SH46: How should “virulent” vs “non-virulent or low virulence” be more objectively defined? If these terms cannot be well defined, should we eliminate them from the diagnostic criteria for PJI?

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Supportive Delegates: Jason Ho; Jay Keener

Response: The terms “virulent”, “non-virulent”, and “low virulence” should be removed from the diagnostic criteria for shoulder PJI.

Strength of Recommendation: Limited

Delegate Vote: 53 (98%) agree; 0 disagree; 1 (2%) abstain

Rationale: A comprehensive literature review was undertaken with a search of Medline, Embase and Cochrane conducted in January 2025 using the search terms arthroplasty, replacement, prosthesis, implants, infection, prosthesis-related infections, bacteria, virulence or virulence factors. Searches were limited to studies in humans. This identified 2,634 articles, once duplicates were excluded. Inclusion criteria were all studies published in English (level I-IV) that reported on the virulence of bacterial infection associated with prosthetic joints. Exclusion criteria included non-English language, abstracts and review articles. No search of the grey literature was conducted. References lists of included articles were reviewed. After review of titles and abstracts, 32 were included for full text review. 17/32 were excluded and an additional 2 relevant articles were identified from the reference lists of included articles. A quantitative analysis could not be undertaken, so a narrative review was conducted.

In the context of bacteria, "virulence" refers to the ability of a bacterial strain to infect and cause damage to a host organism, essentially measuring how severe a disease a particular bacteria can produce within a susceptible host; it is normally a quantitative measure of the pathogenicity of a bacterial strain, considering factors like the number of bacteria needed to cause infection and the severity of the resulting disease.(Casadevall 1999) With the growth of genomics and proteomics, specific virulence factors can be identified including toxins, adhesion molecules, or enzymes that enable the bacteria to infect and damage the host, and the genes that may lead to the expression of these properties.

In prosthetic joint infection there are organisms that are considered to have higher virulence including Staphylococcus aureus, Group A Streptococcus or Enterococcus species. Other species are considered to have low virulence including Coagulase-negative Staphylococci and Cutibacterium (Propionibacterium) acnes. The allocation of species to high and low virulence categories appears to be defined by the clinical presentation; high virulence organisms presenting with early pyogenic infection, low virulence presenting later and without typical clinical features of infection (i.e. erythema, pus).(Zimmerli 2004) This attribution may be considered to be somewhat arbitrary if we consider the harm of prosthetic joint infection to be implant removal, reinfection or death. Published evidence indicates equivalent success from DAIR for all organisms except Enterococcus species, that have been shown to have a higher rate of treatment failure from DAIR. (Jacobs 2019, Nurmohamed 2021). Likewise for single or two stage revision, the infecting organism may not affect the success of treatment. (Bejon 2010, Matar 2021)

Investigation for specific genetic virulence traits in PJI has produced conflicting results. Central to these investigations has been the hypothesis that an organism will be more

virulent if it adheres more readily to the surface of a prosthesis, if it rapidly generates biofilm or if it secretes exotoxins.(Lowbeer 2023) Specific genes thought to enhance biofilm production include icaOperon, icaABD and Insertion Sequence IS256 amongst others.(Galdbart 2000) A number of studies have analysed expression of these genes in PJI but no clear relationship has emerged.(Nilsdotter 2007, Lowbeer 2023, Koskela 2009, Sanchez 2020). Gene expression has been reported to be different between infecting strains and commensal strains of C. acnes (Boyle 2020). Sanchez et al and Mansson et al. have proposed that whilst gene expression varies, it is the property of antibiotic resistance that leads to increased virulence, but again this finding is inconsistent and does not lead us to a clear definition. (Sanchez 2020, Mansson 2021)

The development of disease is not solely attributable to the pathogen. Host factors also play an important role. Specifically, immune-compromise to due chronic disease or iatrogenic causes may increase the likelihood of harm from exposure to a pathogen. Therefore virulence is "contingent on the availability of a susceptible host and the context and nature of the host-microbe interaction".(Casadevall 2001)

Possible markers for virulence of bacteria in PJI have been investigated. D-dimer levels have not been found to be discriminatory (Pannu 2023). Deirmengian et al. have reported that CRP levels are on average lower when infections are attributable to less virulent organisms but not cut-off level was described due to the overlap of the CRP level distributions. Krenn et al. have reported high specificity and sensitivity for the diagnosis of PJI using histological counts of neutrophils stained with an antigen to CD15 (a marker for mature neutrophils) in a high-power field (x20) on microscopy, called the CD15 focus score (accuracy 0.92).(Krenn 2017) The authors report that the accuracy for differentiating organisms defined as high virulence from those defined as low virulence had an accuracy of 0.74 with a cut of value of 106 cells per high-power-field. This finding was not replicated in later studies by the same group. (Liewen 2020)

There is no formal definition of virulence that enables classification of prosthetic joint infection into high-virulence and low-virulence. The evidence that is available is conflicting and low strength. Virulence should be removed from the diagnostic criteria for PJI until there is clear difference in the risk of harm from different pathogens and a reliable method to determine the risk for individual strains.

