according to time to occurrence of PJI are shown in Fig. 1. Gram-positive cocci were by far the most represented pathogens, implicated in 74.8% of PJI regardless of chronology (*S. aureus,* 28.9%; CoNS, 28.6%; streptococci, 13.1%; and enterococci, 4.2%). *S. aureus* was less represented in late chronic PJI (13.1%) than in early/delayed and late acute PJI (37.5% and 30.5%, respectively; p <0.001). Methicillin resistance was noted in 16.1% of *S. aureus* isolates, without difference according to chronology of infection. The prevalence of CoNS tended to be lower in early/delayed (29.2%) than in late chronic (33.9%, p 0.055) PJI and was lower in late acute PJI (8.5%, p 0.001). A total of 58.8% of them were methicillin resistant. In late PJI, *Streptococcus* spp. and *Enterococcus* spp. were less represented than in the early/delayed PJI, accounting for 9.8% vs. 8.7% (p 0.045) and 5.5% vs. 1.5% (p 0.043) of cases, respectively. Anaerobes were more prevalent in late PJI (21.9%) compared to early/delayed PJI (13.5%; p 0.002), among which *C. acnes* counted for 80.0% and 61.4% of cases, respectively. In cases of acute exacerbation of late chronic PJI, *C. acnes* was also statistically more frequent (22.7%, p 0.006) than in early/delayed PJI. Concerning GNB, the high prevalence of *Enterobacteriaceae* disclosed in early (21.6%) and late acute (28.8%) infections was significantly lower in delayed (5.4%, p <0.001) and late chronic (3.8%, p <0.001) PJI. No difference was observed regarding the proportion of nonfermenting GNB according to the period or the suspected mechanism, with a prevalence of *Pseudomonas aeruginosa* of 4.0%, 1.1%, 1.7% and 0 in the early/delayed, late chronic, late acute and late exacerbated PJI, respectively. Of note, no significant variations among time were noted regarding the incidence of the main pathogens (*S. aureus,* CoNS, *Streptococcus* spp., GNB and anaerobes) during the study period (Supplementary Table S1).

Projection regarding empirical antimicrobial therapy

Considering our local epidemiology (comprising a 100% lincosamide susceptibility rate of *C. acnes*), and according to the usual

Table 1
Population characteristics and clinical presentation according to PJI chronology and mechanism of acquisition

