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REVIEW

A comprehensive review of the diagnosis and management of prosthetic joint infections in the absence of positive cultures



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Summary The diagnosis and management of prosthetic joint infections (PJI) with negative cultures remains an enigma without clear definitions and guidelines for its management. In contrast, the literature offers guidelines to the diagnosis and management of culture positive prosthetic joint infections as noted in both the infectious disease literature and the orthopedic literature.

This paper outlines the current state of knowledge of PJI with negative cultures and summarizes the recommendations for the work up and management of this condition. In addition, we propose a simple algorithm that clinicians may find useful for the management of PJI with negative cultures. This algorithm has not been validated with data at this point, but can be applied to practice to help direct the management and diagnosis of prosthetic joint infections in the absence of positive cultures.

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Introduction

Prosthetic joint infections pose an increased problem for physicians due to the lack of standardized guidelines. The risk of an implant infection is high in the first 2 years, but remains a lifelong risk and is related to the presence of a biofilm [1,2]. The current guidelines attempt to address prosthetic joint infections (PJI) caused by the most common bacteria as seen in Table 1.1 [1,3–16], but fail to address PJI with negative cultures. In addition, the type of prosthetic joint infection is also an additive factor. In the early post-operative infections, antibiotics play an important role in detection of the organism, while in the later chronic infections, other factors such as fastidious organisms, patchy distribution of infection, low inoculum of infection, and the presence of non-recoverable biofilm embedded bacteria also play a role in making the diagnosis difficult [5,9,17]. This paper aims to address the risk factors, pathogenesis and diagnostic approach for this group of patients. We have also included a proposal for an algorithm for the approach and management of these patients.

Epidemiology

In 2014, over one million total prosthetic surgeries were performed worldwide with an incidence of prosthetic joint infections ranging from 1 to 4%

Table 1.1 Microbiology of culture-positive PJI [1,3–16].

Gram-positive	>50%
• <i>Staphylococcus aureus</i>	• 24–43%
• Coagulase-negative staphylococcus	• 12–26%
Gram-negative	3–10%
• <i>Enterobacter</i> spp.	• 78%
• <i>Pseudomonas</i> spp.	• 20%
• <i>Escherichia coli</i>	
• <i>Klebsiella</i> spp.	
• <i>Proteus</i> spp.	
Anaerobes	2–4%
Mycobacterium	0.7%
Fungi	1.2%
Polymicrobial	10%

after primary knee replacement and 1 to 2% after primary hip replacement [18,19]. Approximately 15–20% of all prostheses are found to be infected after primary revision surgeries [4,5].

Organism isolated from culture-positive specimens is shown in Table 1.1 [1,3–16], Gram-positive bacteria account for over 50% of all prosthetic joint infections. *Staphylococcus aureus* and coagulase-negative staphylococci are the two most common organisms with incidence rates of 24–43% and 12–26%, respectively [4,5,7]. In addition, it has been found that *Streptococci* occur in 8–10%, *Enterococci* in 3–7%, and *Corynebacterium diphtheria* in 2% of all PJI [5,7,11].

Gram-negative bacilli, although not as common, occur in 3–10% of PJI cases [5,7,8]. *Escherichia coli*, *Enterobacter* spp., *Pseudomonas* spp., *Proteus* spp., and *Klebsiella* spp. are some of the most common Gram-negative bacteria associated with PJI [12]. A study of 242 Gram-negative PJI cases, 78% were *Enterobacter* spp. and 20% *Pseudomonas* spp. [5]. Anaerobes have been found to account for only 2–4% of all PJI [1]. Gram-negative infections and anaerobes are a risk for treatment failure and have been found to require longer treatment durations compared to Gram-positive infections [5]. Gram-negatives and anaerobes have been associated with late-onset infections from hematogenous spread from a secondary infection and frequently present after gastrointestinal or genitourinary tract procedures [5,13].

Mycobacterium spp. and fungi, specifically *Candida* spp. and *Aspergillus* spp., are other causative organisms that are associated with a delay in PJI diagnosis and also often result in treatment failure [5,14]. Bracken et al. reported an incidence rate of 1.2% for fungal PJI out of 3822 culture-positive PJI cases [15]. An extensive literature review in 2013 of all reported *Mycobacterium tuberculosis* PJI cases reported from January 1950 to July 2012 found only 15 cases identified worldwide with an incidence rate of 0.7% [16]. *Mycobacterium* spp. and fungal infections are most often associated with an immunocompromised state and can often precipitate a culture-negative diagnosis due to a lack of proper isolation of the organisms, so these incidence rates are likely underreported [10]. Overall, polymicrobial infections account for 10% of all PJI's [1].

Prosthetic joints with negative cultures are shown in Table 1.2 [8,17,20–24]. These infections account for 5–12% of all PJI [9,25,26] with 98% of them related specifically to knee and hip arthroplasties [17].

