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QUESTION 4: Should organisms (e.g., *Treponema spp., Corynebacteria spp*.) identified through molecular or genetic testing be treated the same as the pathogens isolated by culture?

RECOMMENDATION: No. Because of their associated poor clinical outcomes, unusual organisms resulting in infection should not be treated equivalently to a usual pathogenic organism. Identification of unusual organisms through molecular and genetic techniques should help aid in antibiotic selection in conjunction with surgery, as indicated. Because of the associated poor clinical outcomes of unusual organisms and polymicrobial infections, the results of these newer techniques should not be ignored, but instead used to help inform therapeutic choices.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

There are variety of unusual organisms that can cause periprosthetic joint infections (PJI) aside from *Staphylococcus* species. Unusual organisms represent about 4.5% of the PJIs in the United States, while culture-negative infections account for 18.6% [1]. Many of these uncommon organisms, in addition to the culture-negative organisms, are associated with polymicrobial PJIs [2]. In order to manage such patients, broad-spectrum antibiotics are often required that need tailored to the specific organisms causing the infection due to high rates of antibiotic resistance [2].

In recent a retrospective study, methicillin-resistant *Staphylococcus aureus* (MRSA), Pseudomonas and Proteus-related PJI have been associated with lower infection-free rates, which means more surgery and hospital time are required for definitive treatment [3]. Thus, aside from MRSA, there are other organisms that are associated with poor PJI outcomes.

In polymicrobial PJI, clinical outcomes were reported to be poor when compared to monomicrobial or culture-negative PJI [2]. In addition, polymicrobial PJI had higher rate of amputation (odds ratio (OR): 3.8, 95% confidence interval (CI) 1.34 to 10.80, $p = 0.012$), arthrodesis (OR: 11.06, 95% CI 1.27 to 96.00, $p = 0.029$) and PJI-related mortality (OR: 7.88, 95% CI 1.60 to 38.67, $p = 0.011$) compared with patients with monomicrobial PJI [2]. In such polymicrobial PJI, gram-negative organisms (OR: 6.33, $p < 0.01$), enterococci (OR: 11.36, $p < 0.01$), *Escherichia coli* (OR: 6.55, $p < 0.01$) and atypical organisms (OR: 9.85, $p < 0.01$) isolation were associated with polymicrobial PJIs [2]. PJI due to gram-negative species such as *Pseudomonas aeruginosa, Escherichia coli* and *Klebsiella pneumoniae* have proved to have lower rates of therapeutic success following debridement when compared to gram-positive organisms [4].

Fungal infection should also be recognized as an atypical organism causing PJI. Although the reports describing PJI due to fungal infection are limited, the clinical outcomes of PJI by *Candida* species were unsatisfactory. It was reported that the overall rate of mortality attributable to *Candida* PJI was 25% [5]. Multidrug-resistant gram-negative organisms, such as carbapenemase-producing *Klebsiella pneumoniae,* require aggressive medical and surgical treatment [6]. In a small case series of *Propionibacterium avidum* PJIs, debridement-retention of the prosthesis was not an effective option [7]. Similarly, although *Enterococcal* PJI is not frequent, its successful rate of treatment was reported to be low [8,9].

Because clinical outcomes can be associated with the characteristics of the causative agent, the ideal goal is to properly identify all pathogens responsible for the infection [2]. However, some of these unusual organisms can be difficult to detect or take excessive time to appropriately culture [10]. Negative culture results can pose a challenge for physicians therapeutically, for they lack vital diagnostic information, such as the true identity of the causative agent(s). Recently, research has focused on newer innovative methods of infection detection and identification. At the forefront of these new innovative techniques are molecular and genetic methods such as polymerase chain reaction (PCR) assay. Although current molecular and genetic methods tend to have high sensitivities, their specificities are lower and therefore cannot be used as a single diagnostic test as of now [10]. However, as technologies continue to improve, more insight into the pathologic agents will likely become available allowing physicians to make more informed therapeutic decisions based on information such as the presence of antibiotic resistant genes.

A study by Tarabichi et al. examined the utility of some of the newer molecular and genetic techniques, also known as next-generation sequencing (NGS) [11]. Based on the results of their study, they were able to conclude that NGS may be a useful adjunct to aid in organism identification [11]. Although their study shows much promise, they do note that further larger studies are needed to further validate this new technology.

Although two-stage exchange arthroplasty remains the gold standard for surgical management of chronic PJIs, especially when the causative organism is a resistant microbe or produces biofilm, the emergence of new pathogen identification methods will potentially allow physicians to choose more appropriate antibiotic regimens [9,11,12]. Much research is still needed for further validation of these techniques. However, it is clear that infection secondary to unusual organisms are associated with poor clinical outcomes and therefore should be treated with some variation from standard protocols, even if that is simply a more informed antibiotic regimen choice. Information from newer molecular and genetic techniques shows much promise in aiding in diagnosis of these types of infections.

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