SH60: Should Bacterial Virulence Determine Antibiotic Treatment?

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Recommendation: There is currently insufficient evidence to recommend a different antibiotic regimen for shoulder PJI caused by a highly virulent organism compared to infection caused by a lower virulence organism.

Strength of recommendation: Limited

Rationale: Virulence is a term used to describe the degree to which a micro-organism can infect and inflict damage to a host. Virulence is determined by a combination of factors related to the micro-organism itself but also the characteristics and immune profile of the host and presence of foreign material at the surgical site. This means a typically low-virulence organism may behave differently in a more susceptible host or in the presence of an arthroplasty prosthesis. Generally speaking, bacteria are classified as either high or low virulence. In the setting of shoulder PJI, most infections are caused by low virulence organisms including *Cutibacterium acnes (C. acnes)* and *Coagulase negative Staphylococci (CoNS)* whereas *Staphylococcus aureus (SA)* is responsible for the majority of high virulence infections followed by *Streptococcal* or gram-negative bacteria.

In order to investigate whether bacterial virulence should determine antibiotic treatment we considered three questions. Firstly – is there evidence to suggest that outcome if PJI treatment differs according to the infecting microorganism itself. Secondly, is there evidence that alternate phylotypes of the same bacteria affect outcome of PJI treatment, and finally, are there antibiotic-related considerations that may affect choice of treatment of a given bacteria. A literature search was initially performed using Embase and Ovid databases. 23 potential articles of interest were identified and after abstract and full text appraisal four articles were included. Initially, review articles were excluded, however, due to the wide scope of the research question and the paucity of literature obtained from the initial search contemporary review articles and published clinical guidelines were used to identify further relevant articles.

Does bacterial virulence determine outcome of Shoulder PJI treatment?

There are no high quality randomised or prospective cohort studies in the shoulder literature trying to address this question directly. One interesting recent study sought to retrospectively identify risk factors for recurrence of infection following revision arthroplasty for infection in 790 patients(Givens et al., 2024). The primary aim of the study was to validate the infection probability score developed in the 2018 International consensus meeting(Garrigues et al., 2019). One of the secondary aims was to evaluate factors including bacterial virulence that may contribute to failure of single or two stage revision. The authors reported that in their series, there was a significantly higher rate of recurrent PJI with high virulence *SA* (30.8%; in particular *MRSA*) compared to *CoNS* (5.9%) and *C. acnes* (4%). These findings contradict two other much smaller retrospective studies where *C acnes* was implicated as a risk factor for failure compared to high virulence organisms following two stage revision (Hattrup and Renfree, 2010; Jawa et al., 2011). A potential reason for the discrepancy is that in the study by Givens et al. the majority of revisions were single stage and there was over 30% loss to long term follow up. It could be postulated that with a single-stage approach and relatively short term follow up, highly virulent organisms may have been more likely to cause recurrence compared to lower virulence organisms where failure might develop more slowly

over time. This is in keeping with the findings of a study investigating the re-infection rate in 17 patients with unexpected positive cultures following revision arthroplasty(Grosso et al., 2012). All unexpected cultures were low virulence organisms (56% *C. acnes* & 35% *CoNS*) yet there was only one clinical infection requiring treatment in the cohort (5.6%).

The small numbers of patients within most studies on revision shoulder arthroplasty for infection means that it is hard to quantify the effect of independent risk factors. Furthermore, it is widely accepted that outcome is multi-factorial with the nature and quality of surgical treatment critical along with host factors and antibiotic regime. Two systematic reviews sought to address the issue of small numbers by collating the published case series data. While both studies identified *C. acnes* as the most common causative organism for shoulder PJI, both concluded that the heterogeneity of the data meant that no reliable analysis or conclusions could be made regarding the effect of bacterial virulence on outcome (Nelson et al., 2016; Rodrigues-Lopes et al., 2024).

Outside of the shoulder literature there has also been work done to identify the effect of bacterial virulence on outcome. A prospective database collection study from Australasia including 653 cases of PJI treated with a variety of techniques in 27 different units found that *MRSA* was the highest risk factor for failed treatment followed equally by *MSSA, CoNS C. acnes* and gram-negative rods(Davis et al., 2022). Similarly, in a smaller study Fink et al. found no difference in the rate of successful hip and knee revision arthroplasty according to low or high virulence organisms(Fink et al., 2017).

Debridement Antibiotics and Implant Retention (DAIR) is a viable treatment option for acute PJI with well-fixed implants but antibiotic treatment protocol in DAIR may have to be adapted compared to two stage revision given that the infected implants are retained. Risk factors for failed DAIR have been investigated extensively in the hip and knee literature, however there are conflicting findings in relation to bacterial virulence with some studies reporting worse outcomes with high virulence organisms (Zhu et al., 2021) and others citing increased failures with low virulence bacteria (Kuiper et al., 2013).

