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General Assembly, Diagnosis, Pathogen Isolation - Culture Matters: Proceedings of International Consensus on Orthopedic Infections

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Question 1: What is the optimal methodology for obtaining intraoperative cultures?

Recommendation:

Each tissue sample should be collected using separate sterile instruments and transferred directly into culture bottles and transferred to laboratory as soon as possible. A minimum of three and maximum of five intraoperative cultures (periprosthetic tissue) should be obtained. It is preferable that samples are obtained from the implant-bone interface, whenever possible. Swab cultures should be avoided due to their poor diagnostic accuracy. Synovial fluid should also be collected and placed into blood culture bottles, where possible.

Level of Evidence: Moderate

Delegate Vote: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:

The accurate identification of the microorganism(s) responsible for periprosthetic joint infection (PJI) is a pivotal step in the management of this complication. In addition to confirming the diagnosis, this will enable the administration of specific antibiotics to help optimize infection eradication and joint salvage. Failure to identify the correct microorganism can result in potentially toxic, expensive treatments, as well as possible failure of PJI eradication [1,2]. Consensus is therefore needed to establish standard methods for intraoperative sampling to determine the best type of samples to be cultured, the optimal number of tissue specimens, and the most suitable method of sample transportation to the laboratory.

With regard to the method of obtaining intraoperative cultures, previous studies have demonstrated that tissue cultures have a higher sensitivity and specificity than swab cultures for diagnosing PJI, and therefore swabs should be avoided [3–5]. The most suitable intraoperative samples consist of tissue samples, synovial fluid, and

prosthetic components or entire prostheses. Each tissue sample should be collected using separate surgical instruments to prevent sample cross-contamination and to obtain true independent samples [6]. The biopsies should be taken from the synovial lining and periprosthetic tissues with the aim of targeting visibly inflamed or abnormal tissue [7]. Preference should be given to sampling the membrane at the implant-bone interface as such samples are most likely to yield positive results [8–10]. When histologic examination of the periarticular tissues is planned, it is helpful to obtain paired samples for histopathological and microbiological examination from the same area to enable correlation of results.

The optimal number of intraoperative specimens required to maximize the likelihood of identifying the infecting organism has been extensively investigated. Earlier studies suggested that the highest sensitivity and specificity were achieved by obtaining 5 or 6 samples [11–15]. Recent studies have used different culture media in an attempt to reduce the number of samples required and thereby decrease the technical and financial impact of this diagnostic modality. In a prospective multicenter study, Bemer et al demonstrated that the minimum number of samples required to confirm PJI diagnosis can be decreased to four, as long as each sample is cultured using three different media, including a blood culture bottle [10]. Peel et al [16] also demonstrated that a high level of accuracy for PJI diagnosis is obtained when three periprosthetic tissue specimens are inoculated into blood culture bottles, or four periprosthetic tissue specimens are cultured using standard plate and broth techniques. Gandhi et al [17] also used receiver-operating characteristic curve analysis to demonstrate that the optimal sample number necessary to yield a positive test result was four. We therefore recommend that obtaining four tissue samples provides the best sensitivity without compromising specificity.

Whenever possible, synovial fluid should be sent for analysis as it can be used for both culture and the detection of commonly used PJI biomarkers [18]. With regard to detection of the infecting organism, the sensitivity of the synovial fluid inoculated into blood culture bottles is higher than that of traditional culture [4,19,20].

There are no conclusive studies evaluating the performance of transport media for orthopedic samples as the performance of transportation systems differed depending on temperature, holding time, and bacterial strains. In general, good preservation of samples has been reported for media held at 4°C [5]. Specimens should reach the laboratory as soon as possible, and experimental models suggest that there is a significant loss of the bacterial yield after a 6-hour delay [21]. The latter study suggested that the optimal time for samples to reach the laboratory is approximately 2 hours.

Question 2: What methods can be utilized to increase the diagnostic yield of microbiological culture in SSI/PJI?

Recommendation:

At least four intraoperative cultures should be obtained to increase the diagnostic yield. There is limited evidence to suggest that cultures from the synovium, synovial fluid, or tissue in contact with prosthesis may be more likely to identify a pathogen. The samples should be inoculated in blood culture bottles, and the addition of enriched media (such as a chocolate agar plate and Schaedler broth) or bead mill processing broth may also augment yield.

Level of Evidence: Moderate

Delegate Vote: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)

Rationale:

Identifying an organism from microbiological culture is critical for both the diagnosis and treatment of surgical site infection (SSI) and periprosthetic joint infection (PJI) [22–24]. Two positive cultures from the same joint identifying the same organism by tissue or fluid remains as one of the major criteria for the diagnosis of PJI in total joint arthroplasty. This qualifies as a "major" criterion in both 2013 and 2018 definitions of PJI [23,25]. However, in 7%-35% [4,26–29] of patients, no organisms can be isolated despite meeting other criteria for infection, which defines "culture-negative" PJI patients [24]. In general, and particularly for this cohort of patients, optimizing culture yield can help determine type of surgical procedure, antibiotic therapy, and likelihood of treatment success.

