lence represents a local inflammatory reaction consisting of a high synovial white blood cell count.

Therefore, in the absence of an objective definition, it is difficult to consider purulence as a simple dichotomous variable. Subjective opinion of the surgeon regarding periprosthetic fluid can vary based on their clinical impression or concerns regarding the consequences of misdiagnosing PJIs. Moreover, PJI has a serious impact on patients' health and quality of life because patients may be subjected to additional surgical procedures and long-term antibiotic treatment. Therefore, surgeons should be cautious in applying subjective criteria for ruling in or ruling out PJIs in suspected patients.

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# QUESTION 7: Is aseptic loosening (AL) associated with an undiagnosed periprosthetic joint infections (PJIs)?

**RECOMMENDATION:** Some percentage of AL is due to culture-negative infection, since up to 10% of culture-negative cases contain bacteria when screened by molecular methods. Whether this correlates to an undiagnosed infection causing AL remains unclear. Understanding this issue is limited by the ability of bacterial culture to function as an effective gold standard for detecting infection. The role of molecular techniques such as next generation sequencing in this setting needs to be explored.

**LEVEL OF EVIDENCE:** Limited

**DELEGATE VOTE:** Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

## RATIONALE

Loosening is one of the most common indications for total joint arthroplasty revision. Differentiating between PJI and AL is important in determining appropriate treatment. Loosening is considered aseptic when the radiographic or clinical findings associated with loosening are present in the absence of clinical or laboratory evidence of infection. Radiographic determination of loosening has an excellent specificity and positive predictive value, however, a poor sensitivity and negative predicative value, and thus should not be used to exclude loosening [1].

There is the possibility that microorganisms live on or around implants without signs or symptoms of infection, which can lead to AL. Several prospective and retrospective studies have supported that at least a fraction of cases with AL have been associated with higher rates of bacterial growth. The reported prevalence of unexpected positive cultures (UPC) in presumed aseptic revision arthroplasty varies from 5.9 to 23.9% [2–14]. This major variation might be due to small sample size, different culturing protocols (detection of bacteriologic 16S ribosomal RNA by polymerase chain reaction, sonication fluid cultures and conventional techniques of fluid and soft tissue cultures), laboratory contamination rates, as well as the heterogeneity of patients included in each study (i.e., revisions for isolated polyethylene wear, dislocation, fracture and implant loosening) [2,5]. Kempthorne et al. reported a case-control prospective study comparing AL patients (cases) and patients undergoing revision surgery for other causes (control) with a positive culture rate of 15% [2].

Some authors have related early AL to hidden PJIs [3,7,11]. Ribera et al. and Fernandez-Sampedro et al. have observed a correlation between microbiology and prosthesis-age, which supports the possibility of early loosening being caused by hidden PJIs [3,11]. Among the studies reported, there is no consensus about the prognostic impact of UPC. Some authors have shown that even a single positive intraoperative culture has been correlated to prosthetic joint failure, especially with early loosening [11,12]. On the other hand, Portillo et al. have found that the growth of low-virulence organisms in revisions for apparent AL is not associated with early prosthesis failure [8].

While traditional laboratory analysis to evaluate for infection consists of intraoperative culture of periprosthetic tissue or fluids, it has been well-established that microbial culture is an imperfect means of detecting bacteria, as culture has been shown to fail to detect bacteria in as many as 15% of clinically apparent infectious cases [15]. The increasing utilization of molecular methods in recent years has increased the incidence of bacterial detection in cases of AL. One study of 74 culture negative aseptic implants revealed the presence of bacteria in 9 (12%) after screening with polymerase chain reaction (PCR) assays [16].

The discrepancy between traditional culture methods and culture-independent molecular methods to detect bacterial infection in implants has been discussed extensively in the literature [17]. A number of proposed theories have been put forward to explain the absence of cultured bacteria in clinically infected cases, including the effects of prophylactic antibiotic treatment, growth behavior of biofilms and insufficient growth time to detect orthopaedic-specific pathogens. Regardless of the reason, detection via culture appears to be an inadequately sensitive diagnostic tool for periprosthetic joint infections.

A consistent limitation of studies that compare molecular techniques to culture is a failure to perform complete (deoxyribonucleic acid) DNA sequencing. Without this additional information, confirmation and agreement cannot be made between samples that are both culture and PCR-positive. Additionally, the etiology of culture negative and PCR-positive samples cannot be explored. Studies that have conducted full DNA sequencing have found significant discrepancies between the predominant species in culture versus those found via PCR analysis and the classic bacterial species that would be expected in PJIs [16]. The role of contamination in molecular methods also remains ill-defined. A carefully conducted study directly addressing this question found no significant difference in culture and 16S rRNA PCR of explanted implants [18].

An alternative theory to explain the phenomenon of culture-negative and PCR-positive clinically infected cases is the role of endotoxin. The detection limits for endotoxin are comparable to the stimulatory threshold, possibly resulting in unrecognized endotoxin [19]. Endotoxin alone replicates the effect of aseptic loosening [20] and can also adhere to titanium particles and implant surfaces [21]. In cases where bacteria are truly eradicated, cellular debris may create a false positive PCR, and residual endotoxin may initiate a local inflammatory response, resulting in culture negative loosening [22].

It is apparent that advanced modern molecular techniques detect bacteria in aseptic joints at a greater rate and with greater diversity than traditional microbial cultures. It is likely that a PJI is present in a greater number of cases with implant loosening than previously suspected. More detailed studies are required to determine the true incidence of loosening due to infection and the exact pathogenic process that may differentiate culture and PCR-positive infections from culture-negative, but PCR-positive infections.

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