Pathogenesis of PJI with negative cultures

Culture-negative PJI account for 10% of all prosthetic joint infections [8,17]. This can be compared to the cases of culture-negative endocarditis that account for 20% of all endocarditis cases [8,17]. These infections are often a result of inaccurate and inappropriate diagnostic tools for fungal, zoonotic, and fastidious bacteria that are not easily detected routinely. Million et al. found that 46% of culture-negative prosthetic joint infections were caused by fungi, 43% mycobacteria,

Table 1.2 Microbiology of percentages culture-negative PJI [8,17,20–24].

Fungi	46%
Mycobacteria	43%
Other	11%
<ul style="list-style-type: none"> • <i>Brucella</i> • <i>Coxiella burnetii</i> • <i>Lactobacillus</i> spp. • <i>Listeria monocytogenes</i> • <i>Pasteurella multocida</i> • <i>Propionibacterium acnes</i> • <i>Pseudomonas</i> spp.^a • <i>Serratia marcescens</i> • <i>Staphylococcus</i>^a 	
<i>Streptococcus</i> ^a	
<ul style="list-style-type: none"> • <i>Tropheryma whipplei</i> • <i>Ureaplasma parvum</i> 	

^a Bacteria that cause a biofilm have been shown to be an independent risk factor for treatment failure and cause culture-negative PJI.

and 11% were caused by other bacteria such as *Listeria monocytogenes*, *Propionibacterium acnes*, *Staphylococcus*, *Streptococcus*, *Brucella*, *Coxiella burnetii*, and *Tropheryma whipplei* as shown in Table 1.2 [8,17,20–24]. In 31 cases of atypical culture-negative infections studied, 35% were reported as *Brucella* and 16% was *Coxiella burnetii*, excluding all cases of fungi and mycobacteria [26].

C. burnetii is one example of treatment failure that will result in multiple revision surgeries if left undiagnosed that has been studied more recently. Million et al. showed that the current standard culture methods for PJI missed three out of four cases of positive *C. burnetii* cases that were correctly detected with polymerase chain reaction (PCR) [26]. PCR was done in these cases due to atypical presentations on imaging that suggested a serious infection that was previously missed. Million et al. proposed that all culture-negative cases should be worked up specifically for *C. burnetii* and *Brucella* serology with PCR.

These organisms are similar to those that are found to cause culture-negative endocarditis. *Chlamydia* and *Bartonella* are associated with culture-negative endocarditis, but have not been previously reported in culture-negative PJI [17].

Pasteurella multocida, *Lactobacillus* spp., *Ureaplasma parvum*, and *Serratia marcescens* have also been found to cause PJI that are more difficult to diagnose and associated with PJI with negative cultures [20–23,27]. Failure to properly identify the microorganism results in failure to treat or improper treatment, and subsequently increases the chances of treatment failure [27]. Bacteria

such as *Staphylococcus aureus*, coagulase-negative staphylococcus, and *Pseudomonas* spp. are known to form a biofilm, which subsequently makes the organisms difficult to detect routinely [24].

Treatment failure is a problem for PJI with negative cultures because standard cultures and traditional empiric treatment will not eliminate other organisms, such as resistant, zoonotic, fastidious, or fungi. This has been studied with the commonly used empiric treatment of vancomycin that has not been effective in eliminating culture-negative endocarditis infections caused by these atypical pathogens [17]. Surgical and medical treatments must be tailored to these organisms to effectively clear the infection.

Risk factors

Demographic risk factors for culture-positive and PJI with negative cultures infections are similar and reported in Table 2.1 [9,26,28]. These include a slightly higher incidence rate in men older than 65 years with a BMI greater than 25 that present with multiple comorbidities or in a chronic immunosuppressive state [9,26,28]. Peel reported a 10% increase in risk of infection is associated with every 1 kg/m² increase in BMI with a significant *p*-value of 0.05. Compounding comorbidities associated with an increased risk for PJI include chronic steroid use, chronic renal insufficiency (creatinine clearance <30 mL/min), degenerative joint disease, rheumatoid arthritis, other diseased joint states, diabetes mellitus, liver disease, poor nutritional status (albumin <34 g/L or absolute lymphocyte count <1.5 × 10⁹/L), smoking, and any recent infections within 30 days of surgery [1,5,9,13,29]. Maier et al. found a significant relationship between vitamin D deficiency and PJI with a *p*-value of <0.001 [30]. All of these risk factors are associated with a decrease in the body's ability to fight infection and heal properly.

Previous revision surgeries, superficial surgical site infections, wound drainage, surgical time longer than 2.5 h, and an increased American Society of Anesthesiology (ASA) index are other risk factors that have been found to be associated with PJI. ASA index, wound drainage, and surgical site infections were found to be statistically significant, with *p*-values of 0.05, 0.001, and 0.007, respectively [4,31].