Methods of optimizing culture growth have been divided into preoperative, intraoperative, and postoperative measures. With regard to preoperative measures, the AAOS CPG recommends aspirating a joint for culture at least two weeks after the last administration of antibiotics (moderate recommendation) [22]. If growth is unsuccessful initially, a repeat aspirate is recommended (consensus recommendation for knee, moderate for hip). Finally, if the diagnosis of PJI is suspected but not confirmed, holding antibiotic treatment is recommended in an attempt to identify an organism preoperatively or intraoperatively (strong recommendation) [22]. Intraoperative measures for optimizing culture growth include obtaining multiple cultures before irrigation and obtaining cultures from representative areas (ie, intramedullary, implant interface). The samples for culture should also be obtained using a clean instrument and transferred immediately into the culture bottle for transport. The culture samples obtained should also be transported to the laboratory as soon as collection is complete.

Postoperative measures include choice of growth medium, bead mill processing, timely delivery to the laboratory and processing by the laboratory, use of sonication, and culture duration. The scope of this question will address the following—What is the right number of intraoperative cultures? What type of cultures should be obtained? Which areas should be sampled? Does bead mill processing increase yield? What is the best growth medium? The remainder of the measures to optimize growth are covered by other ICM questions.

The AAOS CPG recommends multiple cultures be obtained at the time of surgery (strong recommendation), but no number was provided. The 2013 ICM recommended 3-5 cultures be taken in the setting of suspected or uncertain PJI (strong consensus) [30]. Previous studies recommended 5 cultures be obtained [12,14,15], but Atkins et al were the first to evaluate this prospectively and perform statistical analysis. They examined cultures grown from 297 revision arthroplasties and found that 5-6 cultures increased the likelihood of diagnosis [11]. In 2016, Bémer et al published a prospective, multicenter study that found using four culture samples on three different growth media was a highly reliable and a cost-saving approach to PJI diagnosis [10]. Gandhi et al corroborated these results by examining 74 PJI patients meeting MSIS criteria [17]. They found that the optimal number of cultures needed to yield a positive test result was 4 (specificity = 0.61 and sensitivity = 0.63) and concluded that increasing the number of samples increased sensitivity but reduced specificity [17]. Finally, Peel et al also determined that a minimum of four cultures was optimal to achieve growth with conventional means, but a minimum of only 3 cultures were required when using blood culture bottles [16]. Some authors have advocated up to 10 cultures in the setting of prior antibiotic use and less-virulent organisms [31], but these situations may be ideal for the use of emerging technologies such as next-generation sequencing [32].

With regard to how samples should be obtained, studies are mixed on whether synovial fluid culture is superior to tissue culture [10,17,33,34]. However, both are often obtained simultaneously in clinical practice and in combination increase the sensitivity for diagnosis [33]. Multiple studies have demonstrated that swabs are not a reliable culture method intraoperatively [4,35]. Owing to their high rate of false-negative and false-positive results [3], their use is

strongly recommended against by the 2013 ICM [30]. It is often stated that cultures should be removed sharply with a scalpel, handled with clean instruments, and placed directly into the sterile container. However, to the authors' knowledge, no studies have investigated the role of the technique to obtain the samples and culture yield.

It is often recommended that cultures be obtained from the intramedullary canal and bone-implant interface [36]. However, Gandhi et al investigated the role of a "best culture." This is a practice used to identify a promising specimen from anywhere in the infected joint that should undergo additional testing (ie, fungal and mycobacterial) beyond routine aerobic and anaerobic cultures [17]. Despite being a visually appealing specimen, this "best culture" practice did not increase the likelihood of growth [17]. In addition, Bémer et al in a multicenter prospective study found that the highest rates of culture positivity from synovial fluid to be 91.7%, followed by tissue in contact with implant material (91.5%), whereas bone samples had the lowest rates of positive cultures (76.6%-87.1%) [10].

Once a culture is obtained, but before inoculation, a process known as bead mill processing may also be used. The process involves placing tissue specimens into sterile vials, adding a small amount of sterile water and beads (glass or metal), and providing mechanized agitation (bead mill) [10,37]. One study has reported improvements in PJI diagnosis when using this technique [37]. Another prospective, multicenter study used this method and also found higher rates of bacteriologically documented PJI than those reported previously in the literature [10].

The use of alternate culture media has also been described to optimize culture growth. Hughes et al reviewed 805 synovial fluid samples from patients suspected of having septic arthritis [20]. The culture results obtained using blood culture bottles were compared with those obtained by a conventional agar plate method. The blood culture method identified significantly more pathogens and fewer contaminants than the conventional method [20]. Similarly, Font-Vizcarra et al retrospectively reviewed 87 cases of PJI in 2010 [4]. They compared culture growth of synovial fluid inoculated into blood culture bottles with that of periprosthetic tissue and swab samples in standard media. Not only did the synovial fluid in blood culture bottles have a higher rate of positivity, this method also had higher sensitivity, specificity, and positive and negative predictive values for diagnosis of PJI when compared with standard tissue and swab samples [4]. Subsequent PJI studies have also demonstrated that cultures of periprosthetic tissue in blood culture bottles increase culture yield compared with those of swabs [38] and standard agar/broth [16,39] and is similar in sensitivity to sonication [40].

