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QUESTION 3: What tools (i.e., kidney, liver, index surgery, cemented prosthesis and C-reactive protein (KLIC) score) are available to help predict successful treatment with debridement, antibiotics and implant retention (DAIR)? What is the accuracy of these tools?

RECOMMENDATION: Two prognostic scoring systems have been published and only one has been validated. While several studies exist confirming the significances of the variables utilized by the two scoring systems, the body of literature is heterogeneous and conflicted, such that general statements of their accuracy and applicability cannot be supported.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 7%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Periprosthetic joint infections (PJIs) are some of the most critical and prevalent complications following total joint arthroplasty. PJIs are associated with considerable healthcare expenses as well as patient morbidities and mortalities. Treatment strategies that have been adopted range from conservative management and antibiotic suppression to surgical treatments, such as debridement of the infected joint with or without modular component exchange, single-stage and two-stage revision arthroplasty, arthrodesis and amputation. It is yet to be determined which treatment strategy is the most effective method for treating PJIs in the patient population, but it has been shown that revision arthroplasties following PJIs fare poorly compared to revision arthroplasties following aseptic causes of prosthetic joint failures. Thus, for each patient population, it is important to identify the most appropriate treatment methods in order to prevent the recurrences of infections following treatment of PJIs. DAIR offers the advantage of physically removing most, if not all, of the infected tissue from the periprosthetic space, whereas conservative or arthroscopic treatments are less effective in removing infected tissues. DAIR also does not require the need for reoperation, making it logistically simpler than the two-stage revision arthroplasty procedure. However, indications for DAIR are generally limited to cases of acute postoperative or acute hematogenous infections not yet involving bone or causing implant loosening. There have been several studies reporting the results of DAIR that analyze factors that are predictive for treatment success or failure. However, these studies lack consistency across inclusion criteria, definitions of failure, surgical technique and timing and antibiotic regimens following surgery. This heterogeneity makes it difficult to compare results and is a likely explanation for the markedly varied risk factors and success rates seen following DAIR (16-100%) [1–3].

Two moderate-quality studies sought to construct predictive scoring tools using the most significant identified risk factors to aid in reliably assessing preoperative risk and appropriate patient selection for DAIR. Tornero et al. describes the KLIC-score to predict early failure of DAIR for acute postoperative PJIs in a retrospective regression analysis of 222 procedures (137 knees, 85 hips) [4]. The diagnosis of acute postoperative PJIs was determined using the MusculoSkeletal Infection Society (MSIS) criteria within three months of the index procedure. Early treatment failures were defined as the need for unscheduled surgery, death related to infection within 60 days of DAIR or the need for chronic suppressive antibiotic treatments. Using a logistic regression model, the authors found five independent preoperative predictors of failure. They included chronic renal failure (K- kidney), liver cirrhosis (L- liver), infection of a revision arthroplasty or arthroplasty for femoral neck fracture (I- index surgery) and cemented prosthesis and presenting C-reactive protein > 11.5mg/dL (C- cemented/CRP). The authors assigned each of these factors a point value based on the odds ratio (Table 1) and stratified the risks of failure based on the sum of these risk factors. Patients with a score of 2 or less had a failure rate of 4.5%, while patients with a score of 4 or more had a failure rate of 60%. Those with a score of at least 7 had a 100% rate of failure. Additionally, a score above 3.5 was shown to have an even balance of sensitivity (74%) and specificity (86%) in predicting early failures of DAIR [4].

TABLE 1. Scoring system of independent preoperative predictors of early failure of DAIR for PJI according to the KLIC-score

Abbreviation	Variable	Score
K	Chronic renal failure (kidney), glomerular filtration rate < 30 ml/min	2
L	Liver cirrhosis	1.5
I	Index surgery = revision surgery or indicated for femoral neck fracture	1.5
C	Cemented prosthesis	2
C	C-reactive protein > 11.5 mg/dl	2.5

K, kidney; L, liver; I, index surgery; C, cemented/CRP (reprinted with permission) [4].

The KLIC-score was later validated by Jimenez-Garrido et al. in a cohort of 30 patients with acute postoperative or acute hematogenous PJIs. They concluded that DAIR was likely to successfully treat patients with a preoperative score of < 3.5 and that DAIR was likely to fail and would not be an appropriate treatment for those scoring > 6 [5]. A subsequent external validation study by Lowik et al. retrospectively applied the KLIC-score to 386 hip and knee patients with acute, early PJI [6]. Logistical regressions showed that each point in the KLIC-score corresponds to a 1.32x increase in odds of failure. A score of 3.5 showed the optimal cut-off point for treatment, with a sensitivity of 52% and specificity of 70%. A score higher than 6 points showed a specificity of 97.9%. The KLIC-score exhibited good predictive accuracy with an area under the receiver-operating characteristic curve (0.64), but this was less than what was found in the initial study by Tornero et al. (0.84). The authors attributed this discrepancy to differences between the cohorts and in the regional epidemiology, which highlights the need for local external validation studies prior to widespread clinical adoption [6].

