test is somewhat difficult to perform as it involves multiple steps for preparation of the sample.

In a recent meta-analysis about synovial fluid biomarkers alpha-defensin and LE demonstrated high sensitivity for diagnosing PJIs, with alpha-defensin being the best synovial marker. However, other synovial fluid tests like synovial fluid leukocyte count, polymorphonuclear (PMN) %, C-reactive protein (CRP), Interleukein-6 (IL-6) and Interleukin-8 (IL-8) that demonstrate good diagnostic performance can also be used in combination for the diagnosis of PJIs [12]. Molecular diagnostic studies, such as synovial alpha-defensin and LE, may provide rapid, accurate identification of PJIs, even in the setting of concurrent antibiotic administration or systemic inflammatory disease [13].

Additionally, there are a few studies exploring potential technologies which were developed as bed-side tests detecting calprotectin [24,25] or bacterial DNA sequences [26,27] as possible diagnostic tools of the future.

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QUESTION 6: What is the prevalence of culture-negative periprosthetic join infections (CN-PJIs) and what are the diagnostic protocols for further investigating these cases?

RECOMMENDATION: The reported prevalence of CN-PJIs in the hip or knee has ranged from 5-42%. Diagnostic protocols for further investigating these cases include repeat sampling, longer incubation of culture samples, sonication of implants, the use of dithiothreitol (DTT) technology, polymerase chain reaction (PCR) and next generation sequencing (NGS).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 8%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Prosthetic joint arthroplasty is one of the most commonly performed surgical procedures in the field of orthopaedics. Among many complications of prosthetic joint arthroplasty, PJIs are among the most catastrophic [1]. It can develop after 1 to 2% of primary hip arthroplasties and 2 to 3% of primary knee arthroplasties [2,3]. The prevalence of PJIs appears to be on the rise because of numerous reasons, most importantly related to the increasing number of patients receiving arthroplasties. Management of PJIs in general, and CN-PJIs in particular, continues to cause challenges.

The incidence of CN-PJI has been reported to range from 5-42.1% in the literature [4–10]. Klement et al. published a study on patients with PJIs who were diagnosed with the MusculoSkeletal Infection Society (MSIS) major criterion or a combination of MSIS minor criteria, and demonstrated that the incidence of CN-PJI was 0.4% and 45.4%, respectively [11].

CN-PJIs are reported to be associated with older age, smoking, referral from outside institutions, preoperative antibiotic treatment and the presence of postoperative wound drainage [1,4].

Some studies reported that 46% of CN-PJI were caused by fungi, 43% by mycobacteria and 11% by other bacteria such as *Listeria monocytogens*, *Cutbacterium acnes (C. acnes),* Brucella, Coxiella burnetii and others [1].

CN-PJI remains a challenging condition to manage, because of the lack of guidelines or protocols to diagnose and manage these patients in particular with regard to the type of antimicrobials needed for treatment [4]. Because an accurate diagnostic algorithm is not available, most clinicians rely on physical examination, clinical suspicion, laboratory tests and radiological findings to reach the diagnosis of PJI in these cases [1]. Clinical and radiographic evaluations are not always reliable for diagnosing CN-PJI and serum indicators may be inconclusive especially in patients with previous antibiotic administration or those infected with slow-growing organisms. Thus, there has been a growing interest in better diagnostic methods that can isolate the infecting microorganisms associated with implant-related infections.

There are a number of efforts that can be made to improve the yield of culture. Obtaining multiple samples, expeditious transfer of culture samples (especially in blood culture bottles) and prolonged incubation of culture samples are proven to be effective [3,12].

Another strategy to improve isolation of infecting organisms is to subject the retrieved implants to sonication in a sterile fluid. This technique was described a few decades ago and popularized by Trampuz et al. who demonstrated that the culture of sonication fluid had a better yield for isolation of infective organisms of hip and knee PJIs than routine culture [12].

Numerous investigators have described the use of molecular techniques in isolating the infective organism. Perhaps the first molecular technique to be evaluated for isolation of infective organisms in PJI was the polymerase chain reaction (PCR) [13–16]. Tuan et al. continued their efforts to optimize the PCR technology and reported their experience with the use of reverse transcriptase RNA (ribonucleic acid) that aimed to reduce the incidence of false-positive cases [15,16]. Other investigators have shown promising findings with the use of PCR as well. Melendez et al. showed that the PCR accuracy for detecting microorganisms in synovial fluid is 88% and these authors demonstrated that PCR can be used to detect unusual species such as Candida and antibiotic-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) [17]. Bereza et al. was able to isolate bacterial DNA using PCR in 90% of patients [18].