Finally, aside from using blood culture bottles, enriched or organism-specific media have also been reported. When suspecting fungi, zoonotic bacteria, mycobacterium, or other unusual microorganisms, routine bacterial and anaerobic cultures will often fail to yield the pathogens [41]. The laboratory should be alerted when these organisms are suspected to avoid accidental exposure, and the right media such as brain-heart infusion, trypticase soy broth, and chocolate agars can be chosen [41]. Bémer et al investigated the question of what is the best growth media and found that the most efficient means to identify PJI per their definition was using a combination of 3 different culture media: a blood culture bottle, a chocolate agar plate, and Schaedler broth [10]. The authors also reported that the chocolate agar plate was more sensitive than the anaerobic agar plate, particularly for the anaerobe *Cutibacterium acnes* [10].

In conclusion, there is evidence to support the use of blood culture bottles, obtaining at least 4 intraoperative cultures (including synovial fluid and periprosthetic tissue), bead mill processing, and enriched media to increase diagnostic yield of microbiological culture in surgical site infection/PJI. Of these, the most studied methods include the ideal culture number and use of blood culture bottles (moderate evidence). The remainder of the interventions listed currently have limited evidence.

Question 3: What is the optimal time for culture processing of tissue or synovial aspirate samples? How long should routine cultures be kept before declared negative?

Recommendation:

Cultures should be maintained for a period of 5 to 7 days. In cases of suspected periprosthetic joint infection (PJI) with low-virulence organisms, or if preoperative cultures have proven to be negative and there is a high clinical suspicion for PJI (culture-negative PJI), the cultures should be maintained from 14 to 21 days.

Level of Evidence: Moderate

Delegate Vote: Agree: 87%, Disagree: 12%, Abstain: 1% (Super Majority, Strong Consensus)

Rationale:

It is believed that most common infecting organisms can be isolated within a few days of conventional culture. In addition, there is currently no reason to extend the culture duration in patients in whom the infecting organism has been isolated preoperatively. Research has focused on the incubation period for samples from patients with suspected periprosthetic joint infection (PJI), culture-negative cases, and patients who may be infected with low-virulence organisms, such as *Cutibacterium acnes* and anaerobes. Unfortunately, there is no consensus on an appropriate culture time, although identifying the responsible infectious agent is critical in PJI [14].

There exists a notion that longer incubation times may increase the possibility of detecting contaminants and thus false positives [42]. However, numerous studies have demonstrated that extending culture time to two weeks significantly increases the culture sensitivity without increasing the risk for the growth of contaminants [5,14,42–44]. Currently, there is no evidence determining the cost-effectiveness associated with holding cultures for one week versus two weeks. Besides the matter of cost, it remains critical that cultures are held for an adequate amount of time in an effort to isolate any potential pathogen for even cases that are presumed aseptic [45,46].

Most tissue or synovial cultures are incubated for 5 days or less [47]; however, there are studies underlying the importance of extending this period [14,44,48]. Butler-Wu et al tried to identify the optimum culture conditions for recovery of *C. acnes* from PJI specimens [44]. They applied 28-day culture incubation to all specimens from 198 revision arthroplasties and found that minimum 13-day culture incubation for both aerobic and anaerobic cultures is necessary for diagnosing *C. acnes*. Incubation beyond this period was nondiagnostic for *C. acnes* isolates. Schaffer et al proposed that microbiological culture should be held for 14 days to diagnose infection in patients after conducting a large prospective study, in which tissue samples from 284 patients were cultured [14]. Although the median time to diagnosis of a suspected organism was only 4 days, additional organisms causing PJI were grown up to 13 days later, further highlighting the polymicrobial nature of PJI. Comparing early- versus late-detected organisms, they demonstrated that the early group was composed of Staphylococci, Enterococci, Streptococci, and Enterobacteria. These organisms grew within the first 7 days of culture. The late group, growing predominantly from 7 to 14 days, exhibited growth from Propionibacterium species, aerobic gram-positive bacilli, and Peptostreptococcus species.

Neut et al evaluated a cohort of 22 patients with suspected septic loosening. They concluded that by prolonging the culture time to 7 days, it increased the detection rate of infectious bacteria from 41% to 64% [43]. Bossard et al recommended that culture

specimens should be kept for at least 10 days to detect *C. acnes* [49]. In their retrospective study examining 70 *C. acnes* infections, they found that by reducing the culture period to 7 days, diagnosis of PJI would have been missed in 21.4% of the cases. Despite their recommendation of a 10-day culture period, 6% of these *C. acnes* infections were identified outside the 10-day culture period. The similar conclusion about *C. acnes* was made by Frangiamore et al who showed that 14% of the culture-positive cases were detected after day 7 in their review of 46 cases [50].