References

Bejon P, Berendt A, Atkins BL, Green N, Parry H, Masters S, McLardy-Smith P, Gundle R, Byren I. Two-stage revision for prosthetic joint infection: predictors of outcome and the role of reimplantation microbiology. Journal of antimicrobial chemotherapy. 2010 Mar 1;65(3):569-75.

Boyle KK, Marzullo BJ, Yergeau DA, Nodzo SR, Crane JK, Duquin TR. Pathogenic genetic variations of C. acnes are associated with clinically relevant orthopedic shoulder infections. Journal of Orthopaedic Research. 2020 Dec;38(12):2731-9.

Casadevall A, Pirofski LA. Host-pathogen interactions: redefining the basic concepts of virulence and pathogenicity. Infection and immunity. 1999 Aug 1;67(8):3703-13.

Casadevall A, Pirofski LA. Host-pathogen interactions: the attributes of virulence. The Journal of infectious diseases. 2001 Aug 1;184(3):337-44.

Galdbart JO, Allignet J, Tung HS, Rydèn C, El Solh N. Screening for Staphylococcus epidevmidis markers discriminating between skin-flora strains and those responsible for infections of joint prostheses. The Journal of infectious diseases. 2000 Jul 1;182(1):351-5.

Jacobs AM, Valkering LJ, Bénard M, Meis JF, Goosen JH. Evaluation one year after DAIR treatment in 91 suspected early prosthetic joint infections in primary knee and hip arthroplasty. Journal of Bone and Joint Infection. 2019 Oct 15;4(5):238-44.

Koskela A, Nilsdotter-Augustinsson Å, Persson L, Söderquist B. Prevalence of the ica operon and insertion sequence IS 256 among Staphylococcus epidermidis prosthetic joint infection isolates. European journal of clinical microbiology & infectious diseases. 2009 Jun;28:655-60.

Krenn VT, Liebisch M, Kölbel B, Renz N, Gehrke T, Huber M, Krukemeyer MG, Trampuz A, Resch H, Krenn V. CD15 focus score: Infection diagnosis and stratification into low-virulence and high-virulence microbial pathogens in periprosthetic joint infection. Pathology-Research and Practice. 2017 May 1;213(5):541-7.

Liewen C, Krenn VT, Dieckmann R, Bause L, Liebisch M, Niemeier A, Trampuz A, Krenn V. Diagnostic value of the CD 15 focus score in two-stage revision arthroplasty of periprosthetic joint infections. Zeitschrift für Rheumatologie. 2020 Dec 11.

Löwbeer N, Stegger M, Söderquist B. Genomic characterization of beta-haemolytic streptococci isolated from prosthetic joint infections. APMIS. 2023 May;131(5):189-96.

Månsson E, Bech Johannesen T, Nilsdotter-Augustinsson Å, Söderquist B, Stegger M. Comparative genomics of Staphylococcus epidermidis from prosthetic-joint infections and nares highlights genetic traits associated with antimicrobial resistance, not virulence. Microbial Genomics. 2021 Feb;7(2):000504.

Matar HE, Bloch BV, Snape SE, James PJ. Outcomes of single-and two-stage revision total knee arthroplasty for chronic periprosthetic joint infection: long-term outcomes of changing clinical practice in a specialist centre. The Bone & Joint Journal. 2021 Aug 1;103(8):1373-9.

Nilsdotter-Augustinsson Å, Koskela A, Öhman L, Söderquist B. Characterization of coagulase-negative staphylococci isolated from patients with infected hip prostheses: use of phenotypic and genotypic analyses, including tests for the presence of the ica operon. European Journal of Clinical Microbiology & Infectious Diseases. 2007 Apr;26:255-65.

Nurmohamed FR, Van Dijk B, Veltman ES, Hoekstra M, Rentenaar RJ, Weinans HH, Vogely HC, Van Der Wal BC. One-year infection control rates of a DAIR (debridement, antibiotics and implant retention) procedure after primary and prosthetic-joint-infection-related revision arthroplasty–a retrospective cohort study. Journal of bone and joint infection. 2021 Jan 27;6(4):91-7.

Pannu TS, Villa JM, Jimenez DA, Riesgo AM, Higuera CA. Does Performance of D-Dimer for Diagnosis of Periprosthetic Joint Infection Change With the Virulence of Infecting Organism?. The Journal of Arthroplasty. 2023 Jul 1;38(7):S389-93.

Sánchez A, Benito N, Rivera A, García L, Miró E, Mur I, González Y, Gutiérrez C, Horcajada JP, Espinal P, Navarro F. Pathogenesis of Staphylococcus epidermidis in prosthetic joint infections: can identification of virulence genes differentiate between infecting and commensal strains?. Journal of Hospital Infection. 2020 Jul 1;105(3):561-8.

Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. New England journal of medicine. 2004 Oct 14;351(16):1645-54.).