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QUESTION 2: What strategies can be implemented to help isolate the causative organism in patients with infection of the foot and ankle?

RECOMMENDATION: Transfer of synovial aspirate in blood culture bottles, obtaining deep biopsy of tissues and bone, obtaining multiple samples, increasing incubation period of cultures and the use of molecular techniques for culture negative cases are some of the strategies that can help improve the ability to isolate the causative organism(s) in infections of foot and ankle.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Given the risk of false positive cultures, it is important to holistically evaluate patients who are suspected to have an infection of the foot and ankle following an algorithm suggested by the Musculoskeletal Infection Society's definition of periprosthetic joint infection (PJI) [1]. It should be noted that these diagnostic criteria have not been evaluated for infections of the foot and ankle. Isolation of the causative organism in orthopaedic infections can be challenging. Culture-negative infections in hip and knee arthroplasty are not uncommon. Using the experience gained from hip and knee arthroplasty surgery and relying on the literature from the same field of orthopaedics, the following strategies may be implemented to improve the yield of culture in foot and ankle infections.

Synovial Aspirate

Synovial aspiration provides a variety of opportunities for testing, including synovial leukocyte esterase (LE) testing, synovial fluid white blood cell (WBC) count and polymorphonuclear (PMN) percentage, alpha-defensin levels, and Gram stain and cultures. In the hip and knee literature, application of synovial fluid to a simple urine test strip evaluating leukocyte esterase levels can be an accurate marker of PJI (sensitivity of 81-93%, and specificity of 87-100%) [2–4]. False positives do occur, and a positive LE strip should not be used in isolation to diagnose PJI. Although specific levels of synovial fluid WBC count and PMN percentage have been reported for diagnosis of PJI in the hip and knee, there is no literature specific to the foot and ankle [5–10]. Although alpha-defensin has been evaluated and is a promising new serologic test in the hip and knee, there is no literature to support its utility in evaluating infections of the foot and ankle [11,12]. While there is currently no literature defining criteria concerning LE, synovial fluid WBC and PMN percentage, or alpha-defensin levels for acute or chronic infection in the native or prosthetic ankle or soft tissue of the foot and ankle, we must use clinical suspicion and abnormal levels established by the adult hip and knee PJI literature until further studies evaluate abnormal levels in the foot and ankle. Several studies have demonstrated low sensitivity with Gram stain testing and poor utility for the diagnosis of PJI [13–15]. However, Gram stain and culture may provide additional information concerning likely causative organism and may help corroborate culture results with Gram stain findings in instances of potential contamination. There is no literature concerning the utility of Gram stain testing in the infected foot or hindfoot, and further studies may be necessary to better understand whether Gram stains aid in the diagnosis or treatment of suspected ankle or hindfoot native infection or PJI.

Blood Culture

Given the role of medical management in PJI with sepsis or bacteremia as well as prognosis, we recommend routine blood cultures for patients with systemic manifestations of infection. Although bacteremia is acknowledged as an etiology of PJI, the role of blood cultures in the diagnosis of PJI remains unknown. Currently, most guidelines state that blood cultures can be considered in light of systemic manifestations of infection but are not routinely obtained [16,17].

However, the care of patients diagnosed with PJI involves a multidisciplinary team, including infectious disease, internal medicine, emergency medicine and critical care physicians. Blood cultures are a staple in the work-up of many other medical conditions and may be acquired by the treating surgeon or more often a collaborating physician. Klement et al. investigated the role that blood cultures play in PJI patients and what association a positive result has on treatment outcome [18]. Blood cultures were obtained from 53.1% of patients (170/320) presenting with PJI at the time of diagnosis, with the same organism being identified 86.0% of the time in both blood and operative cultures. Furthermore, patients with positive blood cultures demonstrated a decreased treatment success rate compared with those with negative blood cultures. Therefore, the presence of positive blood cultures at the time of PJI diagnosis may not only impact the medical management of patients but also serve as a prognosticator towards the likelihood for success.

Tissue vs. Swab Culture

We strongly recommend against the routine use of swabs for surgical culture. In a study of 156 aseptic and septic hip and knee revision arthroplasties, Aggarwal et al. demonstrated that tissue cultures were positive in a higher percentage of septic cases than swab cultures: 28 of 30 (93%) versus 21 of 30 (70%). Surprisingly, tissue cultures were positive in two of 87 aseptic cases (2%), while swab cultures were positive in 10 of 87 (12%) [4]. Tissue cultures demonstrated higher sensitivity, specificity, positive predictive value, and negative predictive value for diagnosing PJI than swab cultures, while swab cultures had more false-negative and false-positive results than tissue cultures [4]. Because swab cultures pose a greater risk of failing to identify or incorrectly identifying causative organisms in PJI, we believe the use of swab cultures in obtaining intraoperative culture specimens should be discouraged.