In addition to the risk factors for all PJI, the major risk factor for PJI with negative cultures is related to prior antibiotic use. In a previous study in 2010, 64% of 135 culture-negative patients were

found to have used antibiotics within 3 months prior to their culture-negative diagnosis and 13% receiving their last dose one week prior [8]. In the same study, Malekzadeh et al. found that postoperative wound drainage was more likely to be associated with PJI with negative cultures as compared to culture-positive. Prior antibiotic use and a postoperative wound drainage were both found to be statistically significant with a *p*-value of <0.001 [8]. A history of prior prosthetic joint infections were found to be associated with 19% of culture-negative infections, while only 8% of culture-positive infections were associated with a prior PJI, with a *p*-value of 0.008 [8].

In a study by Berbari et al. that investigated sixty culture-negative cases, 53% received antibiotics within the last 3 months with 44% receiving antibiotics at the time of tissue culture. The absence of acute inflammation histologically was found to be associated with an increased risk of treatment failure, with a *p*-value of <0.001 [28]. Peel et al. showed that out of nineteen culture-negative cases studied, 92% of patients received antibiotics within one week of their culture [30]. Trampuz et al. reported that antibiotic use within 2 weeks of diagnosis decreased the sensitivity of positive cultures and supports the need to address the current recommendation for prophylactic antibiotic use as a large risk factor for a culture-negative diagnosis [1,31].

The method of culture and the number of cultures obtained are risk factors that should also be considered. PJI with negative cultures are thought to be caused by misdiagnosis, antibiotic use as previously described, usage of inappropriate media, inadequate incubation time, and loss of viability related to transport [8,25]. The study showed that discontinuing antibiotics 2 weeks prior to cultures significantly impacts the sensitivities and diagnosis [8,25]. Tissue culture sensitivity increases with an increased incubation time and when at least 5 cultures are obtained. An incubation time of at least 10–14 days has been shown to identify slow growing (*Propionibacterium acnes*) and fastidious organisms that are often misdiagnosed if not incubated for the proper amount of time [27,32]. DeHaan suggested a new protocol for culture-positive PJI that called for an increased incubation time and increased number of cultures to be obtained. In his study, 21% of missed virulent organisms by routine methods were properly identified by his suggestive approach, eliminating these cases that would have otherwise been identified as false positive culture-negative PJI [32]. He was also able to successfully identify true culture-negative cases as sterile joints in 95% of cases [32].

Table 2.1 Demographics and risk factors for culture-negative PJI [9,26,28].

Gender	Male	53–58%
Age	>65	>50%
BMI ^a	>25	>50%
Comorbidities	• Chronic renal insufficiency	5%
	• Degenerative joint disease	53%
	• Rheumatoid arthritis	15–20%
	• Other joint problem (congenital, avascular necrosis, septic arthritis, psoriatic arthritis, malignancy)	<5%
	• Diabetes mellitus	8–12%
	• Liver disease	3%
	• Vascular insufficiency	7%
Immunosuppression	• Malignancy	17–21%
	• Chronic steroid use	11–18%
Other	• Median joint age	746 days
	• Prior antibiotic use	53–64%
	• History of PJI or surgical site infection	3–8%
	• Previous revision surgery	5%

^a There is a 10% increased risk of infection associated with every 1 kg/m² increases in BMI with a p-value of 0.05 [26].

Biofilm

Biofilms are defined as thin films that adhere to surfaces, commonly associated with implanted devices, prostheses, and damaged tissues [23,24]. Biofilms are formed by certain bacteria that aggregate together and produce an extracellular matrix allowing for the adhesion, evasion, and resistant properties that make these organisms difficult to eliminate. These bacteria are able to inactivate proteins, alter metabolism, increase resistance to host immune responses, and decrease antibiotic effectiveness in a stationary growth phase [33,34].

Many other diseases such as endocarditis, periodontitis, surgical site infections, and catheter related infections are all associated with biofilm-causing organisms. Planktonic, free living, bacteria are easily eliminated by the host immune response and antibiotic therapy, while the majority of prosthetic infections are caused by biofilm forming bacteria [33,34]. These bacteria are in a stationary growth phase that allows for increased resistance to host responses and antibiotic therapy [33,34]. Approximately 80% of all PJIs are associated with bacteria that form a biofilm, rather than planktonic bacteria that are readily detected diagnostically [6].

Staphylococcus aureus and coagulase-negative staphylococcus most commonly develop a biofilm [6]. However, it seems that the quality of biofilm formed by different bacteria varies by species and specific strains and this may also be a compounding factor. Standard antibiotic therapy is effective in treating the symptoms associated with biofilm-causing organisms, but are often unable

to eliminate the bacteria. This is because the bacteria produces aggregates that form a barrier and depletes metabolic nutrients, causing it to be 100–1000 times more resistant to phagocytic host defenses and antibiotic treatments than planktonic bacteria [1,10,33,34]. This mechanism of resistance allows the bacteria in the biofilm to evade the host defense and causes a delay in the clinical presentation with a worse prognosis due to the lack of a systemic response produced [1,10,33,34].

