Authors: Geert Meermans, Brian Hamlin, Ed McPherson

QUESTION 8: Can periprosthetic joint infection (PJI) be assigned a high- or low-grade infection? If so, what is the definition of each grade?

RECOMMENDATION: Yes, PJI can be scored and assigned an "infection grade." At this juncture, we recommend using the McPherson schema as a starting point for grading PJIs, as this system demonstrates outcomes correlating with worsening host and limb scores. We suggest this schema (or a modified version) as a starting point until an international workgroup establishes a codified staging system.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 74%, Disagree: 12%, Abstain: 14% (Super Majority, Strong Consensus)

RATIONALE

Infection severity in PJI depends upon multiple factors. These include: infection duration (i.e., acute, acute hematogenous or chronic), the ability for the patient (i.e., host) to combat the infection, the quality of the tissues around the infected joint, the ability for the limb to heal and the "aggressiveness" of the organism.

The duration of infection relates more to the presence of biofilm. Acute infections are essentially non-biofilm-related infections. They characteristically present with abrupt onset and manifest with rapidly increasing pain, displaying overt signs of infection and, not infrequently, developing systemic effects and sometimes even septic shock. Acute PJIs can be successfully treated with early radical debridement surgery. The success of implant retention long-term depends on many factors including early versus late intervention, host comorbidities and local wound health.

In contrast, a chronic PJI involves biofilm formation. This is important because the clinical manifestation of a PJI developed from a biofilm is markedly different from an acute (non-biofilm) infection. In a biofilm-related infection, bacteria and/or fungi adhere to the implant, colonize and expand in size. Once the colony reaches a genetically predetermined size, the colony undergoes a metamorphosis into a biofilm colony (via phenotypic expression). The microbial biofilm then encapsulates the implant system, erodes into the surrounding bone and eventually enters the medullary canals. Furthermore, biofilm colonies are highly resistant to antibiotics, whereby they become 1,500 to 10,000 times more resistant to typical minimum inhibitory concentration (MIC) of antibiotics.

The clinical presentation of a biofilm infection mirrors the progression of the advancing biofilm. This includes gradually increasing pain and periarticular swelling and warmth on examination. Functional limitations result when implant stability is compromised by marginal erosive osteomyelitis. Biofilm bacteria erode into the periarticular soft tissues, creating multiple loculated abscesses destroying vital joint ligaments, tendons and muscle. Not infrequently, a burrowing abscess will erode to the skin surface creating a chronic sinus tract. The time sequence for developing a mature biofilm is variable, but can develop as soon as a few days after the onset of infection in a patient with a joint arthroplasty in place. The rate of biofilm development depends on host immunity and limb health (i.e., local wound health). Characteristically, biofilm infections are considered "indolent" infections, as patients are not systemically ill. This is because endotoxic or exotoxic responses are not manifested with biofilm infections. A biofilm PJI must be treated with implant removal combined with a radical "tumoresque" removal of adjacent soft tissues and bone. This can be accomplished either with a single or two-stage exchange. The choice of single- versus two-stage exchange again hinges upon host and limb health, which can be scored and rated. In the overall totality of PJIs, biofilm PJIs cause vastly more internal damage to the musculoskeletal system than acute infections. Thus, many physicians and surgeons consider a long-standing chronic biofilm infection to be the more severe infection.

The human immune system plays the most critical role as it relates to infection containment and eradication, for both acute and chronic infections. As a general rule, the weaker the human host, the weaker the immune system and, thus, the greater the severity of infection/conditions. There are numerous medical conditions, medications and treatments that can suppress immune system function and alter the course of a PJI [1]. These conditions that have been shown to increase infection risk are well enumerated in the literature over the last four decades.

Grading Schemes

Several schemata for classifying the human host and PJI have been introduced, beginning in the late 1990's. Several authors, including Tsukayama, McPherson, Hanssen and Wimmer, have proposed staging systems for PJIs [2–7]. These have been based on retrospective studies that rate human host quality (i.e., host grade), correlating host grade with worsening outcomes. McPherson et al. has correlated worse outcomes with declining host grade and limb score in both total hip arthroplasties (THAs) and total knee arthroplasties (TKAs) [4,5]. This has been confirmed by Kaplan Meier survival analysis in a recent retrospective review by Bryan et al. [8]. Recently, another study of second-stage THA for chronic infection correlated infection recurrence directly to a compromised host grade [9]. Generally speaking, many infection-specific societies, such as the European Bone and Joint Infection Society (EBJIS), are adopting the staging of host immunity along with limb scores as a means to compare clinical outcomes. In this manner, future treatments for PJIs can be tailored, similar to cancer therapy, based upon an agreed staging system.

