Pathogen Factors

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QUESTION 1: Does the virulence (low or high) of the infecting organism affect the treatment of acute hematogenous or chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: There is currently no evidence showing that the virulence of an infecting organism affects the treatment of acute hematogenous or chronic PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 69%, Disagree: 27%, Abstain: 4% (Super Majority, Weak Consensus)

RATIONALE

Pathogenicity is the ability of an agent to cause disease. The degree to which a pathogenic microorganism can cause an infectious disease is determined by its virulence. Several factors determine the virulence of bacteria, such as the bacterial capsule, presence of adhesin proteins, degradative enzymes, toxins and mechanisms for escaping elimination by host defenses (e.g., intracellular invasion and survival or production of biofilm). In addition, the host susceptibility to an infection also depends on its immune status and the presence of foreign material [1]. The type of virulence factor(s) expressed participate in the clinical presentation of disease. In general, microorganisms that are considered highly virulent tend to cause acute infections (e.g., *Staphylococcus aureus*, streptococci or gram-negative bacilli (GNB)) [2]. In contrast, pathogens with lower virulency are associated with chronic infections (e.g., *Cutibacterium acnes* (*C. acnes*), *Staphylococcus epidermidis* and other coagulase negative staphylococci (CoNS)) [2]. However, whether all virulence factors of a bacterium become expressed and to which degree, greatly depends upon the presence of specific environmental stimuli [3]. For this reason, we will address this question in two ways; 1) we evaluated whether the difference in virulency between different microorganisms (e.g., classically highly virulent microorganisms versus low virulence microorganisms) affect treatment outcome, and 2) we evaluated whether the degree of virulency factors expressed within one species affect treatment outcome.

Degree of Virulency between Different Microorganisms and its Relation to Outcome

A PubMed search was performed for late acute/hematogenous PJIs and chronic PJIs in relation to treatment outcome. All relevant articles were screened for inclusion and references were checked for additional articles. The total number of patients was counted in both groups and a success rate for all patients was calculated (Table 1) [4–19]. For late acute PJIs, 16 studies were included. Of 948 patients, the success rate with a debridement, antibiotics and implant retention (DAIR) procedure was 56% (range 35 to 94%). For chronic PJIs, one meta-analysis (including 62 studies) and 6 published studies thereafter were included [19–25]. Of 4,570 patients with chronic PJIs, treatment success rate was found to be 90% (range 87 - 100%) with one-stage or two-stage exchange procedures.

The outcome of acute and chronic infections is influenced by many factors, with the greatest difference being the surgical strategy used for acute versus chronic PJI—exchange versus no exchange of the prosthesis respectively. Due to the heterogeneity in treatment methods, it is not possible to conclude whether the worse outcomes observed in acute infections are due to the virulence of the bacteria. There are few studies that evaluate high versus low virulence microorganisms using the same surgical approach. Fink et al. studied 39 patients with early PJIs and 28 patients with acute hematogenous infections all of which were treated with DAIR and followed for a minimum of two years in order to investigate the success rate in infection eradication [27]. There was no difference in outcomes between infection caused by higher virulence pathogens (*S. aureus*, Streptococci, Enterococci, GNB) when compared to lesser virulence pathogens (CoNS and anaerobes such as *C. acnes*) [27].

Other authors have also compared the outcomes between *S. aureus* and CoNS PJIs. One study retrospectively examined chronic PJIs treated with suppressive antibiotic therapy [28], while another investigated the outcome of *S. aureus* PJIs versus CoNS PJIs treated with one- or two-stage revision [29]. Acute hematogenous and early PJI treated with DAIR and chronic knee PJI treated with different surgical modalities has also been examined in the literature. None of these studies found a significant difference in success rate after a minimum follow-up of 3 to 24 months [4,5,13–16]. Some authors have even described a worse outcome in patients with PJI caused by CoNS [4]. These findings suggest that virulence is not a risk factor for worse outcomes in PJI.

There are some observational studies that propose that *Staphylococcus* species are associated with recurrence or persistence of infection, due to the high capacity to form biofilms observed within this genus [30–32]. Others have suggested that *S. aureus* in particular is associated with a worse outcome than other microorganisms in general after DAIR [5,6,33,34] as well as after two-stage revision [35]. However, other studies do not observe any significant differences in outcomes of staphylococcal infections in general [36][37][38].

