

HK14: Which Serological Screening Test(s) Should Be Obtained for Patients Undergoing Revision Arthroplasty?

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Response/Recommendation: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) must be obtained in all patients undergoing revision total joint arthroplasty (TJA), regardless of the presenting complaint.

Level of Evidence: Strong

Delegate Vote:

Rationale:

Periprosthetic joint infection (PJI) is a devastating complication and a major cause of morbidity and mortality following primary and revision total joint arthroplasty (TJA)¹. To date, the orthopaedic community is yet to identify a single absolute test for the diagnosis of PJI². As such, the diagnosis of PJI can be challenging to make and relies on a combination of tests³.

Due to their high negative predictive value, low cost, and widespread availability, serological markers are commonly utilized to rule out chronic infection in patients undergoing revision TJA^{4,5}. At this time, clinical practice guidelines endorse the use of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as first-line tests in this setting⁶. Although a range of diagnostic thresholds have been proposed for CRP and ESR within the arthroplasty literature, a cutoff of 10 mg/liter (L) for CRP and 30 mm/hour for ESR have been shown to have the best overall accuracy for chronic PJI (**Table 1**). However, the vast majority of existing studies on the diagnostic utility of serological markers utilized statistical analyses that maximized both sensitivity and specificity when selecting the optimal cutoffs for these tests. Hence, it is not surprising that a growing body of evidence has demonstrated that serology is normal (i.e., below the above-stated thresholds) in a number of PJI patients, especially in cases caused by slow-growing organisms such as *Cutibacterium acnes* and coagulase-negative Staphylococci^{7,8}. More recently, in an effort to identify the optimal cutoffs of serological markers for use as screening tests, Bingham et al. demonstrated that a CRP and ESR cutoff of five mg/L and 10 mm/hour, respectively, had a sensitivity of 95% for the diagnosis of PJI, minimizing the potential for false-negative results when using these tests⁹. Furthermore, there has been data to suggest that the combination of CRP and ESR improves overall diagnostic confidence in this setting, highlighting the importance of routinely ordering both tests when working up patients undergoing revision TJA (**Table 2**). In one study, the authors found that the combination of CRP and ESR at a cutoff of five mg/L and 10 mm/hour, respectively, had a sensitivity of 100% and a specificity of 55%⁹.

A D-dimer test has garnered attention as a potential serum marker of infection in view of reports demonstrating its ability to identify outcomes in patients who have bacteremia¹⁰. The utility of D-dimer in the diagnosis of PJI has since been established in the orthopaedic literature¹¹⁻¹³, culminating in its inclusion in the 2018 International Consensus Meeting definition (ICM) of PJI¹⁴. Although the 2018 ICM definition utilized a D-dimer threshold of 860 ng/mL, there remains a lack of consensus on the optimal cutoff for D-dimer in the diagnosis of

PJI, precluding it from universal adoption in this setting (**Table 2**). However, it is important to recognize that there are certain clinical scenarios where D-dimer may provide additional diagnostic information. In one study, D-dimer was found to have the highest sensitivity for PJI caused by “low virulence” organisms at 93.8%, when compared to CRP (sensitivity 74.0%) and ESR (sensitivity 78.8%)¹⁵. Similarly, in another study, the authors demonstrated that when evaluating the performance of different serological markers as screening tests (maximizing sensitivity to 100%), D-dimer demonstrated a specificity of 40.2%, outperforming both ESR and CRP¹⁶. Notwithstanding, D-dimer is a non-specific test that has been shown to be elevated in patients who have certain medical conditions, including cancer, systemic inflammatory diseases, history of venous thromboembolism, and recent trauma, reducing its diagnostic utility in these patient populations^{17,18}.

Serum interleukin-6 (IL-6) is a cytokine that stimulates the release of acute-phase reactants from the liver¹⁹. In the orthopaedic literature, there is a growing body of evidence to suggest that IL-6 has excellent utility for the diagnosis of PJI. In a recent meta-analysis by Berbari et al., serum IL-6 was found to have a pooled sensitivity and specificity of 97 and 87%, respectively, for the diagnosis of PJI²⁰. Similarly, in a separate study, Xie et al. demonstrated that serum IL-6 had a sensitivity and specificity of 72 and 91%, respectively, in the diagnosis of PJI²¹. However, it is important to recognize that although the use of serum IL-6 in this patient population was endorsed by the American Academy of Orthopaedic Surgeons (AAOS) clinical practice guidelines, the limited availability and relatively high cost of this test have prevented it from being universally adopted⁶. Furthermore, there remains a lack of consensus within the orthopaedic literature on the optimal cutoff of this marker for the diagnosis of PJI²².