Characteristic	Early (<3 months) PJI (n = 232)	Delayed (3–12 months) PJI (n = 94)	p[a]	Late (>1 year) chronic PJI (n = 182)	p[b]	Late acute PJI (n = 59)	p[c]	Late exacerbated PJI (n = 44)	p[d]
Demographic data									
Sex (male)	121 (52.2%)	46 (49.5%)	0.778	91 (50.0%)	0.791	26 (44.1%)	0.312	24 (54.5%)	0.749
Age (years)	69.6 (59.3–78.7)	68.6 (60.9–78.0)	0.623	70.8 (59.8–78.9)	0.651	74.2 (62.8–81.6)	0.116	69.2 (57.4–80.3)	0.734
Weight (kg)	81.0 (67.0–93.0)	82.6 (68.3–95.0)	0.621	79.0 (64.3–90.7)	0.199	73.5 (63.4–85.3)	0.048	82.8 (62.5–95.8)	0.695
BMI (kg/m^2)	28.4 (24.8–33.8)	28.7 (24.9–34.3)	0.683	27.6 (24.1–32)	0.125	26.8 (22.5–31.6)	0.041	27.9 (22.8–33.5)	0.396
ASA score	2 (2–3)	2 (2–3)	0.542	2 (2–3)	0.377	3 (2–3)	0.317	2 (2–3)	0.498
Type of PJI									
Site									
Hip	123 (53.0%)	46 (49.5%)	0.504	96 (52.7%)	0.844	20 (33.9%)	0.011	22 (50.0%)	0.873
Knee	100 (43.1%)	44 (47.3%)	0.433	76 (41.8%)	0.553	34 (57.6%)	0.062	18 (40.9%)	0.747
Ankle	0	0	—	1 (0.5%)	0.358	0	NC	0	NC
Elbow	2 (0.9%)	3 (3.2%)	0.146	3 (1.6%)	1.000	3 (5.1%)	0.109	2 (4.5%)	0.198
Shoulder	7 (3.0%)	0	0.199	6 (3.3%)	0.559	2 (3.4%)	0.633	2 (4.5%)	0.292
Revision prosthesis	75 (33.2%)	37 (44.6%)	0.090	91 (52.6%)	<0.001	12 (22.2%)	0.042	26 (60.5%)	0.004
Prosthesis number	1 (1–2)	1 (1–2)	0.269	2 (0–2)	<0.001	1 (1–1)	0.028	2 (1–2)	0.007
Chronology of infection									
Delay from symptoms to surgery (weeks)	1.5 (0.4–6.3)	6.45 (0.7–36.5)	0.001	14.1 (3.1–38.8)	<0.001	1.9 (0.7–9.6)	0.776	0.7 (0.1–1.8)	<0.001
Delay from prosthesis implantation to symptoms (weeks)	2.7 (1.6–4.6)	22.7 (16.9–33.4)	<0.001	209.2 (107.2–466.9)	<0.001	212.6 (149.8–591.6)	<0.001	179.2 (102.3–457.3)	<0.001
Clinical presentation									
Fever	83 (36.2%)	36 (40.0%)	0.418	43 (23.9%)	0.002	41 (69.5%)	<0.001	22 (51.2%)	0.096
Draining	141 (61.6%)	21 (23.1%)	<0.001	47 (26.1%)	<0.001	11 (18.6%)	<0.001	11 (2.6%)	0.002
Sinus tract	21 (9.2%)	13 (14.3%)	0.240	36 (20.0%)	0.005	7 (11.9%)	0.829	8 (18.6%)	0.130
Wound dehiscence	115 (50.2%)	1 (1.1%)	<0.001	3 (1.7%)	<0.001	1 (1.7%)	<0.001	2 (4.7%)	<0.001
Pain	132 (57.9%)	78 (86.7%)	<0.001	160 (89.4%)	<0.001	56 (94.9%)	<0.001	39 (92.9%)	<0.001
Local inflammation	131 (57.5%)	45 (50.0%)	0.294	55 (30.6%)	<0.001	48 (81.4%)	<0.001	19 (44.2%)	0.193
Microbiologic documentation									
Negative culture	12 (5.2%)	8 (8.6%)	0.255	36 (19.8%)	<0.001	0	0.054	0	0.149
Polymicrobial infection	64 (27.6%)	10 (10.8%)	0.001	20 (11.0%)	0.002	9 (15.3%)	0.231	3 (6.8%)	0.006