One of the issues related to the use of conventional PCR relates to its extreme sensitivity as it can amplify the DNA of contaminated microorganisms. Because of this issue, PCR has not been used as a first line or a single diagnostic tool in the detection of PJIs [1]. Another issue with the use of conventional PCR is that the type of organisms being sought need to be known to allow for the design of the primer. It is clear that the type of infective organisms is not always known. Thus, a broader approach with the use of multiplex PCR has also been investigated. Jacovides et al. explored the utility of the multiplex PCR using the Ibis Biosciences T5000 biosensor system in a cohort of prospectively collected synovial fluid specimens [19]. In the 23 cases that were considered clinically infected, the PCR panel detected the same pathogen isolated by conventional culture in 17 of 18 cases, and also detected one or more organisms in 4 of the 5 culture-negative cases. In addition, the panel detected organisms in 88% (50 of 57) cases in which revision arthroplasty was performed for a presumed aseptic failure.

Tarabichi et al. first demonstrated the utility of NGS for pathogen detection in PJI with the detection of *Streptococcus canis* in a previously presumed culture-negative case [20]. In a recent report, NGS was demonstrated as a useful adjunct for pathogen detection in 81.8% of culture-negative PJI where intraoperative tissue samples were analyzed [21]. Furthermore, in a series of 86 synovial fluid samples, high concordance with microbiological culture was seen with NGS of synovial fluid alone [22].

Thoendel et al. also showed that metagenomic shotgun sequencing is a powerful tool to identify a wide range of PJI pathogens and may be helpful to diagnose the organism in CN-PJI [23]. Based on their study, metagenomics was able to identify known pathogens in 94.8% of culture-positive PJIs. New potential pathogens were detected in 43.9% (43 of 98) CN-PJIs. Detection of microorganisms in samples from uninfected aseptic failure cases was conversely rare (3.6% of cases).

The analysis of synovial fluid with new biomarkers are currently being studied clinically [3]. The alpha-defensin test shows good results in detecting PJIs [1,3,24,25]. The sensitivity and specificity of the alpha-defensin test is greater than 95% and unlike other biomarkers (i.e., erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), polymorphonuclear (PMN) count) it is not affected by previous antibiotic administration [25–27].

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QUESTION 7: Do patients with adverse local tissue reactions (ALTRs) have a higher incidence of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. Patients with ALTRs appear to have a higher incidence of PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 2%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

The diagnosis of PJI can be extremely challenging in patients with a metal-on-metal (MoM) bearings or modular junction-induced ALTRs. The clinical presentation of ALTR may mimic that of PJI and both serum and serologic markers may be elevated in both conditions. Intraoperative findings may include extensive soft tissue necrosis, macrophage foreign body response, perivascular lymphoid infiltrate and even grossly appearing purulent fluid [1–3]. Preliminary research suggests that MoM wear and corrosion particles may alter the periprosthetic environment, therefore increasing the risk of infection by: 1) impeding the immune system; 2) preventing or accelerating bacterial growth; 3) altering antibiotic resistance and metal resistance mechanisms and 4) providing an ideal milieu for pathogens to proliferate in the necrotic tissues around the joint.

While distinguishing aseptic failure from PJI in a patient with an ALTR can represent a diagnostic challenge, diagnostic cutoffs have been suggested with higher synovial fluid white blood cell cutoffs than chronic PJIs without an ALTR; further, metallic debris can lead to errors in reading the synovial fluid cell count and differential and thus it is recommended to perform a manual cell count in cases of ALTR or metallosis [4]. Despite the vast body of literature investigating both ALTR and PJI following total joint arthroplasty independently, there is a lack of clinical data evaluating the concomitance of these phenomena.

A number of in vitro studies have assessed the effects of metal ion wear production on local soft tissue environment and immune response. Daou et al. noted that increased cobalt concentration in periprosthetic tissue resulted in an inhibitory effect on lymphocyte superoxide production, an impaired leukocyte recovery from acid stress and an improved intra-cellular survival of *Staphylococcus epidermidis* [5]. Akbar et al., likewise noted that high concentrations of cobalt and chromium ions produced an adverse effect on T-lymphocyte function, proliferation and survival [6]. In contrast, Hosman et al. found that high concentrations of cobalt and chromium have bacteriostatic effects as a result of inhibition of biofilm formation and bacterial proliferation [7].

Numerous case reports and small case series have highlighted the issue of concomitant ALTR and PJI [1,8–14]. In one dramatic example, Judd et. al. identified an infection rate of 33% in a series of nine patients revised for ALTR [8]. Two case reports describe concomitant ALTR and infection leading to massive necrosis of bone and soft tissue in a total of four patients, suggesting a possible link between ALTR and severe tissue damage from PJI [9,13].