Number of Intraoperative Samples

We recommend obtaining multiple intraoperative tissue samples for culture in suspected PJI cases or infections of the foot and ankle. Historic hip and knee protocols for periprosthetic tissue collection have been established with a target of five samples [19–21].

However, sensitivity and specificity are maximized with five to six periprosthetic samples being collected [13]. Given the relative difference in the surgical field area in hip and knee versus foot and ankle procedures, culture specificity and soft tissue preservation should not be compromised by taking more than six samples.

Holding Preoperative Antibiotics

We recommend routine holding of perioperative prophylactic antibiotics in all cases with a high suspicion for PJI in which a causative organism has not been isolated. There is mixed literature related to whether routinely holding antibiotics prior to surgery is necessary with no literature specific to foot and ankle. Recent antibiotic administration has been shown to decrease tissue culture sensitivity [22]. However, two prospective (one randomized) studies have demonstrated that prophylactic preoperative antibiotics do not impair the sensitivity of traditional intraoperative cultures [23,24]. Therefore, mandatory withholding of prophylactic antibiotics is not justified in cases where the pathogen has already been isolated preoperatively. Special consideration should be taken into account in cases in which PJI is diagnosed or suspected, but a pathogen has not been identified. In these cases, the use of prophylactic antibiotics is dependent upon clinical judgment.

Frozen Section

Intraoperative frozen section (FS) histopathology should be considered a valuable adjunct to the diagnostic work-up for patients undergoing revision arthroplasty in culture-negative PJI when the potential for infection remains following a thorough preoperative evaluation, but limitations should be noted. An intraoperative FS looking for acute inflammatory neutrophils in tissue obtained from the joint capsule or periprosthetic membrane has been used for intraoperative decision making. Although multiple studies have demonstrated that intraoperative FS of periprosthetic tissues performs well in culture-positive PJI with relatively high specificity, FSs lack the ability to isolate the organism and consistently demonstrated poor sensitivity and ability to rule out this diagnosis [25–29]. The optimum diagnostic threshold (number of PMNs per high-power field (HPF)) required to distinguish PJI from aseptic failure ranges from 5 to 23 with no clear threshold [30–32]. Although the appropriate thresholds for diagnosing PJI in histological analysis is controversial, a maximum tissue concentration between 5 to 10 PMN/HPF in each of 5 or more HPF seems to carry the best diagnostic performance. Neutrophils entrapped in superficial fibrin are not predictive of infection and submitting samples obtained by sharp dissection instead of cautery will help limit false positive diagnoses due to thermal artifacts.

Atypical Cultures – Acid Fast Bacilli (AFB) and Fungal

Mycobacterium and fungi are rare causes of PJI [33–35]. We recommend against routine AFB and fungal testing in suspected septic or aseptic failure except when warranted by patients who are at risk for such infections or when other traditional pathogens have not been identified where clinical suspicion remains elevated. Evidence has demonstrated that routine AFB and fungal testing in presumed aseptic cases does not yield clinically important results nor is it cost-effective [36]. However, when mycobacterium and fungal organisms are considered, AFB and fungal-selective media must be included, and it should be noted that prolonged culture may be required according to national laboratory standards. One should expand diagnostic testing to include tissue samples for histological examination, especially in patients with high clinical suspicions of infection. Resistance of Candida species to fluconazole has been reported in the literature, and susceptibility testing may be requested when resistance to fluconazole is suspected based on isolated species. Antifungal susceptibility testing remains less well developed and utilized than antibacterial testing.

Culture Incubation Period

We recommend that routine cultures be maintained for 5 to 14 days. If PJI by low virulence organisms is suspected, preoperative cultures failed to demonstrate bacterial growth, or if the clinical picture is consistent with culture-negative PJI, the cultures should be maintained for at least 14 days. Evidence demonstrates that extending periprosthetic cultures to two weeks significantly increases culture sensitivity while not increasing the risk of contaminants [21,37–39]. However, we recommend holding cultures for only five days in patients in whom the causative organism has been isolated preoperatively.