In addition, there is literature proposing that a prolonged period of incubation (up to 21 days) is required to minimize the culture-negative PJI rate [24]. Parvizi et al proposed that cultures should be kept for at least 14 days and if no microorganism is isolated, an additional 7 days of incubation may be required. An additional 7 days of incubation may allow for the isolation of slow-growing organisms such as Mycobacterium species and fungi [24]. Utilizing a prolonged incubation period may be useful for cases where no organism is identified preoperatively.

Novel techniques have emerged to increase detection rates and minimize the culture period required in the diagnosis of PJI. In a prospective laboratory study over a 7-month period, tissue samples were taken from patients with suspected PJI [39]. All samples were cultured for 14 days, using a BD BACTEC instrumented blood culture system. All but one of the 66 culture-positive cases of PJI were detected within 3 days of incubation. The use of blood culture bottles was valuable for increasing the diagnostic sensitivity for PJI. A more recent study evaluated culture time for anaerobes and proposed a modern laboratory procedure that could improve detection and shorten culture time [51]. They showed that all pathogens could be identified within 6 days using a highly sensitive media (supplemented liver thioglycollate broth) and with direct identification by matrix-assisted laser desorption/ionization (MALDI-TOF).

To date, there are numerous techniques and methodologies used in conventional culture. Current literature suggests that cultures should be kept and processed on the basis of the infecting organism. Cultures should be processed and kept for at least 5 days. In cases of suspected PJI with low-virulence organisms, or if preoperative cultures have proven to be negative and there is a high clinical suspicion for PJI, cultures should be maintained for at least 14 to 21 days.

Question 4: What is the recommended standardized laboratory culture protocol to minimize differences between medical centers?

Recommendation:

Based on current guidelines from the Infectious Disease Society of America (IDSA), specimens for culture should be transported in sterile containers at room temperature and processed promptly within a 2-hour window to limit specimen contamination or desiccation and subsequent death from nutrient deprivation.

Level of Evidence: Limited

Delegate Vote: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

Rationale:

At present time, clinical microbiological laboratories use various approaches including molecular and classic culture methodologies to properly detect pathogenic microorganisms. However, culture remains to be the current preferred method in identification and subsequent classification of the infective pathogens. The practices in place are essential for assuring the correct determination of sensitivity and suitable treatment for patients following identification of the pathogen that led to surgical site infection and/or periprosthetic joint infection. Standard protocols have been implemented for microbiological laboratories serving both large academic medical centers and smaller community programs to maintain equitable results and a minimum threshold for the quality of specimen culture and subsequently the care of patients [52].

There are a multitude of factors that should be understood when considering the standardization of culture procedures. Culture yield is influenced by laboratory plating technique, the transport vehicle of the specimen, the time frame before reaching nutrients, the type of growth enabling media used, and numerous other factors. A recommendation by the Infectious Disease Society of America (IDSA) states that all orthopedic surgery tissue and fluid specimens sent for culture following intraoperative collection should be processed promptly after placing inside sterile containers and the processing time should not exceed a 2-hour window [52]. This is of the utmost importance in limiting the time frame in which the microorganism is without nutrients and in an uninhabitable environment.

The aforementioned IDSA guidelines outline how delicate the lifecycle of prokaryotic and simple eukaryotic organisms can be and how at any time during the specimen collection, transport, and processing progression it can be disrupted or altered leading to misinterpretation of the final result [52]. Incorrect interpretations of the final result, whether by subjective human nature, automated analyses, or unwanted contamination, can and will have major implications in the management of patients in which these specimens originated.

In an effort to maintain the same level of certainty in the detection of periprosthetic joint infection for revision total joint arthroplasty cases, it has been recommended that a minimum of 3 specimens for culture be taken intraoperatively [16,52]. A prospective study by Atkins et al examined 297 revision total joint arthroplasty procedures using multiple detection methods included in a mathematical algorithm to determine each diagnostic test's performance in identifying cases with infection [11]. They recommended that there should be 5-6 specimens collected from revision arthroplasty procedures to properly diagnose an underlying infection, and at the very minimum, at least 3 specimens collected should yield growth of the underlying microorganism for adequate diagnosis of infection [11]. They further recommended the laboratories should abstain from using gram staining as a clinical diagnostic tool.

Studies have shown that there is much needed research in determining how the eventual use of implant sonication, blood culture bottles, and other novel molecular techniques once brought into standard practice may further the capability of diagnosing orthopedic surgery–associated infections [8,53,54].

Question 5: Does preoperative swabbing of a sinus tract have a role in isolation of the infecting organism?

