DIAGNOSIS

2.1. DIAGNOSIS: DEFINITIONS

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QUESTION 1: What is the recommended time interval that would divide acute and chronic periprosthetic joint infection (PJI) (4 weeks, 90 days, etc.)?

RECOMMENDATION #1: There is no evidence-based time interval that divides acute from chronic PJI. The natural history of infection is a continuum from initiation to chronicity. Surgical treatment for patients with infection should not solely be based on the duration of symptoms or the time from implantation of the prosthesis. Other factors should also be considered such as implant stability, presence of sinus tract, virulence of the infective organism and the general health of the patient. It is important to note that the efficacy of surgical intervention, involving retention of the prosthesis, is more likely to fail as one moves past four weeks from the index arthroplasty and/or duration of symptoms of infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 84%, Disagree: 15%, Abstain: 1% (Super Majority, Strong Consensus)

RECOMMENDATION #2: We recommend moving away from the traditional division between acute and chronic infection based solely on time from index arthroplasty or duration of symptoms. Periprosthetic infection is a continuum that leads to establishment of biofilm.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 60%, Disagree: 34%, Abstain: 6% (Super Majority, Weak Consensus)

RECOMMENDATION #3: Should we have a specific time limit cutoff between chronic and acute infection?

DELEGATE VOTE: Agree: 60%, Disagree: 37%, Abstain: 3% (Super Majority, Weak Consensus)

RATIONALE

According to the *Oxford Advanced Learner's Dictionary*, the term "acute" in the case of illness is defined as "coming quickly to the most severe or critical stage" and the term "chronic" as "lasting for a long time, happening continually." In the case of an acute PJI, this would be translated as a sudden onset of severe joint pain and/or swelling in a priorly symptom-free prosthetic joint, and in case of chronicity, as the presence of mild or moderate pain in which its exact onset is hard to establish. In our opinion, this is the most accurate definition to differentiate acute from chronic PJIs, and reflects the virulence of the microorganism(s) causing the infection. The reason that a certain time frame was subsequently introduced in the world of PJI to divide acute from chronic infections was primarily based on clinical grounds to identify those patients with a high and low success rate when treated with debridement, antibiotics and retention of the implant (DAIR) [1–15].

One of the factors associated with DAIR failure is the presence of a mature biofilm in which embedded bacteria are unresponsive to antibiotic treatment due to multiple phenotypic and genotypic changes [16,17]. In such a condition, a PJI cannot be cured with antibiotics alone without removal of the implant. In which time frame a biofilm reaches maturity is not clear. In vitro studies indicate that biofilm start to form within just hours after inoculation of bacteria [18], but these experiments are performed under "optimal" circumstances for bacterial growth and do not include the complexity of the host's environment and the protective effect of its immune system [19]. Carli et al. observed in a mouse model with a proximal tibial implant infection, using a high initial bacterial inoculum ($3x10^5$ CFU) that a biofilm is evident after two weeks of injection, but extends and is covered by fibrinous tissue and multiple host cells after six weeks [20]. A recent mouse model of knee PJI using a low infecting inoculum of *S. aureus* (10^3 CFU) (which is similar to the expected inoculum during surgery [21]) demonstrated that after a two-weeks incubation period, antibiotic combinations including rifampin were able to eradicate the infection [22]. These studies suggest that a mature biofilm develops within two to six weeks. However, the process of biofilm formation varies greatly among bacterial species, its inoculum and the host [23,24]. Accordingly, it has been demonstrated that the efficacy of DAIR in acute infections is highest when the DAIR is performed as soon as possible after the onset of symptoms [25–36]. Moreover, it is important to note that, since the success of DAIR is determined by many factors, the decision to perform a DAIR procedure should not solely be based on symptom duration and/or time from index surgery in acute PJIs, but should include host related factors, causative microorganism and the stability of the implant. For this reason, we propose not to include a time interval in the definition of acute and chronic PJI since the natural history of an infection is a continuum from initiation to chronicity.

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QUESTION 2: What is the definition of implant “colonization” vs. implant-related infection?