Zimmerli et al. described several studies that showed that biofilm-forming bacteria were significantly more resistant to phagocytosis and host cell responses. Greater than 95% of *Staphylococcus aureus* survived exposure to neutrophils when compared with planktonic *Staphylococcus* in the same environment [7]. Coagulase negative staphylococcus was also found to have a 67% survival rate when compared to identical cloned planktonic *Staphylococci* with only a 21% survival rate [7].

S. aureus (coagulase negative) is the most common organism in PJI. It is dependent on host tissue proteins such as fibronectin, fibrinogen, laminin, and collagen for adhesion to the prosthesis surface that allows for increased resistance. This could be a potential target for therapy in the future if we are able to prevent adhesion and subsequent biofilm formation in PJIs [1,11].

Zimmerli et al. showed that a foreign body, such as an implant, decreased the minimal infecting dose of *S. aureus*, allowing for an increased infection rate and failure rate. Only 100 colonies were needed to infect 95% of implants in the animal models [7]. Colonization of prosthetic devices is related to the microorganism, decreased quantities

needed to cause infection, and the production of a biofilm. These combined all pose a risk for PJI with negative cultures that are difficult to detect with routine culture methods. Granulocytes that would normally clear the infection accumulate around the implant and are unable to phagocytize the biofilm producing bacteria that are adhered to the implant. This causes degranulation and inflammation due to a “frustrated phagocytosis response” that will persist until the infection is successfully cleared [5,7,35].

Clinical picture

Prosthetic joint infections with negative cultures have been found to present as early infections in the elderly as compared to Gram-positive PJI [4]. Early PJI present with acute inflammatory responses including pain, swelling, erythema, and drainage in many cases [4,31]. *Staphylococcus bacteremia* from a distant site poses a risk PJI in about 34% of patients [4]. Chronic infections present with less signs of acute inflammation and are often characterized by chronic pain and loosening of the joint [4].

For this group of patients, history is critical if clinical signs and symptoms are not evident. Assessing the patient’s surgical history, previous infections, comorbidities, and recent antibiotic use are all important in the diagnosis.

The demographics for culture-positive and culture-negative joint infections are similar. An overweight male, older than 65 years, with multiple comorbidities, immunosuppression, and a history of previous revision is the typical clinical picture for culture-negative PJI as shown in Table 2.1 [9,26,28]. This is nonspecific and patients presenting outside these demographics should not be excluded.

Factors that predispose patients to negative cultures depend upon the culture method and diagnosis. Routine cultures are significantly less sensitive than cultures with an increased incubation time of 10–14 days and when at least 5 cultures are obtained as suggested by Dehaan’s protocol [32]. Tissue cultures can be falsely negative due to the location of the culture and how it was obtained. An increased incidence of negative cultures has been found directly around the joint [36]. A lack of access to proper diagnostic tools, such as the facility for sonication and PCR of explanted prostheses to detect the organism can also predispose to a culture-negative diagnosis and should be made note of when considering a culture-negative infection.

Parvizi et al. showed that the current diagnostic tools of tissue and fluid cultures displayed a false positive rate up to 37% and a false negative up to 18% [19]. A review of 651 cases of PJI compared culture-positive cases to 48 cases of culture-negative found and concluded that the traditional culture methods failed to isolate the correct microorganism when it came to fungi, fastidious, or zoonotic organisms causing the infection [19].

Diagnostic approach

Inflammatory markers

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels are non-specific indicators of inflammation and should be evaluated serially in the diagnosis of PJI as a more accurate indicator of the inflammatory trend. CRP and ESR are often raised in PJI, as well as many other conditions, and is elevated post-surgery for several weeks [11]. Bereza et al. showed that the CRP level correlated with the number of positive cultures. A CRP level greater than 10 mg/l was seen in every PJI case studied [36].

A synovial fluid analysis of polymorphonuclear (PMN) cell count showed a sensitivity of 90% and specificity of 88% to detect PJI [37]. Trampuz et al. showed that a synovial fluid leukocyte count of greater than $1.7 \times 10^9/L$ had a sensitivity of 94% and specificity of 88% [1,11]. Normal wear of prostheses overtime can also cause an inflammatory reaction that results in osteolysis and a granulomatous reaction that can lead to bone resorption and loosening of the prosthesis. As a result, ESR and CRP will increase, but is not necessarily due to an infectious cause [38]. Bracken et al. showed that inflammatory markers combined with synovial fluid aspiration and clinical symptoms did not differentiate infections of bacterial versus fungal origin [15].