In patients undergoing revision TJA, there is substantial evidence to support the routine use of CRP and ESR to help rule out infection in cases of low pretest probability. Furthermore, a growing body of evidence has demonstrated that there may be a role for measuring D-dimer levels in cases of diagnostic uncertainty. Notwithstanding, it is important to recognize that when traditional thresholds are used, serology can be negative in a relatively large proportion of PJI patients. Therefore, physicians must employ a high index of suspicion for infection and have a low threshold for arthrocentesis in all patients undergoing revision TJA.

Table 1. Diagnostic utility of serum CRP and ESR spell out as demonstrated in the literature.

Study and Publication Year	Definition of Infection	Cutoff	Sensitivity (%)	Specificity (%)
<i>C-reactive protein</i>		mg/L		
Glehr et al., 2013 ²³	2011 MSIS	10.2	91	72
Alijanipour et al., 2013 ²⁴	2011 MSIS	10.0	97	70
Shahi et al., 2017 ²⁵	2013 ICM	10.0	79	80
Klim et al., 2018 ²⁶	2011 MSIS	10.3	90	67
Fu et al., 2019 ²⁷	2011 ICM	10.0	80	80
Wu et al., 2020 ²⁸	2013 ICM	10.8	73	95
Bingham et al., 2020 ⁹	2013 ICM	10.0	85	67
Bingham et al., 2020 ⁹	2013 ICM	5.0	95	63
<i>Erythrocyte sedimentation rate</i>		mm/hr		
Bottner et al., 2007 ²⁹	(+) Histology or ≥ 2 (+) cultures	32	81	89
Ghanem et al., 2009 ³⁰	Sinus tract or ≥ 2 (+) cultures	31	94.5	72.2
Xiong et al., 2019 ³¹	2011 MSIS	30	73	100
Bin et al., 2020 ³²	2011 MSIS	31	77	97
Huang et al., 2020 ³³	2013 MSIS	30	81	88
Yang et al., 2021 ³⁴	2018 ICM	36.5	70	86
Tarabichi et al., 2024 ¹⁶	2018 ICM	41	74	85

MSIS, musculoskeletal infection society; *ICM*, International Consensus Meeting.

Table 2. Diagnostic utility of the combination of CRP and ESR spell outas demonstrated in the literature.

Study and Publication Year	Definition of Infection	CRP cutoff (mg/L)	ESR cutoff (mm/hr)	Sensitivity(%)	Specificity(%)
Ghanem et al., 2009 ³⁰	Sinus tract or ≥ 2 (+) cultures	30	10	87.8	88.1
*Alijanipour et al., 2013 ²⁴	2011 MSIS	13.5	48.5	85.7	60.6
†Alijanipour et al., 2013 ²⁴	2011 MSIS	23.5	46.5	95.6	54.0
Shahi et al., 2017 ²⁵	2013 ICM	10	30	84	47
Bingham et al., 2020 ⁹	2013 ICM	10	30	88.8	71.7
Bingham et al., 2020 ⁹	2013 ICM	5	10	100	54.7
*Yu et al., 2023 ³⁵	2011 MSIS	30	10	70.1	88.8
†Yu et al., 2023 ³⁵	2011 MSIS	30	10	78.3	88.8
Tarabichi et al., 2024 ¹⁶	2018 ICM	7	51	82.4	84.1

*Hips only

†Knees only

MSIS, musculoskeletal infection society; *ICM*, International Consensus Meeting.

Table 3. Diagnostic utility of D-dimer as demonstrated in the literature.

Study and Publication Year	Definition of Infection	Cutoff (ng/mL)	Sensitivity(%)	Specificity(%)
Shahi et al., 2017 ²⁵	2013 ICM	850	89	93
Li et al., 2019 ³⁶	2013 ICM	1,250	64.5	65.0
Pannu et al., 2020 ³⁷	2013 ICM	850	96	32
Xu et al., 2021 ³⁸	2013 ICM	800	85.7	47.8
Muñoz-Mahamud et al., 2022 ³⁹	2018 ICM	950	91	64
Tarabichi et al., 2023 ¹⁵	2018 ICM	664	81.3	81.7

ICM, International Consensus Meeting.

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