Is there evidence that alternate phylotypes of the same bacteria affect outcome of PJI treatment?

Staphylococci

With advances in bacterial sub-typing, it has become apparent that variants of the same bacteria exhibit differing degrees of virulence according to variations in their virulence factors, response to environmental stimuli and ability to form biofilm. Determining the clinical effect of the molecular variations within the same species of bacteria commonly associated with PJI has the potential to offer patients individualised treatment.

Trobos et al. investigated the associations between clinical outcome and the individual microbiological characteristics of 111 strains of *S Aureus* and *S Epidermidis* in 66 patients with hip and knee PJI (Trobos et al., 2022). The authors identified particular strains of *S aureus* associated with strong biofilm forming capability and strains of *S epidermidis* with increased antibiotic resistance facilitated by individual virulence factors exhibited by these strains. Both these groups were correlated to inferior clinical outcome in terms of treatment failure compared to other strains of the same bacteria. Furthermore, resistance to rifampicin was noted in certain *S Epidermidis* strains suggesting that routine use of rifampicin should be tempered without knowledge of resistance patterns. Tande investigated the effect of staphylococcal phenotypes with small colony variants (SCV) in 113 patients with staphylococcal PJI(Tande et al., 2014). These variants are thought to have superior biofilm forming capability and therefore have been implicated with higher rates of PJI treatment failure. Despite this, the authors found that there was no significant difference in the relapse rate following PJI treatment in infections caused by

SCVs (24%) versus normal phenotypes (32%). Interestingly they did find that the duration of symptoms and numbers of pre-existing treatments were significantly higher in the SCV group suggesting that this group may behave in a less virulent manner than a normal variant staphylococci which typically causes more overt signs of infection.

C. acnes

The observation that some *C. acnes* strains produce haemolysis when cultured has been studied as a factor associated with increased virulence of these strains. Hsu et al. demonstrated greater biofilm forming and haemolytic activity in C. acnes isolated from explanted prostheses compared to *C. acnes* cultured from the skin of healthy volunteers (Hsu et al., 2022). Interestingly there was no significant difference in the strains of *C. acnes* identified in the two groups despite the different virulence properties recorded. Similarly, in a series of 48 patients with a positive *C. acnes* culture taken during revision shoulder surgery, Boyle et al. demonstrated that the presence of haemolysis was 100% specific and 80% sensitive for diagnosis of a shoulder PJI and was also associated with elevated systemic inflammatory markers and clindamycin resistance(Boyle et al., 2019b). The same group also investigated the genetic variation of *C. acnes* sampled from infected versus aseptic shoulder revision arthroplasties. While there were only three patients in each group, they demonstrated similar gene expression in the infected samples which was significantly different to the gene expression in the aseptic samples(Boyle et al., 2020).

In contrast Mahylis et al. tested 39 samples of *C. acnes* grown at the time of revision surgery and demonstrated no significant difference in the clinical effect of haemolysis which was identified in 51% of samples. There were also no significant differences in resistance or inflammatory markers, although haemolysis positive *C. acnes* patients had more preceding surgeries and a longer duration of infection than non-Haemolysis patients. One aspect of this study that could have affected the results was that testing was done retrospectively on samples stored at -70°C (Boyle et al. 2020).

Antibiotic Considerations

One of the most problematic issues in discerning the magnitude of an individual factor on the outcome of PJI treatment is that in surgical studies, antibiotic regimen is rarely standardised or described in detail. In addition, antibiotic usage varies widely according to geographic location. Some interesting themes are nevertheless noteworthy. Whilst *C. acnes* is usually susceptible to a range of antibiotics, there are reports of increasing resistance to clindamycin and rifampicin particularly when used as monotherapy (Achermann et al., 2014; Boyle et al., 2019b). Rifampicin has become a commonly used agent in PJI treatment, particularly in the setting of retained implants, due to its favourable activity against biofilm, as demonstrated in animal models(Furustrand Tafin et al., 2012). Rifampicin has also been shown to have a relatively high rate of gastrointestinal complications (Reinecke et al., 2023) and because there are no randomised studies studying its effect in *C. acnes* treatment, whether to use it remains contentious (Boyle et al., 2019a)(Achermann et al., 2014).

Summary: This review has indicated that there is some evidence that outcome of PJI treatment may be affected by overall bacterial virulence and the virulence of different strains within the same species. However, the quality of this data is heterogeneous, conflicting and subject to bias, meaning that there is currently insufficient evidence to support a tailored treatment plan for shoulder PJI according to bacterial virulence. A consistent theme is that optimising surgical management is of paramount importance to yield a successful result. Modifiable host factors and identification of variations in bacterial virulence and pathogenicity are clearly important factors that warrant continued research.

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