Limb tissue health also plays an important factor in infection treatment. Poor tissue health correlates with poor healing and infection persistence. Many factors have been described that limit healing, including arterial and venous insufficiency, sensory and motor neuropathies, soft tissue loss and tissue quality (e.g., irradiation, burns and/or multiple incisions). A poor "limb score" should correlate with reduced outcomes scores, however measured. There are quantifiable parameters with retrospective data supporting this concept. McPherson's schema is thus far the only system that rates limb health and has shown a correlation of impaired limb scores with worsening functional outcomes [4,5,9].

Aggressiveness of an organism is hard to quantify and qualify. The organisms more likely to form a biofilm and persist have multiple techniques to adhere to an implant surface and form a

biofilm. In contrast, organisms that present with acute infections frequently produce toxins that result in a systemic toxicity and eventually shock. Vasso defined a low-grade infection as one that is not causing systemic illness [10]. Symptoms are sometimes ill-defined. Lab serologies may be slightly elevated and cultures can be difficult to grow. When an organism is isolated it is often a low-virulent organism, such as *Staphylococcus epidermidis* or *Cutibacterium acnes* (formerly *Propionibacterium acnes*). In contrast, a high-grade infection has not been as well-established in the literature [11]. One can deduce that it would be caused by an organism causing systemic illness/sepsis or acting aggressively at the site (i.e., severe pain, swelling, drainage, etc.). Currently, there is no method of qualifying these parameters. Medical advancements, such as 3rd and 4th generation deoxyribonucleic acid (DNA) sequencing, will help make it a possibility to identify genetic sequences that correlate with "organism aggressiveness" and poor outcomes. Only then will we be able to truly "rate" the severity of an invading organism.

Conclusions

In summary, there is substantive data that supports the concept of grading or rating a PJI. The data that supports grading PJI severity is retrospective in nature. There is not yet an international codified system that multiple investigators have agreed upon. Our recommendation is to gather an international workgroup to establish a PJI grading system, utilizing current tools and data available. The system of grading should be reviewed and upgraded every five years, as newer diagnostic tools and outcome data become available. For now, the McPherson schema has taken hold and is used in presentations worldwide over the past three to five years. We suggest using this system (or a modified version) as a starting point until an international workgroup establishes a codified staging system upon which the majority agrees.

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2.2. DIAGNOSIS: ALGORITHM

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QUESTION 1: Do you agree with the American Academy of Orthopaedic Surgeons (AAOS) algorithm for the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. However, since the introduction of the AAOS algorithm for diagnosis of PJIs, numerous new tests and diagnostic modalities have become available. The proposed evidence-based and validated algorithm includes the guidelines from AAOS and the 2013 International Consensus Meeting (ICM) on PJIs. A stepwise algorithm first using serological markers followed by more specific and invasive tests continues to be recommended.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 73%, Disagree: 23%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The guidelines for the diagnosis of PJIs introduced by the AAOS provided useful parameters for clinicians and a framework for diagnosing PJIs [1,2]. These guidelines have been widely adopted and were endorsed at the last ICM on PJIs in 2013 with slight modification [3]. While the existing algorithms are widely accepted, they are not completely evidence-based and have not been validated. Furthermore, several new synovial [4], serum and molecular biomarkers [5–10] have been introduced in recent years, which have increased confusion as many surgeons are unsure how to incorporate these tests into their practice and into the previously established guidelines.

With the introduction of new diagnostic tests and the need for validation of the guidelines, we have been prompted to expand on the prior guidelines and to develop an evidence-based, validated diagnostic algorithm. A multi-institutional study was performed by members of this workgroup, to generate a stepwise approach using random forest and multivariate regression analyses to generate relative weights and to determine which variables should be included