The value of monitoring inflammatory markers after total joint arthroplasty

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Abstract

Introduction

Periprosthetic joint infection is a frequent and dreadful complication after total joint arthroplasty. Serological inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are widely available and easy to use. As such, they are often used as preliminary diagnostic as well as follow-up tools during the course of treatment.

The information they carry is not the same in every clinical scenario, and they should be interpreted accordingly. This review confronts the reader with different doubtful clinical situations and then provides the necessary tools to interpret ESR and CRP in each of them: the immediate postoperative period, the chronic painful arthroplasty and between two-staged revision of infected cases.

Conclusion

Serological inflammatory markers have different diagnostic thresholds in acute and chronic situations. Follow-up measurements during treatment are informative, but complete normalization is not a mandatory requirement for successful outcome.

Introduction

Total joint replacement, especially hip and knee, is one of the most successful surgeries in orthopaedics. The demand for total hip and knee arthroplasty is increasing and is expected to grow even further over the coming decades. Infection is arguably the most challenging and certainly one of the most frequent complications after joint replacement. Despite modern surgical prophylaxis, the incidence of this complication is rising worldwide. It is therefore likely that an increasing number of orthopaedic surgeons and other clinicians will encounter this problem.

Periprosthetic joint infection (PJI) is typically classified according to the timing of symptom development and the mechanism of bacterial contamination as acute postoperative, acute delayed (haematogeneous) or chronic. This simple classification scheme greatly influences treatment options. Timely recognition of this grievous complication is crucial as it may make the difference between successful and failed outcome.

Definitive diagnosis is often challenging as a real ‘gold standard’ has yet to be determined. Currently, it can only be determined after culture results of samples taken during surgery. As such, preoperative diagnosis is forced to rely on clinical suspicion as well as on careful scrutiny of laboratory and imaging modalities. In this setting, serological inflammatory markers, specifically erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are often used as initial tests even when there is a low suspicion of PJI. They are also commonly used in monitoring response to therapy since they are inexpensive, non-invasive and widely available tests.

This review confronts the reader with real daily practice doubtful clinical situations and then provides the necessary tools to interpret ESR and CRP values in three different key periods: the immediate postoperative period, diagnosis of a suspected chronic infection and between stages of treatment of an infected total joint arthroplasty. The different thresholds and diagnostic accuracy in each instance will be presented.

Discussion

Immediate postoperative period

Clinical case

An otherwise healthy 73-year-old man underwent right total knee arthroplasty (TKA) for primary knee osteoarthritis. The first few days after the procedure were uneventful and the patient was discharged on the fifth postoperative day. On discharge, ESR and CRP values were 100 mm/h and 49.2 mg/L respectively. On the 18th postoperative day, the patient presented to the outpatient clinic with scarce serous wound drainage through a small area of macerated-looking skin wound. Blood tests revealed normal leukocytes and elevated ESR and CRP: 84 mm/h and 6.2 mg/L respectively. The patient was sent home with no antibiotics and was seen again a week later. Small and seemingly superficial area of skin necrosis was present, and there was no drainage or obvious inflammatory signs (Figure 1). ESR was 102 mm/h and CRP was 7.9 mg/L.

Is it normal?

ESR is the rate at which red blood cells sediment in 1 h. It is a nonspecific haematological test routinely used as an indirect measure of inflammation. CRP is a major acute-phase protein produced by the liver and increases as a response to acute injury.

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inflammation/infection and other tissue insults such as surgery. To understand the importance of these markers in the postoperative period, it is essential to know their normal kinetic patterns after uncomplicated arthroplasty.

As one would expect, both these markers rise after surgery. The peak is significantly higher after TKA in comparison with THA because the bone and soft tissue trauma is higher in TKA. Due to the very high inter-individual variations of these values, it is not possible to find a threshold that predicts the presence of infection.

Nonetheless, after the initial peak, these values should steadily decrease after uncomplicated arthroplasty. ESR levels usually peak on the fifth postoperative day and drop close to preoperative levels by the end of the third week after THA and the ninth month after TKA. Some studies show that ESR can take up to 1 year to return to normal levels after uncomplicated arthroplasty. ESR levels usually peak on the fifth to seventh day and may take up to 2 months after TKA.