Buller et al. published a nomogram scoring system based on their retrospective regression analysis of 309 hip or knee PJIs treated with DAIR [7]. The authors found that independent predictors of

failure included a longer duration of symptoms of PJI prior to DAIR, elevated erythrocyte sedimentation rate (ESR) at presentation, previous PJIs, previous infections in the same joint and infections caused by *Staphylococcus aureus* (methicillin-resistant and sensitive), vancomycin-resistant *Enterococcus*, methicillin-resistant *S. epidermidis* or coagulase-negative staphylococcal species compared to other causative microorganisms. Those variables plus other patient characteristics, such as Body Mass Index, immunocompromised status, white blood cell count, hemoglobin and whether the hip or the knee is involved are used to calculate a composite score which predicts 1-, 2-, 3-, 4- and 5-year survivals of DAIR [7]. To the investigators' knowledge, this study has not been validated or utilized in subsequent citations.

With respect to the accuracy of these scoring systems, one has been validated in a 30-patient cohort and in an external validation study, but neither has been widely adopted in the literature [5,6]. However, the majority of relevant citations, despite their variability, identified predictive factors that coincide with some of the elements of the KLIC-score and the nomogram. The duration of symptoms of infection prior to DAIR, for instance, was the most widely identify factor associated with treatment outcome, with a longer duration corresponding to increased odds of failure [1,8–15]. In keeping with both systems' scoring methodologies, others have found that elevated inflammatory markers are associated with higher failure rates [8,12,16–18] and DAIR for infected knee arthroplasty has generally less favorable published results compared to their hip counterparts [2,13,19]. Performing DAIR for PJIs of revision arthroplasty [20], arthroplasty for femoral neck fracture [19] or of a cemented prosthesis [21] has also been shown to be predictive of failure in other studies. Other than the KLIC validation studies, there has been one study to identify chronic kidney disease as a predictor of DAIR failure, albeit in a cohort of exclusively gram-negative PJIs treated with DAIR [22]. No other citations, to our knowledge, have correlated liver cirrhosis to DAIR failure.

There are several other associated factors in the literature not captured by the scoring systems. Exchanging the polyethylene or modular components during debridement is consistently described as a predictor of successful treatment [20,23–25] – contemporary publications and reviews conclude that exchange of these should be standard in DAIR based on these results. Postoperative antibiotic treatments greater than 21 days, and more often at least 42 days, have also been described as positive predictors [26–28]. Appropriate antibiotic treatment varies based on causative organisms [22], but multiple citations conclude that the addition of rifampin to the antibiotic regimen is indicated for *S. aureus* infections [16,25,29–32].

The time from index surgery to PJI has had conflicting associations. Some studies show that late (i.e., acute hematogenous) infections have poorer outcomes compared to acute postoperative infections [1,8,13,24,25,33,34], while others show non-inferior results of DAIR for acute hematogenous infections as long as the duration of symptoms is short [15,34,35]. The McPherson host grading classification system, though originally described to predict successful two-stage treatment for PJI, was recently shown in total hip arthroplasty patients to predict success with DAIR [36,37]. McPherson grade A hosts failed at significantly lower rate (8%) compared to grade B (16%) and grade C (44%) hosts [37]. Preoperative anemia (hematocrit < 32.1) was recently shown to predict treatment failure after DAIR (odds ratio 6.7) [38]; anemia was included in the analysis but not found to correlate with failure in the nomogram scoring system by Buller et al. [7].

The majority of relevant citations also describe treatment rates that are pathogen-dependent. Staphylococcal species are overwhelmingly associated with high failure rates, vs. other etiologies [8,39] and most, but not all, show *S. aureus* infections to fail at significantly higher rates than other staphylococcal infections [10,26,28,40–44]. Species and antibiotic sensitivity are generally not clinically available at the time of DAIR using commonly contemporary diagnostic methods, making it impractical to include in a preoperative risk assessment system. It was not included in the KLIC-score, though the citation describes pathogen-dependent results consistent with the literature [4]. It was, however, included in the nomogram, which limits its ability to be adopted as a preoperative tool [7].

Despite the promise of these two reported scoring systems, well-controlled, high-quality studies confirming their accuracy are still lacking. The heterogeneity of the relevant literature supports both scores' methodologies, but not without some degree of conflict or inconsistency. Thus, we conclude that there exist two prognostic scoring systems: one which is a validated, preoperative assessment of risk of early failure for DAIR and one which is a non-validated nomogram of perioperative characteristics predicting 1- through 5-year survivability. Further studies adopting these scores are needed to identify those PJI patients most appropriate for treatment with DAIR.

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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.