Degree of Virulence within the Same Species and its Relation to Outcome

Environmental stimuli play a large role in the phenotypic expression of virulence factors [3]. For example, it has been demonstrated that the amount of magnesium present in the environment of *S. aureus* determines the down or up regulation of specific virulence genes [15]. The resulting phenotypes have been shown

TABLE 1. Late acute/hematogenous PJI treated with DAIR

Article, Year	N	Success Rate	Comments
Wouthuyzen-Bakker 2018 [26]	340	55%	Unpublished data
Lora-Tamayo 2017 [7]	242	59%	Only streptococci
Akgün 2017 [8]	16	69%	Only streptococci
Tande 2016 [9]	35	74%	Only *S. aureus* bacteremia, 2y survival 62%
He 2016 [10]	11	82%	
Koh 2015 [11]	20	55%	
Holmberg2015 [13]	12	75%	
Puhto 2015 [12]	35	46%	
Koningsberg 2014 [5]	42	76%	
Geurts 2013 [14]	6	83%	
Lora-Tamayo 2013 [15]	52	35%	Only Staphylococci
Kuiper 2013 [4]	32	59%	
Rodriguez 2010 [16]	50	48%	
Byren 2009 [6]	12	83%	Only hips
Giulieri 2004 [17]	27	78%	
Everts 2004 [18]	16	94%	Only streptococci, only 1 patient had formal microbiological cure
TOTAL	**948**	**56%**	

TABLE 2. Chronic PJI treated with One-stage or Two-stage Exchange

Article, Year	N	Success Rate	Comments
Beswick 2014 [19]	4,197	90%	Meta-analysis comprising 62 studies with one-or two-stage exchange. Subanalysis of 11 studies with 1225 patients and only one-stage: success 91.4%
Singer2012 [21]	63	95%	Only 1st. exchange for TKA
Jenny 2013 [22]	47	87%	Only 1st. exchange for TKA
Haddad 2015 [23]	28	100%	Only 1st. exchange for TKA
Tibrewal 2014 [24]	50	98%	Only 1st. exchange for TKA
Zahar2016 [20]	70	93%	Only 1st. exchange for TKA
Gooding 2011 [25]	115	88%	2-step exchange for TKA
TOTAL	**4570**	**90%**	

to be associated with different infection outcomes in a murine model [15]. In addition, there is much debate over which virulence determinants of *S. aureus* are primarily responsible for infection severity in osteomyelitis [4,14,16]. Although some studies identified virulence determinants or bacterial strains involved in bone and joint infections [6,13,16,17], few evaluated whether the presence or absence of these virulence factors in PJI determine treatment outcome [6,17,18].

The literature search revealed three studies that examined the virulence within one species in relation to clinical outcome [4,15,16]. Tande et al. evaluated the outcome of PJIs caused by staphylococcal small colony variants (SCV), a phenotype that has been associated with intracellular persistence and biofilm formation [28]. Despite the general hypothesis that this phenotype is responsible for persistent and relapsing infections, treatment failure was 23.7% in staphylococcal PJIs caused by SCV compared to 30.7% failure in staphylococcal PJI with a normal phenotype ($p = 0.51$) resulting in a hazard ratio of 0.78 (confidence interval (CI), 0.36-1.69) [28]. The second study performed by Post et al. observed a clear relation between the degree of biofilm formation of *S. epidermidis* strains and clinical outcome in 104 patients with orthopaedic device related infections [39]. Weak biofilm formation was associated with a cure rate of 82%, while the formation of a strong biofilm was associated with a cure rate of 66.7% [39]. This difference however was not statistically significant. Strong biofilm formers were primarily observed to possess the of *icaA* gene (intracellular adhesion protein associated with biofilm formation) but the presence or absence of the gene itself was not related to clinical outcome [39]. In contrast, the presence of the gene *bhp* (cell-wall associated biofilm gene) was related to clinical failure, but only in infections of the lower extremity ($p = 0.023$) [39]. Morgenstern et al. conducted a similar study, however they found no statistically significant relationship between *S epidermidis* biofilm forming capabilities and cure rate ($p = 0.076$) [40].