Recommendation:

Superficial cultures obtained from a sinus tract should be discouraged in the setting of an infected arthroplasty. Cultures from superficial swabbing of a sinus tract exhibit a low rate of concordance with deep cultures; thus, the value of obtaining such cultures is limited. Furthermore, these cultures can confound the decision process in management of periprosthetic joint infection (PJI).

Level of evidence: Moderate

Delegate Vote: Agree: 96%, Disagree: 3%, Abstain: 1% (Unanimous, Strongest Consensus)

Rationale:

Patients may develop a draining wound in the early postoperative period after hip and knee arthroplasty or a sinus tract in the setting of a chronic periprosthetic joint infection (PJI). Oftentimes, cultures are obtained from these superficial areas in an attempt to either diagnose a deep infection or identify the infecting microorganisms. The Musculoskeletal Infection Society (MSIS) definition for PJI and the recent validated definition of PJI

introduced in 2018 include the presence of sinus tract communicating with the prosthesis as a major diagnostic criterion for PJI [25,55]. The direct communication of the sinus tract with the epithelial surface of the skin results in contamination of the tract by organisms that may not be the infective agents in causing the underlying PJI. Although culture of the sinus tract and the draining wound is likely to be positive and isolate organism(s), the infecting organisms isolated by such method are not thought to be representative of the underlying PJI.

Historically, the swabbing of the sinus tract most likely derives from clinical practice in the diagnosis and treatment of osteomyelitis in which it was assumed to accurately identify the causative organism [56]. There is scarce literature regarding the use of superficial cultures in the diagnosis of PJI [3,57,58], and previous studies predominantly deal with sinus tract sampling in the setting of chronic osteomyelitis [59,60].

In 2013, the International Consensus Meeting (ICM) on PJI recommended against taking wound swab cultures [61]. Tetreault et al [57], in a prospective, multicenter study, evaluated the utility of culturing draining wounds or sinus tracts after a hip or knee arthroplasty. This study included 55 patients and reported that superficial cultures were concordant with deep cultures in less than half of the cohort (47.3%) and were more likely to generate polymicrobial results (27.3% versus 10.9%; $P = .023$). In 23 cases (41.8%), the superficial cultures would have led to a change in antibiotic regimen. Furthermore, in 8 of 10 patients the sinus swab yielded a positive result for an organism, which was not supported by other tests. The authors concluded that obtaining superficial cultures of the sinus tract should be discouraged in the setting of a hip or knee arthroplasty. These results were consistent with prior studies in chronic osteomyelitis [59,60], which also demonstrated low correlation between sinus tract and bone cultures.

Similarly, Aggarwal et al [3], in another prospective study, demonstrated that swab cultures are not as effective as tissue cultures used for the diagnosis of PJI; they had more false-negative and false-positive results than tissue cultures leading to an increased risk of not identifying or incorrectly identifying the infecting organisms in PJI.

Based on the available evidence, it can be surmised that sinus tract swabs do not have a role in the isolation of the infecting organism in patients with underlying PJI.

Question 6: How should synovial fluid sample be sent (via laboratory vacuum tube, syringe, blood culture tubes, etc.) for culture to increase the culture yield?

Recommendation:

The IDSA recommends that synovial fluid specimens for culture be transported at room temperature in sterile containers, and when ample amounts are available, additional procurement should be made in blood culture bottles (aerobic, and anaerobic if enough specimen volume exists to do so) alongside traditional culture methods in an effort to increase culture yield.

Level of Evidence: Moderate

Delegate vote: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

Rationale:

For centuries, the “gold standard” in the identification of disease-causing microorganisms has been microbiological culture. The culture techniques described by Koch in the 19th century has undergone little to no changes. There are numerous issues associated with culture. One of the major issues relates to maintaining the viability of organisms for proper growth and identification during the process of transport [62]. Clinical microbiological laboratories have well-defined methodologies in place to maximize culture yield in an effort to better serve and manage patients who are at risk for developing surgical site infections and periprosthetic joint infections (PJIs). There is limited evidence to show what optimal method of transport (ie, container and movement) allows for the highest culture yield possible. No studies have outlined the differences between transport via hospital personnel versus automated vacuum tube transport and its effects on culture yield.

Despite the limited evidence, the Infectious Disease Society of America (IDSA) recommends PJI synovial fluid samples be procured at room temperature in a sterile container that is to be processed and incubated within a 2-hour window for optimal culture results [52]. They also suggest that when there is abundant specimen, an additional 10 mL be transferred aseptically into an aerobic blood culture bottle and processed using blood culture study methods. Studies have shown that the blood culture broth may allow for the dilution of host immune cells including inflammatory factors and polymorphonuclear leukocytes, which may permit subsequent growth of organisms not obtained by traditional culture [20,63]. Evidence does show that using blood culture bottles for synovial fluid from patients with suspected septic arthritis enhances the yield of pathogenic bacteria, albeit at a small cost of increased isolation of contaminants [16]. A study by Peel et al. found that in using blood culture bottles for collection of periprosthetic tissue samples, they were able to drastically increase detection rates of underlying infection [16]. Other methods in the procurement process have been attempted to increase the sensitivity and detection rate in the overall culture process. A study by Sebastian et al. found that sonication of implants and fluid improved the culture's diagnostic sensitivity for PJI [64]. However, this is after transport and after procurement, which was done in standardized sterile transport containers. There is a current void in research regarding the optimal method for synovial fluid specimen transport, and further research is needed in an effort to determine methodologies capable of producing the highest culture yield.