RECOMMENDATION: Colonization is the presence of microbiota in a joint with growth and multiplication of the organism, but without interaction between the organism and the host’s immune response thus avoiding any clinical expression. Infection is the invasion of a joint by disease-causing organisms that results in an interplay with the host’s immune response, causing a clinical expression and disease state.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 8%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Over the last few years, extensive research efforts have been invested in the diagnosis of implant-related infection or periprosthetic joint infection (PJI) and numerous definitions have been proposed [1–3]. Infections result in an immune response, thus all definitions rely on a combination of clinical findings, laboratory results from peripheral blood and synovial fluid, microbiological data, histological evaluation of periprosthetic tissue and intraoperative findings. The advancements in the field of diagnostics and statistics have allowed us to establish a validated, evidence-based definition for PJI as presented in another section.

On the other hand, research into colonization of a prosthetic joint implant is scarce and currently there is no universally-accepted definition for implant colonization. Colonization and infection are two different processes. There are approximately 10 times as many bacterial cells in the human flora as there are human cells in the body, thus all multicellular organisms are colonized to some degree by extrinsic organisms. The human microbiome is the collection of all the microorganisms living in association with the human body. Microbiome and host form a complex relationship, where microorganisms can confer symbiotic benefits to the host in many key aspects of life [4]. However, defects in the regulatory circuits of the host-microbiome interaction may disturb this symbiotic relationship and promote disease [5]. The difference between an infection and colonization is often only a matter of circumstance. Non-pathogenic organisms can become pathogenic given specific conditions, and even the most virulent organism requires certain circumstances to cause a compromising infection.

Analysis using next-generation sequencing (NGS) has improved understanding of the microbiome [6,7]. Recent studies suggest the presence of microbiome in aseptic deep tissue [7–9]. This is a fascinating discovery, as it suggests that microorganisms may inhabit organs previously thought to be sterile, given that they do not communicate with the outside world. In a recent study using NGS, an organism was identified in 6 of 17 patients undergoing primary arthroplasty, with no clinical or laboratory evidence of infection [10]. In another recent study NGS frequently identified multiple organisms in an infected sample and the question remains whether these infections are the result of a single dominant organism or multiple pathogenic organisms [11]. This becomes of particular concern when considering that the majority of patients who fail treatment for infection are infected with a different organism [12,13].

As we forge new alliances in our quest to eliminate prosthetic joint infections, we should also consider a call to new and mutually-beneficial ways of coexisting with the microbial flora of the world. Novel molecular techniques for organism detection provide comprehensive information on the organisms occupying the joint and thus hold the promise for a better understanding of joint colonization.

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QUESTION 3: What is the definition of a sinus tract?

RECOMMENDATION: A sinus tract has the following characteristics: (1) it is an abnormal channel through the soft tissues that allows communication between a joint prosthesis and the outside environment, known or presumed to be colonized by bacteria and (2) its presence may be confirmed with direct visualization of an underlying prosthesis, evidence of communication with fistulogram, ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI).

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 97%, Disagree: 2%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

The presence of a sinus tract communicating with a total joint arthroplasty (TJA) is one of the two major criteria for the diagnosis of periprosthetic joint infection (PJI) proposed by the Musculoskeletal Infection Society (MSIS) and the International Consensus Meeting [1]. Therefore, consistently defining what constitutes a sinus tract in this context has significant implications for the appropriate diagnosis and treatment of PJI. Interestingly, there is a paucity of information in the arthroplasty literature that defines the characteristics of a periprosthetic sinus tract. Many investigations discuss the presence and subsequent surgical management of sinus tracts in the setting of knee and hip arthroplasty but do not provide consistent or detailed descriptions of the cutaneous pathology. Given the lack of information and evidence, it is important to develop a comprehensive and standardized method for characterizing a soft tissue sinus tract surrounding a total joint prosthesis.

A sinus tract (latin: hollow, cavity) is an abnormal channel connecting a cavity lined with granulation tissue to an epithelial surface [2]. Although a fistula and a sinus tract are technically separate entities, with the former representing an abnormal connecting channel between two epithelialized cavities specifically, [2] they are frequently grouped together.

Given the relationship between infection and the development of sinus tracts and vice versa, it is not surprising that there exists a rich accounting of draining wounds and sinus tracts throughout medical history. In fact, a likely description of a draining sinus tract, secondary to chronic shoulder infection and osteomyelitis, is included in the Edwin-Smith Papyrus [3], the oldest surgical treatise in existence. Centuries later, Hippocrates [4] would provide various descriptions of sinus tracts and fistulae and extensive options for remedies, including topical, oral and surgical.

