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QUESTION 7: Do patients with adverse local tissue reactions (ALTRs) have a higher incidence of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. Patients with ALTRs appear to have a higher incidence of PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 2%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

The diagnosis of PJI can be extremely challenging in patients with a metal-on-metal (MoM) bearings or modular junction-induced ALTRs. The clinical presentation of ALTR may mimic that of PJI and both serum and serologic markers may be elevated in both conditions. Intraoperative findings may include extensive soft tissue necrosis, macrophage foreign body response, perivascular lymphoid infiltrate and even grossly appearing purulent fluid [1–3]. Preliminary research suggests that MoM wear and corrosion particles may alter the periprosthetic environment, therefore increasing the risk of infection by: 1) impeding the immune system; 2) preventing or accelerating bacterial growth; 3) altering antibiotic resistance and metal resistance mechanisms and 4) providing an ideal milieu for pathogens to proliferate in the necrotic tissues around the joint.

While distinguishing aseptic failure from PJI in a patient with an ALTR can represent a diagnostic challenge, diagnostic cutoffs have been suggested with higher synovial fluid white blood cell cutoffs than chronic PJIs without an ALTR; further, metallic debris can lead to errors in reading the synovial fluid cell count and differential and thus it is recommended to perform a manual cell count in cases of ALTR or metallosis [4]. Despite the vast body of literature investigating both ALTR and PJI following total joint arthroplasty independently, there is a lack of clinical data evaluating the concomitance of these phenomena.

A number of in vitro studies have assessed the effects of metal ion wear production on local soft tissue environment and immune response. Daou et al. noted that increased cobalt concentration in periprosthetic tissue resulted in an inhibitory effect on lymphocyte superoxide production, an impaired leukocyte recovery from acid stress and an improved intra-cellular survival of *Staphylococcus epidermidis* [5]. Akbar et al., likewise noted that high concentrations of cobalt and chromium ions produced an adverse effect on T-lymphocyte function, proliferation and survival [6]. In contrast, Hosman et al. found that high concentrations of cobalt and chromium have bacteriostatic effects as a result of inhibition of biofilm formation and bacterial proliferation [7].

Numerous case reports and small case series have highlighted the issue of concomitant ALTR and PJI [1,8–14]. In one dramatic example, Judd et. al. identified an infection rate of 33% in a series of nine patients revised for ALTR [8]. Two case reports describe concomitant ALTR and infection leading to massive necrosis of bone and soft tissue in a total of four patients, suggesting a possible link between ALTR and severe tissue damage from PJI [9,13].

Registry data from the Mayo Clinic reveals an increased risk of PJI among patients who underwent a primary MoM total total hip arthroplasty (MoM THA). Prieto et al. reported a 5.6% rate of revision for PJI in 124 patients who had undergone MoM THA [15]. While this exceeded the historical incidence of 1.3% and the authors postulate that the increased infection risk may be due to molecular effects of ALTR, they note that a causal relationship cannot be established since histologic evidence was not seen in all cases. Another study from the Mayo Clinic registry similarly noted an increased incidence of PJI requiring re-revision among patients revised for failed hip resurfacing. While not all of these revisions were directly attributed to ALTR, Wyles et al. did note that among eight patients revised for ALTR, two were found to be infected [16].

Multiple studies have identified a high incidence of PJI among patients being revised for ALTR [1,15–18]. However, few of these studies have provided a clear definition of how ALTR was diagnosed, and fewer still have utilized MusculoSkeletal Infection Society (MSIS) criteria to establish the diagnosis of PJI. Donell et al. reported a high rate of early failures in 652 MoM THAs with 90 (13.8%) hips revised over 9 years [1]. In their revision cohort, 9 patients (10%) were noted to have a deep infection. While intraoperative findings consistent with ALTR were described as 'sometimes seen,' no clear link was established between these findings and the cases of PJI.

Efforts to clearly define the features of septic MoM THA failures have contributed greatly to our understanding of the incidence of PJI in patients with ALTR. In a series of 104 MoM THA revisions, Grammatopolous et al. identified seven cases of PJI (6.7%) [19]. All PJI cases were strictly defined by the presence of positive cultures in two separate tissue samples and were noted to also have an ALTR. The use of more stringent criteria than MSIS guidelines led the authors to acknowledge that some cases of PJI could have been missed. The author concluded that the 6.7% incidence noted in their study was very high for presumed aseptic revisions as compared to a rate of 2.7% at their institution for a prior revision series with hard on soft bearings. In contrast, Kwon et al. reported on a cohort of 62 patients revised for ALTR, diagnosed based on clinical and MRI findings. Using MSIS criteria they identified seven cases of PJI (11%) which the authors felt were consistent with the published literature for revision of metal on polyethylene bearings citing prior studies.

There are a few studies that refute a possible link between ALTR and a higher incidence of PJI. Dimitriou et al., Liow et al. and Matharu et al. each reported PJI rates of 2% or less in their cohorts of 178, 102 and 64 ALTR revisions, respectively [20–22]. However, no description of the diagnostic criteria used to identify PJI was provided in any of these studies.

A growing body of both in vitro and clinical evidence suggests that ALTR may foster periprosthetic soft tissue changes that predispose to the development of PJIs. However due to small sample sizes, marked heterogeneity in study design and lack of consistent use of strictly defined diagnostic criteria, the quality of the evidence is currently limited. In conclusion, while conflicting evidence from few case series and some in vitro work make definitive conclusions difficult, the preponderance of the evidence suggests that the incidence of PJI is increased in this patient population.

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