ASA, American Society of Anesthesiologists; BMI, body mass index; PJI, prosthetic joint infection.
[a] Early vs. delayed PJIs.
[b] Late chronic vs. early/delayed PJIs.
[c] Late acute vs. early/delayed PJIs.
[d] Late exacerbated vs. early/delayed PJIs.

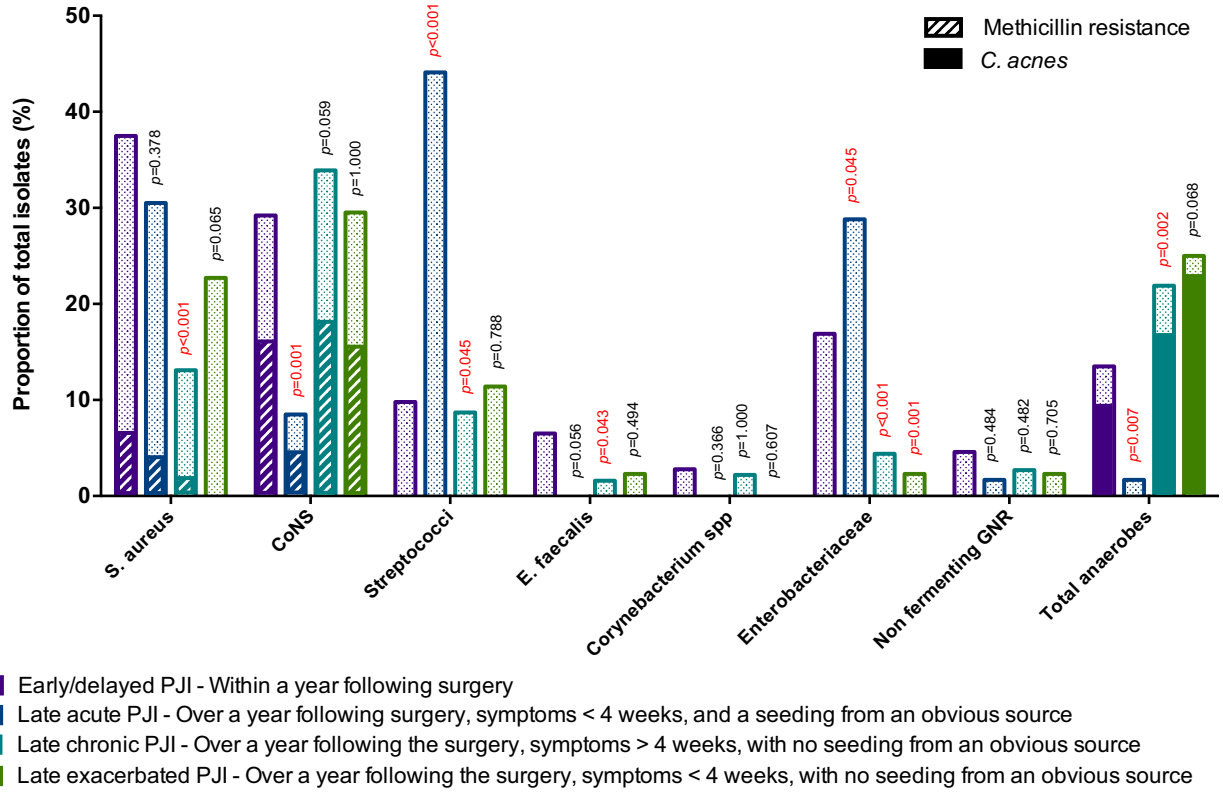

Fig. 1. Microbiological etiology of PJI according time to occurrence, and comparison between early and late infections. PJI : Prosthetic joint infection, CoNS : Coagulase negative staphylococci, GNR : Gram negative rods, ND : non documented.

susceptibility of the different pathogens encountered, 217 (93.5%) and 84 (89.4%) patients with early and delayed PJI would have been covered by the combination of vancomycin with a broad-spectrum β-lactam. Twelve (6.6%) of the 183 patients with a late chronic infection would have required the use of the broad-spectrum β-lactam only. Different projections according to the time to occurrence of PJI and the mechanism of infection are presented in Fig. 2.

Discussion

This large cohort study describes microbiologic epidemiology of PJI according to the chronology of infection, giving a basis for refining the choices of empirical antimicrobial strategies. As previously described, Gram-positive cocci, and especially staphylococci, were the most represented pathogens, regardless the time of occurrence [4,17–21]. Even if the prevalence of MRSA remains low in France, the proportion of methicillin-resistant CoNS, reaching almost 60%, makes the use of glycopeptide (vancomycin) or lipopeptide (daptomycin) necessary in early as in late PJI. The rate of methicillin resistance of CoNS may vary according to local epidemiology, but most of the studies in France and other countries highlighted high and increasing resistance rates [6,9,21,22]. GNB represented the third aetiologic agents of early PJI, reaching almost 30% of late acute PJI, thus justifying the use of a broad-spectrum β-lactam, as recommended [2,3]. However, they were involved in 4% of late chronic infections only, including a low proportion of non-fermenting GNB. This low prevalence compared to other cohort studies in the literature, which described up to 25% of GNB in late infections [4,6,8,10,23], probably occurred because most of them were classified as PJI according to the time to occurrence (early, delayed or late) [8,9], without considering the mechanism of acquisition (late chronic postsurgical infection or acute haematogenous spread) [24], which is of great important, as emphasized by our results. Indeed, late GNB PJI were mostly acute haematogenous infections that originated from urinary tract infection. Consequently, the use of a broad-spectrum β-lactam might be spared in case of late PJI if an acute haematogenous origin can be ruled out.

Low-virulent and slow-growing pathogens were responsible for an important part of chronic PJI. In our study, anaerobes were significantly more represented in late chronic than early PJI, among which *C. acnes* was by far the leading aetiologic agent (80.0%). Considering the overrepresentation of *C. acnes* and CoNS in late chronic PJI and their usual susceptibility profile [25]—including a 100% lincosamide susceptibility rate of *C. acnes* in our institution—vancomycin and clindamycin could provide an optimal combination therapy against the most prevalent pathogens.

Acute exacerbation of chronic PJI can be misleading for the physician. Clinically speaking, it appears as an acute haematogenous PJI, with the same brutal clinical setting. Importantly, microbiologic documentation appeared to be similar to chronic infections in our series, mostly including staphylococci and anaerobes and very few GNB. Empirical antimicrobial therapy can consequently be similar. However, a late infection with acute clinical presentation without obvious origin must evoke an acute exacerbation of a chronic PJI, and a prosthesis exchange should be considered.

