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QUESTION 4: (A) What is the optimal follow-up plan (i.e., schedule, exam maneuvers, labs, imaging) for patients being treated for periprosthetic joint infections (PJIs)? (B) How frequently should the inflammatory biomarkers be measured after the resection arthroplasty performed as part of two-stage exchange?

RECOMMENDATION:

(A) At present, there is no consensus regarding the optimal follow-up schedule for patients being treated for PJIs and no specific research discussing this topic. In the absence of evidence, we recommend that the patients should be followed at 6 weeks postoperatively, 3 months, 6 months, 12 months, and annually thereafter, with adjustments being made based on individual circumstances. Inflammatory markers should be measured on a weekly basis after resection arthroplasty.

(B) As of now there is no study to assess the frequency with which the biomarkers need to be checked during the course of a two-stage exchange for PJIs. Most of the available studies have checked the available diagnostic battery of the tests, including serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as synovial fluid white blood cell (WBC) count, polymorphonuclear (PMN) and leucocyte esterase (LE) at least once prior to the second stage (reimplantation). However, there is no unified protocol that provides recommendations on the timing of these tests. Future studies in this field are required to guide the orthopaedic community and help form a consensus.

LEVEL OF EVIDENCE: (A) Consensus, (B) Consensus

DELEGATE VOTE: Agree: 85%, Disagree: 7%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

The treatment of PJIs includes debridement, antibiotic and implant retention (DAIR) with or without exchange of mobile parts, single-stage exchange, two-stage exchange, long-term antibiotic suppression and salvage procedures (i.e., excision arthroplasty/arthrodesis/amputation) [1]. Due to the unavailability of specific study on this topic, all the papers on PJIs which had contents concerning the follow-up schedule were divided into groups based on specific treatments and reviewed respectively to summarize a relatively ideal follow-up timeline. The overall recommendation for follow-up visits are at 6 weeks, 3 months, 6 months, 12 months postoperatively, and yearly thereafter [2,3]. Zeller et al. [4], in their prospective cohort study on one-stage exchange arthroplasty, and Frank et al., in their multicenter randomized controlled trial that studied the effects of oral antibiotics on the reinfection rates after two-stage exchange, both have implemented the aforementioned follow-up protocol [5].

The follow-up of patients being treated for PJIs needs to be individualized based on their needs and the clinical progress. However, patients with PJIs who have undergone surgical procedures may be at higher risks of complications and issues and hence need to be followed-up more regularly. In addition, part of the clinical progress of these patients is measured using serological inflammatory markers. Thus, more regular follow-up allows the treating orthopaedic team to determine the best course of action. The latter is particularly true for patients who have undergone resection arthroplasty. These patients need to be monitored closely to determine the optimal timing of reimplantation. In addition, these patients need to be seen by the infectious disease specialists to monitor treatment response, and possibly adverse reactions, to the administered antibiotics. Although the inflammatory markers do not exactly determine the timing of reimplantation, it is important that the level of these inflammatory markers declines in the interim stage between resection and reimplantation. Additionally, determining when infection is eradicated and when reimplantation should occur remains relatively unknown which makes recommendations for follow-up also difficult.

Despite the wide array of diagnostic tests that can be used to work up a patient for PJIs, a clinical suspicion is mainly based on the initial history and physical examination [6]. They can not only help to diagnose PJI but also to identify the type of PJI encountered and assess the patient's risk factors as well as the treatment protocols.

The most common physical examinations include evaluation of the appearance of the joint, temperature of the joint skin, swelling, erythema, wound healing issues and pain with range of motion according to a systematic review of the literatures and documents regarding PJIs [6–11]. Acute infections are easier to diagnose due to the typical signs of inflammation including pain, swelling, erythema and warmth of the affected joint, accompanied by impaired wound healing postoperatively. Systemic symptoms such as fever and chills may also occur [11]. However, these typical clinical signs and symptoms may be unreliable or even entirely absent in delayed or chronic infections, especially in slow-growing organisms. The presence of a sinus tract is one of the main diagnostic criteria for PJIs [12]. Persistent pain in the artificial joint with occasional implant loosening or secondary implant failure should be considered as suspicious infections until proven otherwise [13,14].