In the absence of data, we recommend that the guidelines of the IDSA regarding culture procurement be followed. Culture samples taken during orthopedic procedures should be collected using sterile instruments, transferred directly into sterile bottles, and transported to the laboratory as soon as possible. The cultures may be transferred at room temperature. Culture yield will be increased by transporting and processing synovial fluid in one or more blood culture bottles albeit with slightly higher bacterial contamination rates. Time to culture medium inoculation and/or loading onto incubation machines should be minimized, and a separate EDTA or heparin tube for a cell count should be provided, with consideration of primary specimen preservation for onward molecular analysis if necessary.

Question 7: Should perioperative antibiotics be withheld prior to obtaining an intraoperative aspirate and/or tissue samples for culture in suspected infected revision total joint arthroplasty cases?

Recommendation:

Administration of perioperative antibiotics during revision arthroplasty should be based on the degree of suspicion for PJI and the results of preoperative culture. If suspicion for PJI is low or if the infecting organism in a PJI case has been preoperatively identified, then perioperative antibiotics should be administered. In patients with high suspicion for PJI in whom preoperative cultures are negative, perioperative antibiotics should be withheld to improve the yield of intraoperative samples taken for culture.

Level of Evidence: Moderate

Delegate Vote: Agree: 81%, Disagree: 16%, Abstain: 3% (Super Majority, Strong Consensus)

Rationale:

Chronic periprosthetic joint infection (PJI) remains one of the most difficult conditions to treat in the field of arthroplasty. Furthermore, when such infections are culture-negative, they become even more difficult to treat, as targeted antibiotic therapies are impossible. It has been previously demonstrated that antibiotic administration before establishing a causative organism increases the risk of culture-negative infection [65]. However, the need to withhold pre-incision antibiotic prophylaxis remains controversial.

A comprehensive review of the literature identified eight applicable studies that evaluated the impact of perioperative antibiotic prophylaxis on culture yield. Two were randomized clinical trials [66,67], and two more were prospective cohort studies [68,69]. One was a systematic review of the literature [70]. Three were retrospective studies [71–73] with large cohorts of patients who had both preoperative and postoperative cultures available for comparison, making all three very high-quality retrospective studies.

Overall, the literature overwhelmingly supports giving prophylactic antibiotics at the onset of the case rather than holding them for cultures to be obtained. The first study to critically examine the issue was a retrospective review of 171 patients with PJI [71], all confirmed by a positive preoperative culture. In this study, the authors observed a nearly identical false-negative culture for those patients who had received preoperative antibiotics at the onset of the case (12.5%) and for whom antibiotics were withheld before culture (8%) ($P = .34$). Furthermore, in all cases, intraoperative cultures isolated the same organism as preoperative cultures. In a follow-up prospective study [69] analyzing a separate patient population, the same group identified twenty-six infected knee replacements and compared intraoperative cultures after prophylactic antibiotic administration with preoperative aspirations. In all cases, the intraoperative cultures yielded the same organism as the preoperative aspiration.

Similarly, a randomized clinical trial of sixty-five confirmed PJI patients [67] demonstrated concordant intraoperative cultures in 82% of patients who received prophylactic antibiotics, compared to 81% in patients for whom antibiotics were withheld. In addition, a smaller randomized clinical trial [66] found identical rates of positive intraoperative culture between patients who received antibiotics before incision and those who did not.

In a prospective study utilizing an intraoperative control, Bedenčič et al [68] took cultures before and after administration of antibiotics from the same surgical site and demonstrated no statistical difference in colony forming units between the two sets of cultures. Furthermore, antibiotic concentrations from the surgical bed were above the minimum inhibitory concentration at the time of the second culture. The only false negatives observed were in cases of coagulase-negative *Staphylococcus* and *Cutibacterium acnes*.

In a recent systematic review of the literature [67,70], pooled results from seven studies demonstrated a statistically significant difference in false-negative cultures if antibiotics were withheld; however, a subgroup analysis of chronic PJI failed to reproduce this result.

Most recently, a retrospective review of 425 revision total knee arthroplasties [72] compared culture yield in 114 patients who received preoperative antibiotic prophylaxis with 284 patients in whom antibiotics were withheld preoperatively. The authors observed no significant difference in culture yields between the two groups ($P = .78$). Furthermore, when these patients were classified in accordance with the Musculoskeletal Infection Society (MSIS) diagnostic criteria for PJI, there remained no significant difference in infection rates seen between the two groups (7.1% in the preoperative prophylaxis group vs. 6.7% in the antibiotic withheld group; $P = .88$). The authors concluded withholding preoperative prophylaxis to maximize culture yield is likely not as critical as previously thought.