However, perhaps the most important of the historical treatments of sinus tracts comes from the 1686 *Chirurgical Treatises* of Richard Wiseman [5]. In his chapter titled "On Fistulae," which appears in the appendix to his treatise on gunshot wounds, Wiseman describes a fistula as a sinuous ulcer, which has actively been draining for at least two to three months. He associates the draining sinus fistula with a "long pipe of skin" and the presence of "callus" which has been "hastened by the transpiration and resolution of the thin and subtill humours." Like Hippocrates, Wiseman advocated for treatment with either medications or surgical debridement. Of note, Wiseman specifically commented upon the particular difficulty of curing sinus tracts associated with joints.

Since Wiseman, there have been numerous additional descriptions of sinus tracts associated with bones and joints. However, one of particular interest to the field of arthroplasty dates from the early 1700s [6]. Johanne Daniele Schlichting describes a case report from 1730 of a 14-year-old girl suffering from disability due to a hip infection associated with a large draining sinus tract. Schlichting also describes his method of treatment including removal of the femoral head and in doing so provided the first report of a proximal femoral resection in the medical literature. Throughout surgical history, a sinus tract has been pathognomonic for deep infection. The same is true in TJA, but the terms of the definition have not been established.

Sinus tracts are currently synonymous with PJI [7]. Fistulas in TJA have been noted to form connections between the prosthesis and vascular channels [8], the ureter [9], bladder [10,11], colon [12], rectum [13] and vagina [7], and are clearly a risk for the development of PJI when associated with bacterially-colonized cavities. Additionally, there is little information differentiating a communication that originates from inside the joint versus outside the joint.

There has been a significant amount of effort spent on determining the yield of culture samples from sinus tracts and fistulas originating from or terminating at joint arthroplasties [8,13–20]. Although this has provided insight as to the utility of sinus content cultures in the diagnosis of the responsible pathogens, it has not further assisted in defining the pathology. For the purposes of PJI diagnosis, we suggest that sinus tracts and fistulas communicating with bacterially-colonized areas should be grouped together, regardless of origin from within the joint or without, in order to fulfill the major criterion for the diagnosis of PJI.

The majority of information regarding the definition of a sinus tract in the presence of musculoskeletal infection has been studied in the context of osteomyelitis. There are multiple classification systems for sinus tracts, with varying degrees of focus on associated soft tissue compromise. The Cierny-Mader classification is perhaps the most commonly-referenced system, and involves categorical divisions staged by combining anatomic class (I: medullary, II: superficial, III: localized and IV: diffuse) and host physiologic class (A: normal immune function, B: local or systemic immune compromise and C: treatment worse than disease) [21]. A sinus tract leading to exposed bone is the hallmark of Stage II (superficial) osteomyelitis and occurs on a continuum with Stage III and IV disease. Although further details of sinus tract characteristics aside from direct contact with osseous structures are not included, treatment with thorough debridement is consistently advocated [21,22]. Conceptually similar to the anatomic class used by Cierny and Mader, Ger proposed a classification system in 1984 that focused on the wound, separating simple sinus, chronic superficial ulcer, multiple sinuses and multiple skin-lined sinuses [16]. Similarly, these pathologic conduits tunneled directly to bone. Currently, no analogous method is used to characterize sinus tracts associated with PJI. However, a patent channel through soft tissue connecting the outside environment directly to a total joint prosthesis should be considered a sinus tract.

Chronicity of drainage and of associated symptoms is an important consideration. Although it has been noted that postoperative wound drainage lasting longer than five to seven days is unlikely to remit without intervention [14], differentiating between simple prolonged postoperative drainage and early sinus tract formation is difficult. Galat et al. [15], reviewed the records of over 17,000 primary total knee arthroplasties and identified a 5.3% to 6.0% risk of deep infection in knees with persistent wound drainage within a 30-day postoperative time frame. However, "surgeon judgment" rather than objective testing played a significant role in the diagnosis of deep infection in many cases and may have skewed results. Another series of over 11,000 arthroplasty procedures identified 300 patients who developed wound drainage lasting > 48 hours following surgery [17]. Although persistent wound drainage was noted to cease in the majority of patients between postoperative days 2 to 4, 28% continued to drain and underwent further surgery. Surgical debridement was adequate to resolve the wound issues in the majority of cases but 20% required additional intervention in the form of two-stage exchange, resection arthroplasty or antibiotic suppression. In this series, the mean interval between the onset of drainage and surgical treatment was 10 days in patients who required further intervention.