Histopathology

The use of histopathology can help to confirm the presence and extent of inflammation with a sensitivity of greater than 80% and a specificity of greater than 90% in culture-positive PJI [1,11]. There are no current guidelines that confirm the use of histopathology in culture-negative PJI. Barbari et al. reported that out of 60 primary cases of PJI with negative cultures 78% displayed acute inflammation on histopathological exam [28]. A synovial tissue biopsy must be obtained in order to send the suspected periprosthetic material for

histopathology evaluation. This can be achieved routinely to aid in the diagnosis of culture-negative PJI.

Imaging

Imaging modalities, such as plain films, computed tomography (CT), and magnetic resonance imaging (MRI) are nonspecific for all PJI, and will not specifically aid in the diagnosis of culture-negative PJI. These images can help to determine the current state of the joint by showing changes, loosening, fluid collections, or signs of inflammation [11,36]. Sinus tract formation and the new formation of bone are specific signs seen on imaging for all PJI [11].

Though not widely used, fluorodeoxyglucose-positron emission tomography (FDG-PET) has been investigated as an imaging tool in diagnosing PJI. FDG-PET has been found to have a sensitivity of 82% and specificity of 87% [37]. It should be noted that FDG uptake can be increased post-surgery for up to 6 months. It has also been associated with bone fractures and atherosclerotic lesions [10].

Antigranulocyte scintigraphy has also been studied in PJI and was found to have a sensitivity of 83% and specificity of 80% for detecting tissue inflammation. Technetium-99m scans have also been found to have an accuracy rate of 81% in detecting PJI [1,11]. The combined use of labeled leukocyte imaging and Technetium 99m labeled sulfur colloid may have a higher diagnostic yield.

Diagnostic methods

Peri-prosthetic cultures

The current diagnostic criteria from the Infectious Diseases Society of America updated in 2013 defines a prosthetic joint infection as having one of the following: presence of a sinus tract communication with the prosthetic joint, purulence without a known cause surrounding the prosthetic device, acute inflammation on histopathological examination of periprosthetic tissue consistent with infection, synovial fluid with leukocytosis and/or with the predominance of neutrophils, or growth of identical microorganisms in at least two intraoperative cultures [7–9,39].

In the case of a low virulent microorganism, such as coagulase negative staphylococci or *Propionibacterium acnes*, a combination of preoperative aspiration and intraoperative cultures are necessary to make a diagnosis. If the

organism has increased virulence, such as *S. aureus* or *Escherichia coli*, a single specimen growth in either synovial fluid, periprosthetic tissue culture, or sonication fluid with at least one other criterion above must be met to be classified as a prosthetic joint infection [28,39,40].

PJI with negative cultures were originally defined by Berbari as no growth of either aerobic or anaerobic cultures taken from periprosthetic tissue with either the presence of periprosthetic purulence, presence of acute inflammation histopathologically, or a sinus tract communicating with the prosthesis [9,28,29,41]. There is currently no gold standard for diagnosis of PJI or specifically culture-negative PJI. Many diagnostic tools are being researched to determine their accuracy when applied to PJI to define a more reliable method than what is currently used [37].

A recent study showed that 46% of 111 PJI cases were found to be classified as early, 22.5% delayed, and 31.5% late [6,11]. This shows the importance of a rapid, accurate diagnosis. Due to the difficulty of diagnosing culture-negative PJI, a full clinical evaluation and workup should be implemented to determine the diagnosis. This includes a complete patient history, clinical evaluation, laboratory tests, and imaging to rule out other diagnoses [1,36]. Pasticci et al. recommended that a full microbial investigation should become the standard protocol regardless of negative laboratory or imaging findings in any previous or suspected case of PJI [40].

Sonication of explanted implant

Microorganisms that aggregate and form a biofilm that adheres to prostheses can be disrupted by sonication of explanted prostheses to increase the sensitivity of the culture. These bacteria are in the stationary phase and can be broken down into planktonic bacteria that are easily detected [36].

Trampuz et al. showed that sonication of explanted prostheses had a 78.5% sensitivity and 98.8% specificity. Tissue culture without sonication was shown to have a 60.8% sensitivity and 99.2% specificity, with a *p*-value of <0.001. Sensitivities for both tissue and sonicated cultures were still decreased in patients who received antibiotics 2 weeks prior to culture [31].

Sonication of temporary spacers that are removed in 2-stage revision is a predictor of reinfection and is associated with a 50% treatment failure rate when results are positive within 24 months [42,43]. Small colony variants of *S. aureus* and coagulase-negative staphylococcus are also difficult to detect with traditional

diagnostic approaches and often asymptomatic leading to late infections. Sonication is able to detect these small colony variants and should be considered in all culture-negative infections [8,44].