Routine Sonication of the Prosthesis or Implants

We are unable to recommend for or against the routine utilization of sonication of explants. The consideration of its use should be limited to cases with high suspicion for PJI or proven PJI cases in which preoperative aspiration fails to yield positive culture. Explant sonication utilizes ultrasonic energy to a fluid immersed sample to dislodge bacteria embedded in biofilm and has been shown to increase the likelihood of isolating pathogens without increasing the risk of contaminants [40–46]. Several studies have demonstrated better efficacy in dislodging bacteria from biofilm on titanium or stainless steel implants and improved sensitivity of cultured samples compared to scraping with a surgical blade [42]. In the hip and knee arthroplasty literature, Trampuz et al. demonstrated that sonication increases the rate of positive cultures and the sensitivity of sonicated fluid to identify that a causative organism was superior to that of tissue culture (78.5 vs. 60.8%) [40]. Similarly, Holinka et al. and Shen et al. found sonicate fluid to have a sensitivity greater than tissue (83.3 vs. 72.2%) as well as synovial fluid (88 vs. 64%), respectively [47,48]. When comparing sensitivities of cultures from sonicated fluid versus tissue samples, Yano et al. identified a sensitivity of 90.4 vs. 56.8%, respectively, in a large cohort of 180 fracture fixation explants [49]. In a mixed cohort of explanted joint prostheses and fracture fixation explants, Portillo et al. demonstrated improved sensitivity of cultures with 100 vs. 87 vs. 59% following inoculation of sonicated fluid in blood culture bottle compared to regular culture of sonicated fluid and tissue cultures, respectively [50]. The sonication of explants is an expensive procedure that is likely not justified in most assumed aseptic cases. In a large prospective study, the greatest benefit of explant sonication over standard tissue culture was found when antibiotics were provided within two weeks of surgery [41]. Although early literature is promising with possible greater sensitivity and improved bacteria detection with sonication, more literature is necessary to demonstrate the clinical efficacy and relevance prior to supporting broad utilization in the foot and ankle.

Fluorescence In-situ Hybridization (FISH)

We recommend against the routine use of FISH in order to evaluate for suspected infection of the foot and ankle. This process utilizes fluorescent probes to stain bacterial ribosomal ribonucleic acid, thus allowing direct visualization of the organisms in a native biofilm. Although FISH techniques have proven to be a highly reliable nonculture method to demonstrate the presence of pathogens even in the presence of biofilm, this technique is limited by its inability to provide speciation or antimicrobial susceptibility testing on the identified organisms [51,52].

Polymerase Chain Reaction (PCR)

We recommend against the routine use of nucleic acid-based testing for diagnostic testing for infection of the foot and ankle. In limited cases with high clinical suspicion of infection but negative cultures, PCR may help identify the unknown pathogens or antibiotic sensitivity. Although PCR techniques have proven to be more sensitive than traditional techniques, the number of false-positive results, as well as cost and availability of this technology, preclude routine screening. PCR should be reserved for limited cases with high clinical suspicion but negative cultures [53,54].

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QUESTION 3: What is the optimal method to perform bone biopsy (method, location, imaging use) for patients with foot and ankle infections?

RECOMMENDATION: A bone biopsy should generally be performed in a percutaneous fashion, particularly in cases where surgical debridement is not considered necessary.

If surgical debridement is considered necessary, then an open biopsy can be performed as part of the debridement.

Percutaneous biopsy should be performed under sterile conditions by an interventional radiologist or other physician trained in image-guided techniques.

The location of the biopsy will depend upon the clinical and radiographic evaluations, with a goal of maximizing the yield of the biopsy while minimizing the risk of injury to surrounding and/or overlying soft tissue structures.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection in the foot and ankle bone or soft tissues can be associated with significant morbidity and even mortality. Prompt diagnosis and treatment are paramount. Often, diagnosis can be made based on a combination of clinical examination, radiographic imaging and laboratory data. Bone biopsy is considered the gold standard for the diagnosis of osteomyelitis [1–5].

Bone biopsy can be particularly helpful when the clinical exam, radiographic imaging and laboratory data are not clearly confirmatory of an underlying infection. Additionally, a bone biopsy can allow for identification of the infecting organism(s), and therefore allow for a more tailored treatment regimen. It can also exclude rarer causes of bone disease, such as malignancy or osteonecrosis [6,7].

A percutaneous bone biopsy is generally preferable to an open biopsy, particularly in cases where surgical debridement is not considered necessary. Percutaneous techniques are less invasive, less costly and are associated with less morbidity [7–10]. A percutaneous bone biopsy should be carried out under image guidance, generally either fluoroscopy or computed tomography (CT) and should be performed by an interventional radiologist or other physician trained on image-guided techniques. Image guidance allows for specimens to be obtained from specific targeted areas. The choice of imaging technique used to guide the biopsy depends on the anatomic location, availability and practitioner preference. Fluoroscopy can be used for more superficial lesions and allows for real-time guidance. Its main limitation is its two-dimensional nature. CT guidance provides visualization of not only osseous structures but also important soft tissue structures, such as neurovascular structures, within a three-dimensional framework. Its main limitation is the increased radiation exposure in comparison to fluoroscopy. There are reports in the literature regarding magnetic resonance (MR) guided percutaneous bone biopsies, but the availability of MRI-compatible instruments and accessories limits its use [11,12].

The choice of anatomical region to perform a biopsy will depend on the state of the overlying soft tissues and the radiographic findings. The goal should be to increase the yield of the biopsy while minimizing potential risk to nearby soft tissue structures. In general, more superficial areas of concern are targeted. If multiple areas of concern exist, one will also want to prioritize the site which is likely to provide the highest diagnostic yield. The procedure should be performed under sterile conditions to reduce the risk of contamination of skin flora. If possible, multiple samples should be obtained utilizing multiple trajectories within the bone to increase the diagnostic yield of the procedure.

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