As of now, there is no study that has specifically investigated the optimal exam maneuvers for patients being assessed for PJIs. However, a prospective study from China was performed to monitor changes in the overlying skin of knees for 12 months following unilateral total knee arthroplasties (TKAs) due to primary osteoarthritis. The authors concluded that different skin temperatures up to 12 months postoperatively may be a normal surgical response and further investigations are required to confirm if increased local skin temperatures are indeed associated with PJI [15].

The majority of studies used a follow-up plan that examines the levels of inflammatory biomarkers, but the frequency of laboratory testing is reported in very few cases. Different schedules consider ESR and CRP monitoring values every week, every two weeks, or every four weeks. However, most of the studies have monitored these biomarkers at least once after antibiotic therapy completion, prior to definitive reimplantation.

According to a study by Ghanem et al. [16], monitoring ESR and CRP before reimplantation can only poorly predict reinfections. This is true when either the absolute value at explantation or the differences between base-line values and those reported at the time of reimplantation are considered. In a study by Hoell et al. [17] they used Interleukin-6 (IL-6) as a biomarker in the follow-up plan. Their study showed that IL-6 levels prior to reimplantation are significantly higher in patients with persistent infection. However, their study was limited by sample size. Serum D-dimer has shown promising results in diagnosing PJIs. Therefore, it was suggested that this test can be used in early diagnosis of acute PJIs and determining the reimplantation timing and infection eradication [18]. However, as mentioned earlier there is no gold standard for diagnosing PJIs, and to confirm or refute the presense of infection, it is highly recommended to use a combination of tests to gather as much information as possible on the systemic response and combine it with physical exam.

Plain X-rays are the primary radiographic tool for assessing prosthetic joints. They are used to detect possible complications, including mechanical loosening, particle disease, component wear, dislocation, fracture, heterotopic ossification and infection. However, X-rays are neither sensitive (only 70%) nor specific (only 50%) [19,20]. It is usually required to compare serial images over a long period of time to be able to properly identify the changes of imaging signs such as radiolucency, osteolysis and migration of implants or spacers. Despite their low sensitivity and specificity in diagnosing PJIs, plain radiographs should be routinely performed to assess patients being treated [10,21,22].

Ultrasound has limited utility for assessing joints and is mostly used to identify the presence of significant local joint effusion [23] and to assist in the joint aspirations. CT scans and MRIs are not the optimal diagnostic tool for patients with prosthetic implants. The presence of metallic implants causes beam hardening and dephasing artifacts. However, both techniques are useful in detecting soft tissue abnormalities, such as joint effusion, sinus tracts, soft tissue abscesses, bone erosions and periprosthetic lucencies.

In terms of positron-emission tomography (PET) scans and other forms of nuclear imaging, further studies are needed because the present data regarding their accuracy is conflicting [24–26].

Bone scans have become less popular, as they have low sensitivity and specificity. The rates can be improved when a dual tracer technique, such as an indium-111-labeled leukocyte scan, is performed simultaneously with a technetium-c99m diphosphonate scan. A systematic review and meta-analysis published in 2016 has investigated the accuracy of imaging techniques in the assessment

of periprosthetic hip infections. The results showed that combined leukocyte and bone marrow scintigraphy was the most specific imaging technique for diagnosing periprosthetic hip infections. Fluorodeoxyglucose PET has an appropriate accuracy in confirming or excluding periprosthetic hip infection, but may not yet be the preferred imaging modality because of its limited availability and relatively higher cost [27].

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QUESTION 5: Is there a benefit for the engagement of a multidisciplinary team for the management of patients with periprosthetic joint infections (PJIs)?

RECOMMENDATION: The treatment of PJIs takes a multidisciplinary approach, with interactions between the orthopaedic surgeon, anesthesiologist, infectious disease specialist, medical microbiologist, plastic surgeon and ancillary service teams. It is demonstrated that centers with experience in the treatment of PJIs, or those adopting standardized protocols, have improved outcomes with lower complications. Until further research demonstrates otherwise, patients with PJIs should be cared for in centers that use a multidisciplinary approach and have experience in the management of PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Although there are a number of reports on the advantages of multidisciplinary or interdisciplinary teams (MDT/IDT) in prevention of PJIs, there is limited data on its impacts on the outcomes of PJIs. To date, no study has evaluated MDT/IDT interventions in a randomized manner and no meaningful systematic collection of data can be found.

Nevertheless, when PJIs occur, at least in specialist centers in developed countries, a number of medical, surgical and allied health