PCR (molecular methods)

Synovial fluid analysis through PCR (molecular method using broad spectrum PCR-16s rDNA) and mass spectrometry has been shown to have a sensitivity of 81% and a specificity of 95% for PJI and is able to detect greater than 3400 types of bacteria. Melendez et al. proved this diagnostic approach to be valuable by detecting microorganisms in synovial fluid in 88% of patients diagnosed with aseptic prosthetic failure. This method can be used to detect forty species of *Candida* and four common antibiotic resistant genes, including *mecA* for MRSA, *vanA* & *B*, and *bla* KPC [44]. This was supported by the use of PCR with mass spectrometry that was shown to isolate four out of five culture-negative cases with increased sensitivity for these resistant genes [16]. Bereza et al. showed that bacterial DNA was isolated with PCR in 90% of patients with negative synovial fluid cultures [36].

PCR of tissue cultures have been shown to have an overall sensitivity of 50–86% [10]. In a previous study, PCR analysis of sonicated cultures of explanted prostheses yielded a 72% detection rate compared to 22% sonication only, and 4% traditional cultures [2]. In a similar study, it was found that the sensitivity of PCR of sonicated cultures in patients with previous antibiotic use was 42%, but was 100% when PCR of sonicated fluid with a *p*-value of 0.001 [10]. Sonication combined with PCR increases the sensitivity in detecting PJI with negative cultures with atypical organisms, biofilms, small colony variants, and in those patients who have received antibiotics previously [36,44].

Sonication combined with molecular based methods, such as PCR, should be implemented in the future as research continues to show the accuracy in detecting culture-negative PJI. Specific resistance genes, such as *mecA* for MRSA, should also be considered in the management, diagnosis, and as a possible target for these patients [45].

Treatment failure

The risk of infection with the presence of a foreign body, such as prosthesis, is greater than 100,000 fold as studied in animal models comparing infection rates with prosthetic implants [8,35]. This increased risk of infection, combined with an increased resistance of bacteria, and difficulty isolating certain organisms addresses a need for a

proposed guideline and a standard approach for the proper diagnosis and treatment for PJI with negative cultures.

Barbari et al. showed that in ten cases of PJI treatment failure, 50% were culture-negative infections [28]. These patients had a 29% failure rate when treated with retention and incision and drainage (I&D) of the prosthesis compared to only a 6% failure rate when two-stage revision was performed [28]. A similar study showed that with culture-negative infections, treatment failure was 50% with I&D and 29.6% with two-stage revision [25]. Malekzadeh et al. showed that these patients had a 22% two-year failure rate with I&D compared to a 14% failure rate with I&D in culture-positive PJI [8]. These studies showed that culture-negative infections exhibit a poor response to therapy without the use of one or two-stage revision, which is necessary to completely eradicate the infection.

This can be compared with the *MSSA* failure rate when treated with I&D that has been found to be 66.7% and only 8.5% with two-stage revision [10]. *MRSA* has a failure rate of 51.1% with I&D and 27.8% with two-stage exchange. Gram-negative infections treated with I&D and retention were found to have a failure rate of 30% and 25% with two-stage revision [10]. Failure rates related to fungal infections were 50% when treated with two-stage revision [10].

The increased failure rates related to Gram-positive infections as compared to Gram-negatives are thought to be related to the increased resistance, low levels of colony forming units causing infections, and the biofilm production more commonly associated with Gram-positive bacteria [46]. In contrast, Aboltins et al. showed a favorable failure rate for I&D of 6% when treated with an oral fluoroquinolone for a median duration of 12 months [2]. This suggests that once the correct pathogen is identified in a culture-negative diagnosis, there can be a favorable outcome when the correct antibiotic therapy and surgical management are applied.

Treatment

The classification of PJI's is important to consider when determining treatment management. Early infections occurring within 3 weeks post-surgical can be treated with retention of the prosthesis and antibiotic therapy with a success rate of 70–90% [10]. It is recommended that the prosthesis be removed for delayed and late infections to effectively eliminate the infective biofilm. This highlights the need for rapid diagnosis for all PJIs

to allow the patient to retain their prosthesis and be treated successfully [40]. Unfortunately, the current literature does not specifically address the management for culture-negative PJIs.

In a one-stage revision, the infected prosthesis is removed and replaced with a new sterile prosthesis at that time. The most common treatment and gold standard for all PJIs is the two-stage revision [46]. In a two-stage exchange, the prosthesis is removed and either replaced with an antibiotic-coated spacer or left without any device until the infection is cleared with antibiotic treatment. Once the infection is eliminated, the prosthesis is replaced. It has been shown that one-stage revision has an 86–92% success rate and two-stage has a 75–100% success rate in eliminating culture-positive infections [40,47]. Two-stage revision followed by 6 weeks of antibiotic therapy has been shown to be successful at all stages of PJI with 94.4% early, 93.8% delayed, and 94.5% of late infections being eliminated [47].