Another recent retrospective review of 110 patients [73] undergoing orthopedic joint procedures assessed the influence of antibiotic prophylaxis within 30 to 60 minutes before surgery with respect to positive *C. acnes* culture and joint infection [73]. The study categorized patients into two cohorts: infected cases, if two or more positive cultures, and contaminated cases, if less than two positive cultures, resulting in 64 infected patients and 46 patients with contaminated cultures. Although patients in the infected cohort received perioperative prophylaxis more often (72.8% vs 55.8%; $P < .001$), no difference was found with respect to time to positive culture regardless of administration of perioperative antibiotics (7.07 days vs 7.11 days, $P = .300$). Furthermore, no association was found between administration of perioperative antibiotics and the proportion of sample positivity (71.6% vs 65.9%; $P = .390$).

Similar to the previously mentioned studies, the authors concluded in favor of administration of preoperative antibiotic prophylaxis to protect against surgical site infection.

Overall, the literature supports not withholding pre-incision antibiotics for cases of suspected prosthetic joint infection. It should be noted that one common limitation in the aforementioned studies was the consistency with diagnostic tests (ie, variable number of intraoperative cultures and no use of sonication). However, given the fact that there is a relatively significant false-negative rate of intraoperative cultures, especially in cases of lower-virulence organisms, we recommend obtaining preoperative aspiration after an antibiotic holiday to help identify a causative organism before revision surgery.

Question 8: How should divergent results between intraoperative tissue cultures and sonication of the prosthesis be managed?

Recommendation:

Evidence on how to address contradictory results between intraoperative tissue cultures and sonication of the prosthesis is still lacking. Current research shows that sonication yields superior sensitivity and specificity over intraoperative tissue culture for the pathogen identification of prosthetic joint infection. There is statistical support for ≥5 CFU as optimal threshold defining a positive sonicate fluid culture; however, clinical outcomes and validation are lacking. We recommend that the data be evaluated in light of clinical picture presented.

Level of Evidence: Moderate

Delegate Vote: Agree: 86%, Disagree: 6%, Abstain: 8% (Super Majority, Strong Consensus)

Search Methodology

The literature search was performed utilizing the OVID-MEDLINE search database. Search terms included prosthetic joint infection sonication and total joint sonication. A total of 134 articles were returned. Abstracts were reviewed, and the articles read when necessary to determine inclusion. Exclusion criteria included non-English language and review articles, case reports, non-orthopedic and nonclinical studies, or studies that did not include tissue culture. Thirty-two articles were available for inclusion. These articles were reviewed in entirety, including their bibliography for other potential sources. Eleven of these manuscripts compared sonication fluid culture (SFC) to tissue culture (TC) and reported on discoordinate culture results [42,74–82].

Rationale:

A major challenge in the diagnosis and management of periprosthetic joint infections (PJIs) is the accurate identification of the causative organism [11]. Traditional culture methods of synovial fluid and intraoperative tissue cultures have an unacceptably low sensitivity (0.65) [11,74,77,83–85]. Most organisms found in PJI reside in a biofilm wherein they are less metabolically active and are surrounded

by a protective glycocalyx that shields them from antibiotics and the host immune system [86]. Sonication is a process by which the biofilm is dislodged from the removed prosthesis using ultrasound, permitting these bacteria to be accessible for cultures [74].

SFC has shown consistently superior sensitivity over intraoperative TC in the diagnosis of PJI [74–78,80,81]. Trampuz et al. from the Mayo Clinic published one of the earliest and most notable prospective case series utilizing sonication for the diagnosis of PJI [74]. They reported on 331 patients, both aseptic (n = 253) and septic (n = 79) failures and compared synovial fluid, tissue, and sonicate fluid culture. The sensitivity and specificity of sonicate fluid culture were 78.5% and 98.8%, respectively, and were significantly greater those that of synovial fluid (56.3% and 99.2%) and tissue (60.8% and 98.1%). Recently, Rothenberg et al published a study on 503 sonicate cultures and found a sensitivity of 97.0% and specificity of 90.0%, whereas in tissue culture was 70.0% and 97.0%, respectively [80]. Two meta-analyses have been published regarding sonication and the diagnosis of PJI [87,88]. Zhai published the first in 2013 and reported a pooled sensitivity of 80% and specificity of 95% [87]. Liu, in 2017, corroborated these results and, with additional studies included, reported a sensitivity of 79% and specificity of 95% [88]. In addition, sonicate fluid cultures increase the isolation of pathogens when antibiotic therapy is stopped within 2 weeks of surgery [74].

