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F- 40 - ORG IDENTIFICATION STRAT

F- 40 - What strategies can be implemented to help isolate the infecting organism in patients with infection of the foot and ankle?

Response/Recommendation:

Transfer of synovial aspirate in blood culture bottles, obtaining deep biopsy of tissues and bone, obtaining multiple samples (between 3 to 5), 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 infecting organism (s) in infections of foot and ankle.

Strength of the Recommendation: Moderate

Rationale:

Given the risk of false positive cultures, it is important to holistically evaluate patients who are suspected to have infection of the foot and ankle following an algorithm suggested by the Musculoskeletal Infection Society's definition of PJI.(Parvizi, Zmistowski, *et al.*, 2011) It should be noted that this diagnostic criteria has not been evaluated for infections of foot and ankle. During this consensus algorithm for evaluation of patients with possible infection of foot and ankle will be offered. Isolation of the infecting organism in orthopedic infections, including foot and ankle infections, can be challenging. Culture negative infections in hip and knee arthroplasty are not uncommon. Using the experience gained from the hip and knee arthroplasty surgery and relying on the literature from the same field of orthopedics 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 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 81-93%, specific 87-100%).(Parvizi, Jacovides, *et al.*, 2011; Wetters *et al.*, 2012; Aggarwal, Tischler, *et al.*, 2013). False positive do occur, and a positive leukocyte esterase 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 (Mason *et al.*, 2003; Trampuz *et al.*, 2004; Bedair *et al.*, 2011; Cipriano *et al.*, 2012; Zmistowski *et al.*,

2012; Dinneen *et al.*, 2013). 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. (Deirmengian *et al.*, 2015; Wyatt *et al.*, 2016) While there is currently no literature defining criteria concerning leukocyte esterase, synovial fluid WBC and PMN percetnage, and 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 diagnosis of PJI.(Atkins *et al.*, 1998; Oethinger *et al.*, 2011; Zywiel *et al.*, 2011) However, gram stain and culture may provide additional information concerning likely infecting 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.(Parvizi e Della Valle, 2010; Parvizi *et al.*, 2013)

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. Blood cultures were obtained from 53.1% of PJI patients (170/320) at the time of diagnosis. The same organism was identified 86.0% of the time in blood culture and operative culture. Patients with positive blood cultures demonstrated a decreased treatment success (65.1%) compared with those with a negative blood cultures (85.0%). 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 likelihood for success.(Klement *et al.*, 2018)

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 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%).(Aggarwal, Higuera, *et al.*, 2013) Tissue cultures demonstrated higher sensitivity, specificity, PPV, and NPV for diagnosing PJI than swab cultures while swab cultures had more false-negative and false-positive results than tissue cultures.(Aggarwal, Higuera, *et al.*, 2013) Because swab cultures pose a greater risk of

failing to identify or incorrectly identifying infecting 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 at least 3 distinct intraoperative tissues 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 5 samples.(Kamme e Lindberg, 1981; Mikkelsen *et al.*, 2006; Schäfer *et al.*, 2008) However, sensitivity and specificity is maximized with 5 to 6 periprosthetic samples being collected.(Atkins *et al.*, 1998) Given the relative difference in 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 6 samples.

Holding Preoperative Antibiotics:

We recommend routine holding of perioperative prophylactic antibiotics in all cases with a high suspicion for PJI in which an infecting 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.(Zappe *et al.*, 2008) However, two prospective (one randomized) studies have demonstrated that prophylactic preoperative antibiotics do not impair the sensitivity of traditional intraoperative cultures.(Burnett *et al.*, 2010; Tetreault *et al.*, 2014) 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 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 frozen section 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 frozen section of periprosthetic tissues perform well in culture-positive PJI with relatively high specificity, frozen sections lack the ability to isolate the organism and consistently demonstrated poor sensitivity and ability to rule out this diagnosis.(Nuñez *et al.*, 2007; Morawietz *et al.*, 2009; Stroh *et al.*, 2012; Tsaras *et al.*, 2012; George *et al.*, 2016) The optimum diagnostic threshold (number of PMNs per high-power field) required to distinguish periprosthetic joint infection from aseptic failure ranges from 5 to 23 with no clear threshold.(Fehring e Mcalister, 1994; Lonner *et al.*, 1996; Ko *et al.*, 2005) Although the appropriate thresholds for diagnosing PJI in histologic 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 – AFB & Fungal:

Mycobacterium and fungi are rare cause of PJI.(Marculescu *et al.*, 2006; Azzam *et al.*, 2009; Hwang *et al.*, 2012) 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.(Tokarski *et al.*, 2013) 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. In specific cases one should expand diagnostic testing to include tissue samples for histological examination, especially in cases where there is a high index of clinical suspicion. 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 routine cultures be maintained for 5 to 14 days. If PJI with low virulence organisms or if preoperative cultures failed to demonstrate bacterial growth is suspected or if the clinical picture is consistent with PJI (i.e. suspected culture-negative PJI), the cultures should be maintained for at least 14 days. Evidence demonstrates that extending periprosthetic cultures to 2 weeks significantly increases culture sensitivity while not increasing the risk of contaminants.(Neut *et al.*, 2003; Schäfer *et al.*, 2008; Butler-Wu *et al.*, 2011; Larsen *et al.*, 2012) However, we recommend holding cultures for only 5 days in patients in whom the infecting 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 or proven PJI in which preoperative aspiration fails to yield positive culture and/or antibiotics have been administered within the prior 2 weeks. 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.(Trampuz *et al.*, 2006; Trampuz *et al.*, 2007; Bjerkan *et al.*, 2009; Kobayashi *et al.*, 2009; Monsen *et al.*, 2009; Piper *et al.*, 2009; Achermann *et al.*, 2010) 79-83). Several studies have demonstrated better efficacy dislodging bacteria from biofilm on titanium or stainless steel implants and improved sensitivity of cultured samples compared to scraping with a surgical blade (Bjerkan *et al.*, 2009). In the hip and knee arthroplasty literature, Trampuz demonstrated that sonication increases the rate of positive cultures and improves the sensitivity of sonicate fluid to identify a causative organism was superior to that of tissue culture (78.5 vs. 60.8%).(Trampuz *et al.*, 2006) Similarly, Holinka and Shen found sonicate fluid to have a sensitivity greater than tissue (83.3 vs 72.2%) as well as synovial fluid (88 vs. 64%), respectively.(Holinka *et al.*, 2011; Shen *et al.*, 2015) When comparing sensitivities of cultures from sonicated fluid versus tissue samples, Yano identified a sensitivity of 90.4 vs 56.8 %, respectively, in a large cohort of 180 fracture fixation explants.(Yano *et al.*, 2014) In a mixed cohort of explanted joint prosthesis and fracture fixation

explants, Portillo 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 sonicate fluid and tissue cultures, respectively.(Portillo *et al.*, 2015) Sonication of explants is a time- and resource-intensive procedure that is likely not justified in presumed aseptic cases. Further, the equipment to perform sonication is not widely available. In a large prospective analysis of 331 cases, the greatest advantage of explant sonication over standard tissue culture was appreciated when antibiotics were provided within 2 weeks of surgery. (Trampuz *et al.*, 2007) 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 foot and ankle.

Fluorescence in-situ hybridization (FISH):

We recommend against the routine use of fluorescence in-situ hybridization (FISH) for evaluating for suspected infection of the foot and ankle. This process utilizes fluorescent probes to stain bacterial rRNA 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.(Mcdowell e Patrick, 2005; Tzeng *et al.*, 2015)

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.(Panousis *et al.*, 2005; Gomez *et al.*, 2012)

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