PJI with negative cultures have been found to have a 50% failure rate with I&D compared to 29.6% failure rate with 2-stage [40]. This illustrates the challenges in management and need for revision to eradicate resistant, fungal, or atypical organisms associated with culture-negative infections.

Antibiotic therapy

Long-term antibiotic use in addition to surgical intervention is necessary to effectively eliminate infection in a PJI with negative cultures. Bacteria that produce a biofilm remain in the slow growth, stationary phase. For an antibiotic treatment to be successful in eliminating these organisms, it must have a higher than normal minimal bactericidal concentration.

Current recommendations for culture-positive PJI in the hip and knee suggest 3 or 6 months of antibiotic therapy based on the organism identified in addition to 2-stage revision. Rifampin has been shown to disrupt the biofilm produced by *Staphylococcus* and is recommended in combination with a fluoroquinolone for use against Gram-negative biofilm-producing bacteria [10,40]. Due to the increased failure rate associated with MRSA infections, an alternative for treatment would include rifampin plus vancomycin or linezolid [10]. These current recommendations for culture-positive infections can also be applied to PJI with negative cultures if suspicion for culture-negative is high and thought to be related to these organisms but were not properly isolated.

Proposed algorithm

There are no current guidelines that exist to outline the diagnostic methods and management of PJI with negative cultures. It is important to accurately diagnose all prosthetic joint infections by changing the current protocol that calls for only synovial fluid and tissue culture required for diagnosis for PJI.

For this reason, it has been shown that the production of a biofilm is an independent risk factor for treatment failure and is a cause of culture-negative PJI [5]. For this reason, we suggest that sonication of explanted prostheses is a method that should be routinely employed to detect biofilm-associated bacteria to aid in the diagnosis of culture-negative PJI.

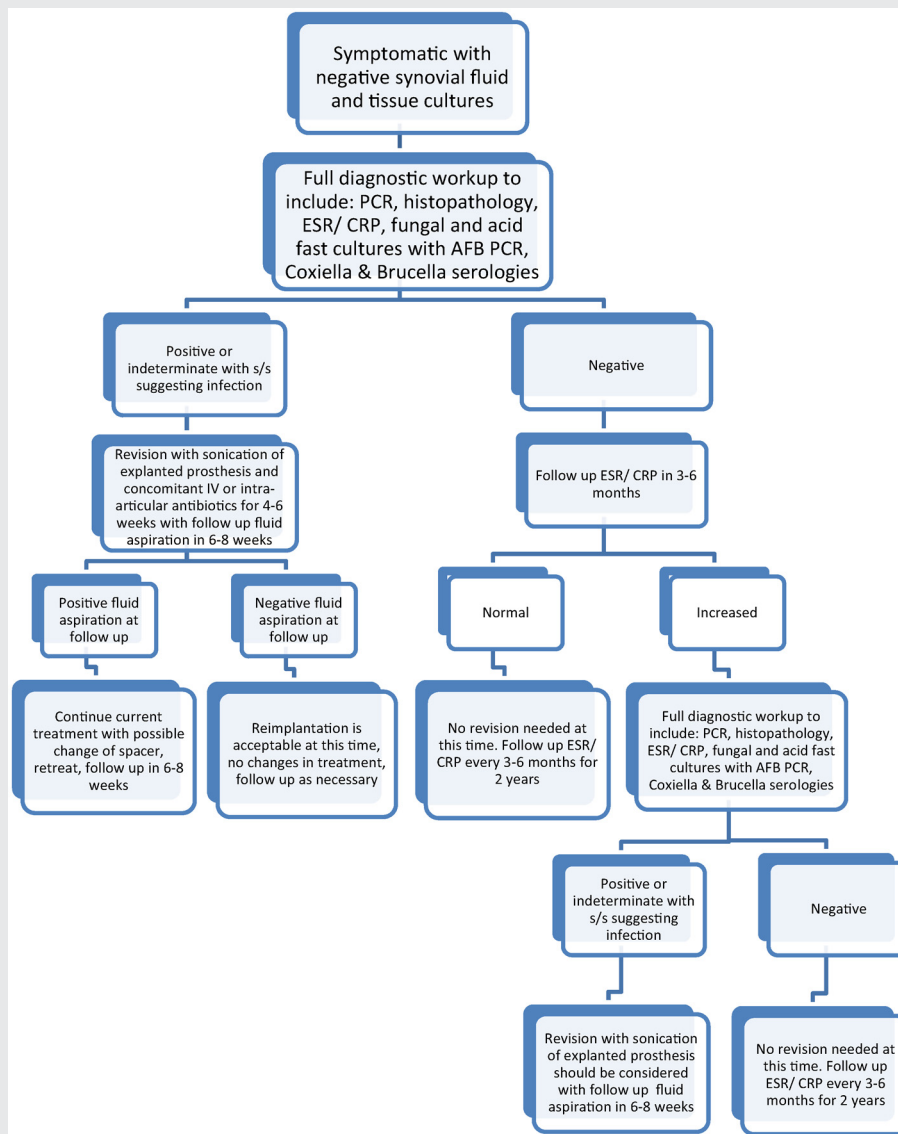
In a study by Bereza et al. using ultrasound, sonication and PCR to detect bacteria associated with loosening of hardware in PJI, he reported that ultrasound and sonication were the best diagnostic tools used on explanted devices to detect specific microorganisms. Ultrasound and sonication are able to disrupt biofilms, forcing stationary bacteria into an active phase that is easily detected. He also showed that when combined with PCR, the sensitivities of culture significantly increased with these diagnostic methods [36].