Our study had several limitations. The single-centre nature of the study exposes it to a risk of local epidemiologic bias, especially because our centre is a referral site for the management of complex PJI. Additionally, and even if there is no consensus in the current literature, our choice of PJI definitions might be controversial; the chronologic cutoff of 1 year chosen for late infection can be debated and might increase the specificity of a true chronic infection and consequently decrease the odds of isolating virulent microorganisms such as GNB; and if the distinction between late exacerbated

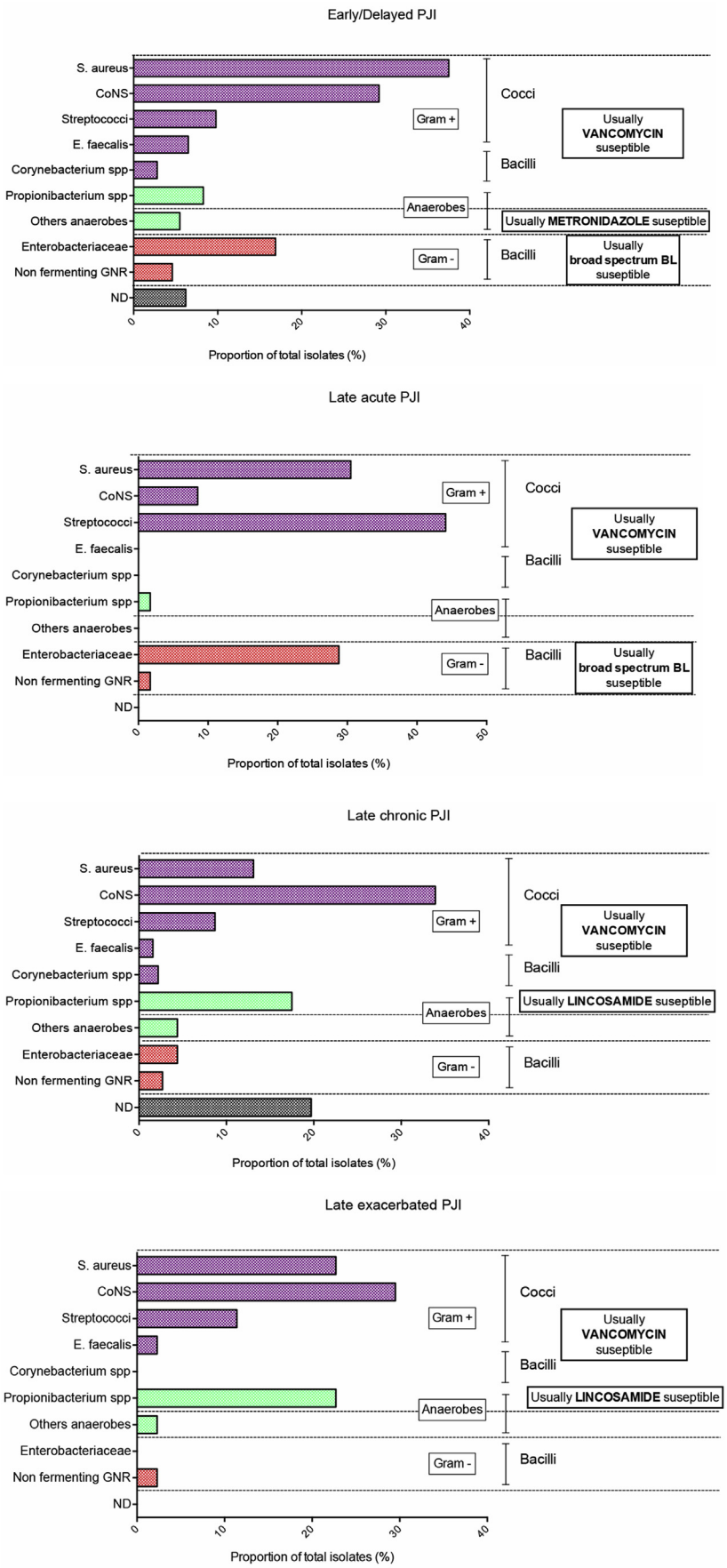

Fig. 2. Impact of microbiologic aetiology of PJI on empirical antimicrobial therapy according to time to occurrence and suspected mechanism of infection. PJI, prosthetic joint infection.

and late haematogenous theoretically makes sense, it represents one of the most challenging diagnosis problems in the field.

In conclusion, the currently recommended antimicrobial empiric therapy based on the combination of vancomycin with a broad-spectrum β-lactam appears relevant for early (<3 months after prosthesis implantation) postoperative and late acute haematogenous PJI. However, the microbiologic aetiology of late chronic PJI is clearly dominated by CoNS and *C. acnes*, and the weak amount of GNB might lead us to propose the combination of vancomycin and lincosamide, thus sparing patients from the use of a broad-spectrum β-lactam while optimizing the coverage of the leading aetiologic agents, especially when a two-time exchange is considered. In light of this microbiologic and clinical analysis, the real initial challenge when aiming to refine the empirical antimicrobial therapy of PJI is to accurately classify the infection, not only in terms of the chronology of infection but also in terms of our desire to apprehend the suspected acquisition mechanism of infection.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2018.04.035.

Transparency declaration

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