Other studies have suggested that drainage of greater than 5 days imparts a 12.5-times risk of developing infection [23] and each day of continued drainage increases the risk of wound infection by 42% in hips and 29% in knees [24]. However, these studies do not subdivide the portion of superficial wound infections that progress to true PJI. In addition, surgery on a draining wound performed following 12 days of continuous drainage was noted to yield positive cultures in only 25% of cases [25]. While the distinction between persistent wound drainage and a developed sinus tract is not defined in the acute setting following surgery, there is likely a time after which persistent drainage should be deemed a sinus tract. Currently, there is no evidence to guide us, to our knowledge, in understanding this distinction. Regardless of the definition, persistent drainage in any form is clearly concerning for PJI.

There is a strong association between chronically-draining wound sinus tracts and deep infection of prosthetic hip and knee joints [26]. However, it is important to draw a distinction between the presence of a sinus tract *de facto* as a diagnostic criterion for PJI and the utility of sinus tract cultures in guiding infection treatment. Wound sinus cultures for osteomyelitis have notoriously low sensitivity and specificity [20,27,28]. The same has proven true for deep prosthetic joint infection. Two studies have been conducted to determine the correlation between superficial cultures from wounds or draining sinus tracts and a deep pathogen in the setting of prosthetic joint infection. Cune et al. evaluated the usefulness of wound culture results in the treatment of acute postoperative prosthetic joint infection. They found 80.3% agreement between superficial and deep surgical cultures in this setting with high sensitivity and specificity for *Staphylococcus aureus* and gram-negative bacilli [29]. Tetreault et al. performed a similar analysis comparing superficial and deep cultures in patients with deep prosthetic joint infection. Their results showed a 47.3% concordance between superficial and deep cultures, and in 41.8% of cases, the superficial organism wound has guided therapy with a different antibiotic than deep cultures [30]. There is likely a gradient of organisms within a sinus tract community, but the biology of the sinus tract microenvironment has not yet been studied. Therefore, although the presence of a sinus tract should be considered equivalent to a deep prosthetic joint infection, cultures of the fluid cannot be relied upon to guide treatment.

In general, for the diagnosis of PJI, a sinus tract should demonstrate clear communication between the prosthesis and a non-sterile environment. The most obvious method is to directly visualize the underlying prosthesis through the lumen of the sinus or directly access the prosthesis with a sterile probe. However, to corroborate physical exam findings or evaluate a suspicious channel, various imaging methodologies may be utilized to confirm the presence of a true sinus tract that communicates with a TJA. Conventional radiography may be helpful in identifying areas concerning for infection with a sinus tract in combination with subcutaneous or intraarticular gas. However, plain X-rays may be negative in more than 50% of cases and may be of minimal diagnostic utility in acute infection [31]. Instead, conventional X-ray with the addition of arthrography or fistulography may drastically increase the diagnostic yield by illuminating infectious channels and accumulations [32,33]. Traditionally, more advanced imaging modalities such as CT and MRI were believed to be of limited use in evaluating the soft tissues immediately around a total joint prosthesis due to large amounts of metal artifact and image distortion. Recent developments, including metal artifact reduction sequence (MARS) MRI and three-dimensional reconstruction, allow for a much more detailed evaluation of periarticular structures and the presence of sinus tracts. However, given the dynamic nature of soft tissues and underlying infection, imaging studies may not provide sufficient evidence to verify the existence of a sinus tract as these may fluctuate in their patency and extent. Therefore, imaging modalities should not solely be relied upon for the identification of a sinus communicating with a joint prosthesis.

In summary, an established sinus tract or fistulous connection between a deep prosthetic joint and another space known to be colonized with pathogenic microorganisms should be considered tantamount to deep prosthetic infection. Although the literature does not provide clear guidelines regarding the time at which a draining wound becomes a sinus tract, it is clear that prolonged drainage from an arthroplasty wound increases the likelihood that deep infection will occur. While literature does not support the use of superficial sinus cultures to guide treatment of deep PJI, clinicians should rely on the presence of a sinus to justify surgical treatment. Therefore, any suspected connection between a deep prosthetic joint and an area colonized by pathogenic microorganisms should be considered seriously and evaluated thoroughly.

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