We suggest a different approach in this group that will help guide physicians in the diagnosis and management of these infections as illustrated in Table 3.1.

First, we suggest an increase in the number of cultures and incubation time for all cultures obtained, with a minimum of five cultures as suggested by DeHaan et al., in addition to a histopathological examination [32]. Fungal and atypical cultures (AFB) should be obtained in all cases, as studies have shown routine blood, tissue, and synovial fluid cultures will not detect or differentiate these organisms [15]. We also suggest that sonication and PCR of the explanted prosthesis be performed in all culture-negative cases or when clinical suspicion is high for an atypical diagnosis. Inflammatory markers (ESR/CRP) should then be monitored serially every month for 2 years, as studies have shown the risk for PJI is the highest in the first 2 years post-surgery [1,2].

When suspicion or diagnosis for culture-negative PJI is high, we propose that the following algorithm in Table 3.1 be employed. We use the definition of PJI with negative cultures as defined by Berbari et al. [28]. Symptomatic is defined as acute inflammatory signs and symptoms of fever, pain, tenderness, erythema, warmth, swelling, effusion,

Table 3.1 Suggested algorithm for culture-negative PJI.



and purulence at the surgical site. Purulence, pain, and erythema were found to be the most common presenting symptoms [4,11,26].

The negative synovial fluid and tissue cultures should follow Dehaan's suggestion with a minimum of 5 cultures taken with extended incubation time to increase the sensitivities of the cultures and diagnosis of slower growing bacteria that is often missed, such as *Propionibacterium acnes*. In all cases, we recommend the next step being a full diagnostic workup to determine only the true-positive cases of culture-negative PJI. A full diagnostic workup would include additional fungal and acid fast cultures, acid fast bacilli (AFB) PCR, PCR of the all cultures, *Brucella* and *Coxiella*

serologies, histopathological evaluation, and serial inflammatory markers (ESR/CRP).

For symptomatic patients, if any of the diagnostic workup that is implemented is positive or has indeterminate results with signs or symptoms suggestive of a PJI, but do not completely fulfill the criteria for clinical infection on the diagnostic workup, we suggest that a revision (one or two-stage) with sonication cultures of the explanted prosthesis be performed in addition to combined PCR (broad spectrum) of the sonicated cultures to further increase the diagnostic sensitivities in detecting the organism causing the infection with the proper concomitant IV or intra-articular antibiotics for 4–6 weeks minimum. After revision, we

suggest follow up in 6–8 weeks with aspiration of fluid. If the fluid is negative at that time, reimplantation can be done at that time with no changes in treatment, and follow up as necessary. If the fluid is positive, continue with the current treatment or consider changing the spacer, retreating, and follow up in 6–8 weeks.

For patients with completely negative results on the full diagnostic workup, we suggest follow up in 3–6 months with new ESR/CRP levels. If the ESR/CRP is still normal at that time, we suggest trending the ESR/CRP levels every 3–6 months for 2 years due to the increased likelihood of infection in the first 2 years post-surgery, and without revision at this time.

If the ESR/CRP are found to be increased, a full diagnostic workup as listed above should be employed again. If the results on the diagnostic workup are again negative, we suggest continuing to trend the inflammatory markers (ESR/CRP) every 3 months for 2 years. If the ESR/CRP are with normal limits in 3 consecutive tests or 2 years post-operation has been reached without cause for follow up, no revision or further evaluation is needed.

If the ESR/CRP are found to be increased or if any of the diagnostic workup at that time is found to be positive, we suggest revision with sonication of the explanted prosthesis be highly considered with follow up fluid aspiration in 6–8 weeks.

Conclusion

PJI with negative cultures accounts for 10% of all PJIs, but poses a serious problem in regards to the proper diagnosis and management. The approach to these infections should include a complete and thorough microbiological evaluation with a minimum of 5 cultures that are kept for several weeks, the use of newer methods for the identification of these microbes such as sonication, DNA PCR, and histopathology. Successful treatment involves exchange arthroplasty with concomitant antibiotic treatment based on the possible pathogen.

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None declared.

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