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QUESTION 2: Is there a difference in the treatment outcome for periprosthetic joint infections (PJIs) caused by a single organism and a polymicrobial PJI?

RECOMMENDATION: Polymicrobial PJIs demonstrate inferior treatment outcomes when compared to monomicrobial PJIs. This finding is true for both patients treated with irrigation and debridement and two-stage exchange arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

PJIs are not uncommon with a reported rate between 6 and 37% [1–4]. Although common organisms such as *Staphylococcus aureus* are commonly isolated in these infections, more virulent organisms such as Enterococcus species, gram-negative bacilli, methicillin-resistant *Staphylococcus aureus* (MRSA) and anaerobic bacteria are more commonly associated with polymicrobial rather than monomicrobial infections [5]. Despite the relative frequency of polymicrobial PJI, there is minimal literature regarding treatment outcomes of polymicrobial PJIs and how they compare to monomicrobial PJIs.

The literature demonstrates that polymicrobial PJIs have inferior outcomes when compared to monomicrobial PJIs. Tan et al. demonstrated that patients with polymicrobial PJI had a higher failure rate (50.5%) compared with monomicrobial (31.5%) and a higher rate of amputation (odds ratio (OR) 3.80, 95% confidence interval (CI), 1.34-10.80), arthrodesis (OR 11.06, 95% CI, 1.27-96.00), and mortality (OR 7.88, 95% CI, 1.60-38.67) compared with patients with monomicrobial PJI [6]. Similarly, Wimmer *et al.* demonstrated that the infection free rate after two years was 67.6 % for polymicrobial infections vs. 87.5 % for monomicrobial infections in a series of 77 polymicrobial PJIs [7]. Furthermore, Marculescu *et al.* demonstrated that the two-year cumulative probability of success of polymicrobial PJIs was 63.8% (95% CI, 43.8%–80.5%) and of monomicrobial PJIs was 72.8% (95% CI, 63%–80.9%). However, this difference was not significant.

The outcomes appear to be poor for polymicrobial PJI regardless of surgical treatment. Tan *et al.* demonstrated that the infection free survivorship for polymicrobial PJI was 55.4%, 49.3% and 49.3% for the two-stage exchanges and 43.2, 43.2 and 38.4% for irrigation and debridement (I&D) at 2, 5 and 10 years [6]. Although this result was not statistically significant, there was a trend towards higher treatment success (p = 0.164) for two-stage exchange arthroplasty. In Marculescu et al., the 2-year survival free of treatment failure for polymicrobial PJIs was 77.7% and 52.7% compared to 83.9 and 54% for monomicrobial PJI for, two-stage exchange arthroplasty and I&D, respectively. This rate was higher but not, statistically significantly different than of polymicrobial PJI treated with similar surgical modalities (p = 0.24 and p = 0.64) [5]. Bozhkova et al. also revealed that treatment success after the first stage of the two-stage procedure was considerably higher (74.8 %, $n = 101$) in patients with monomicrobial infection, compared to only 27.8 % ($n = 15$) in the polymicrobial group ($p < 0.0001$). [8] Furthermore, they found that gram negative PJIs in polymicrobial PJI were associated with failure as the proportion of polymicrobial PJI caused by gram-negative pathogens was 61.5 % in patients with recurrent infection and only 26.7 % in patients with treatment success (p = 0.03). According to data of Tornero et al., for I&D and retention of the prosthesis polymicrobial infection was significantly associated with failure in the global cohort (59.3% vs. 40.7%, p = 0.036) [9]. Only one study did not show the difference between outcome of polymicrobial and monomicrobial PJI [10]. However, this can be explained by insufficient number of PJI cases (only 15 cases) and pathogen properties (*Cutibacterium acnes* (*C. acnes*) in isolation or together with coagulase-negative staphylococci).

There are several explanations for the increased rate of failure in patients with polymicrobial PJIs. One factor is that drainage and the presence of a soft tissue defect have been found to be associated with polymicrobial PJIs [5,6]. Another is that polymicrobial PJIs are associated with organisms that are difficult to treat such as enterococcus and gram negatives [5,6,11] that have been associated with worse outcomes [12,13]. In addition, several studies have demonstrated that patients with polymicrobial PJIs have increased comorbidities and are older than patients with monomicrobial PJIs [5,6], which likely affects their ability to eradicate an infection.

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