Fungal Periprosthetic joint infection

4.1. FUNGAL PERIPROSTHETIC JOINT INFECTION: DIAGNOSIS AND TREATMENT

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QUESTION 1: What is the optimal method to diagnose fungal periprosthetic joint infection (PJI)?

RECOMMENDATION: Diagnosis of fungal PJIs is established by incubating joint aspirations or tissue samples collected intraoperatively on specialized culture media. Furthermore, isolation of fungal species may take up to four weeks. However, given the shortcomings associated with the use of culture, alternative techniques capable of detecting fungi, such as molecular techniques, may be used as an adjunct.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

PJIs can be caused by an expanding number of infecting organisms. While the vast majority of these organisms are gram-positive cocci, atypical organisms such as fungi have also been shown to be associated with PJIs and present an even more difficult diagnostic challenge [1,2]. In the largest series published, 31 fungal PJIs presented with indolent onset of joint swelling and pain frequently without other systemic symptom or signs of infection [3]. In another series, about 50% of patients who had fungal PJIs had radiographic evidence of loosening [4] and could be misdiagnosed as aseptic loosening, especially for those having normal serum inflammatory markers [5]. Serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) joint fluid cell counts and bone scintigraphy have limited value for diagnosis of fungal PJIs [6–8]. While the aforementioned tests all help to establish the presence or absence of an infection, they provide no information regarding the identity of the infecting organism.

Perioperative cultures, such as aspirated synovial fluid, as well as intraoperative tissue and swab samples, have been considered diagnostic standards for fungal PJIs [3,4,10,11]. Unfortunately, culture has been shown to have sensitivity as low as 50%. Given that these studies were assessments of the overall accuracy of culture in diagnosing PJI and not fungal infections specifically, culture may even perform worse in the setting of fungal PJIs [12–16]. Fungi are notoriously difficult to isolate in culture due to several reasons. First, culturing fungi requires the use of specialized media, with various modifications needed in order to isolate different species of fungi [17]. The universal media for most fungi is Sabouraud dextrose brain heart infusion (BHI) agar or plain BHI agar [18]. A blood-containing media such as BHI agar with 10% sheep blood improves the sensitivity or recovery of dimorphic fungi. Special media are required for fastidious organisms, such as bird seed agar for *Cryptococcus neoformans*, chromogenic agar for Candida, dermatophytes' test medium for dermatophytes, and longchain fatty acid supplementation for *Malassezia furfur* [19]. Second, the traditional duration to culture slowly growing fungi requires four weeks or longer. A study of 3,036 fungal cultures showed that an incubation period of two weeks is sufficient for the detection of yeast or molds, whereas, a four-week incubation period is necessary for dermatophytes [18]. Given the potential for identifying a fungal organism up to a month following resection arthroplasty, more expeditious methods of pathogen identification are needed. The vast majority of techniques have focused on sequencing of the 16S segment, a highly conserved region of bacterial DNA that allows for identification of bacteria at the species level [15,20,21]. Thus, many of these techniques are unable to identify fungal organisms; however, sequencing of the Internal Transcribed Spacer segment, a fungal sequence analogous to the 16S segment [22,23], demonstrated a sensitivity of approximately 90%, with a turnaround time of a week, a massive improvement over culture [24].

In conclusion, culture remains the primary method for identification of fungal organisms in the diagnosis of PJIs. However, in light of the difficulties associated with isolation of fungal organisms, alternative techniques are needed. Techniques capable of detecting fungal organism, such as next generation sequencing (NGS), may be used as an adjunct in the diagnosis of fungal PJI.

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QUESTION 2: Should patients with periprosthetic joint infections (PJIs) caused by a fungus undergo the typical two-week antimicrobial holiday prior to reimplantation?

RECOMMENDATION: There is no conclusive evidence to support the use of an antimicrobial holiday period prior to reimplantation in case of fungal PJI treated with staged revision.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 5%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The review of the literature on fungal PJIs treated with staged revision shows only 8 retrospective cohort studies (level of evidence IV) and 13 case reports (level of evidence V) (Table 1). We have been able to find only 21 papers (104 patients) regarding fungal PJI treated with two-stage exchange arthroplasty. In 68 cases (from 14 different studies), a drug holiday of at least two weeks was applied before reimplantation. No drug holiday was prescribed in two cases. For the remaining 34 patients, there was no data available about this aspect. Candida spp. (especially *albicans* or *parapsilosis*) was the main causal agent. Most patients had at least six weeks of systemic antifungal treatment after first operation, in agreement with the 2013 Consensus Conference conclusions. Following reimplantation, antifungal agents were continued for from two weeks to six months in six studies (69 patients). The agent most frequently used was fluconazole. Among reviewed papers, most authors seem to prefer a drug holiday of two or more weeks before second surgical stage. This approach is consistent with the conclusion of the previous Consensus Conference in 2013. No study compares the results of the two different strategies.

In conclusion, antifungal therapy could be stopped before reimplantation but there is no high-quality evidence to support this opinion.

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