As with any microbiological process, sonication has the potential for contamination producing false-positive culture results [77,83,89]. Therefore, an essential designation when analyzing SFC results is defining what qualifies as a positive culture. Sonicate cultures are often quantified using colony-forming units (CFUs). Trampuz recommends ≥5 CFUs as a cutoff for positivity to optimize specificity and limit false-positive results [74]. Rothenberg et al. analyzed their results of 503 sonicated prostheses and independently determined ≥5 CFUs is the optimal threshold for diagnosing infection with a sensitivity of 0.97 and specificity of 0.90 [80]. Other published studies have reported cutoff values of 1, 3, 5, 20, and 50 CFUs but omit the statistical method by which the cutoff was determined [75,81,84,90–95]. In the meta-analysis published by Zhai, the authors reported that the optimal cutoff is ≥5 CFUs [87].

Trampuz identified 14 of 79 (18%) patients with PJIs that had positive sonicate fluid cultures but negative tissue culture [74]. Holika et al. found that the bacteria species cultured differed between SFC and TC in 6 cases [75]. Portillo reported that SFC detected significantly more pathogens than TC (62 vs. 45; $P < .001$) as well as more cases of PJI than TC (56 vs. 41; $P < .01$) [42]. Other studies have reported greater bacterial isolation in SFC than TC [76,78,79,81,82]. There was no clinical intervention or follow-up reported in any of these studies. A recent study published by Rothenberg et al. reported results of 503 revision procedures with 2-year follow-up [80]. Three hundred twenty-five of these patients were presumed aseptic at the time of surgery based on the Musculoskeletal Infection Society criteria; 53 of 325 had positive SFC and negative tissue culture postoperatively, and 24 had ≥5 CFUs/plate. Ultimately, 18 of 53 (34%) were treated with antibiotics as per the discretion of the treating surgeon and infectious disease team. At the average follow-up of 22 months, only 4 of 53 patients (7%) required surgical intervention. Only 3 of 24 patients (13%) with ≥5 CFUs required reoperation. Further study is needed to clinically validate the recommendation of ≥5 CFUs as a true infection.

Although several studies exist that support sonication as a superior method for microbiological diagnosis over tissue culture, there are several limitations. First, studies before the publication of the MSIS definition of infection used a more abbreviated system that may have misdiagnosed patients as not infected [93]. In addition, the number of tissue samples collected varied widely between studies from 2 to 9 per case [75,76,81]. Finally, in regard to sonication, studies differed in reporting CFU cutoff for positive culture results and lack of clinical correlation. These inconsistencies influence the reported sensitivity and specificity within this report and limit the strength of recommendation. Further studies with clinical outcomes and validity are warranted.

Question 9: Is there a role for routine acid-fast bacilli (AFB) and fungal testing in suspected SSI/PJI cases?

Recommendation:

No, testing for acid-fast bacilli (AFB) and fungi should not be performed routinely in suspected SSI/PJI. Testing of suspected cases of SSI/PJI should be limited to only those patients at higher risk of atypical infections which included the following:

a. Immunocompromised host.

b. Previous history of atypical infection.

c. Patient is living in an area with endemic atypical infections.

d. Culture-negative PJI.

Level of Evidence: Limited

Delegate Vote: Agree: 90%, Disagree: 6%, Abstain: 4% (Super Majority, Strong Consensus)

Rationale:

Periprosthetic joint infection (PJI) caused by mycobacteria and fungi is very rare [94,95]. In an international, multicenter study, the rate of mycobacterial and fungal PJI was reported to be 0.3% and 1.2%, respectively [96]. The practice of routine culture for AFB and fungi in suspected cases of SSI/PJI increases cost to individual patients and the health care system [97,98]. Therefore, it has been suggested that only patients with a higher than usual likelihood should be evaluated for atypical pathogens [41,99].

Patients who have PJI and whose surgery findings include gross appearance or histological findings suggestive of granulomata disease should have culture samples evaluated for atypical infections. Evaluation of culture samples for atypical pathogens may also be performed if, after seven days, the culture is negative for any pathogen in the case of a PJI. In this regard, Wadey et al described an approach to be used during surgeries wherein parts of tissue from each routine culture sample are saved but not cultured for 7 days after surgery. Then, if concerns about a possible atypical pathogen appear postoperatively or after surgical pathology is available, mycobacterial cultures and fungal cultures can be performed using the stored specimens [97]. The delay in culturing would need to be approved as microbiologically acceptable.

This rationale is subject to change as the occurrence of mycobacterial and fungal PJIs may become more prominent. Just as *Mycobacterium avium*–intracellulare musculoskeletal infection emerged as a prominent problem with onset of the AIDS epidemic, reactivation of endemic dimorphic fungal infections could become a major problem as antitumor necrosis factor therapy continues to broaden its spectrum of effectiveness.

The literature review provided no high-quality studies on routine testing of fungal and AFB in suspected SSI/PJI. On the basis of the available literature [41,94,97,100], we recommend selective AFB and fungal cultures in suspected SSI/PJI cases only in the following circumstances:

a. Immunocompromised host.
b. Previous history of atypical infection.
c. Patient is living in an area with endemic atypical infections.
d. Culture-negative PJI.

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