Understanding this normal pattern after uncomplicated arthroplasty is the key to better using these inflammatory markers to our advantage in the diagnosis of early acute PJI. Although recent reports have questioned the real value of irrigation and debridement as a means to achieve eradication of infection under specific circumstances, it is still widely recommended in acute postoperative infections especially in the first 3–4 weeks after surgery. This simple procedure entails reopening the joint through the original incision, removal of unhealthy tissues, thorough irrigation and exchange of modular components, while retaining fixed components.

It is therefore crucial to make an accurate and timely diagnosis to increase the chances of success. Clinical circumstances, however, are not always clear-cut. A red and swollen joint or even superficial inflammatory signs are not always indicative of infection in the early postoperative period. Scarce serous wound drainage may be normal but, if persistent, it is a known risk factor for infection. Maathuis et al. proposed a protocol using ESR and CRP as an adjunct to clinical judgement to help dictate the need and timing for debridement in patients with persistent drainage after total joint replacement. Serial measurements of these inflammatory parameters were taken in suspicious circumstances, and only a decrease in ESR and CRP or a decrease in drainage could postpone or alter the decision to perform open debridement.

The increase in ESR and CRP values guided the decision to perform irrigation and debridement of the knee joint in the presented clinical case. Intraoperative microbiology samples confirmed a polymicrobial infection by methicillin-sensitive *Staphylococcus aureus* and *Enterobacter cloaca*. Appropriate antibiotic therapy was given after surgery, and 2 years after the surgery, the patient remains free of infection.

**Painful Arthroplasty**

**Clinical Case**

A diabetic 63-year-old woman presented complaining with pain in her right knee. TKA had been performed 16 months earlier. The first few postoperative weeks were uneventful, but a relentless pain had been bothering her ever since. There was no knee stiffness and radiographs showed no significant findings (Figure 2). No fever, sinus tract or inflammatory signs were ever present. Blood tests were performed: ESR was 29 mm/h and CRP was 17.3 mg/L. Subsequently, a knee arthrocentesis was performed and synovial fluid leukocyte count was 33,250/µL (98% neutrophil percentage). An infection diagnosis was made and a two-stage procedure was recommended.

**Is it infected?**

Preoperative identification of PJI in patients presenting with a painful total joint replacement is often
The major finding common to all these studies is that the negative predictive value when both ESR and CRP are under the threshold value is over 95%. Positive predictive value however, even when both markers are elevated, is not as impressive. In other words, the inflammatory parameters should serve as an initial screening test. If both are negative, the probability of an infection is very low. If at least one of them is positive, a subsequent confirmatory evaluation should be undertaken.

Although there is no absolute consensus as to the exact cut-off points of both ESR and CRP, there is enough evidence that they are useful screening tests. However, caution should be observed when using ESR and CRP to assert infection. Except in clinically obvious scenarios, such as chronic sinus tract communicating with the joint, a confirmatory test should follow when studying a painful total joint with positive ESR and/or CRP. Increasing diagnostic thresholds values to increase specificity should be interpreted with caution to avoid significantly lowering the negative predictive value (i.e. missing infected cases).

Between stages of treatment
Clinical case
A 66-year-old man with a history of right total hip arthroplasty for primary osteoarthritis 3 years ago presented with a painful hip and a chronic draining sinus tract communicating with the prosthesis. ESR was 17 mm/h and CRP was 14.8 mg/L. A diagnosis of PJI was made and the two-stage exchange was selected.

First-stage surgery was performed and coagulase-negative Staphylococci grew on several intraoperative samples (Figure 3). After 2 weeks of IV antibiotics, the patient was discharged and sent home with oral antibiotics for another 4 weeks. Consecutive ESR and CRP measurements showed persistent elevation of ESR (Table 1).

Figure 2: Normal radiographs of a painful right total knee replacement.


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Competing interests: none declared. Conflict of interest: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
While reimplanting a new prosthesis in a persistently infected site is a concern, overreliance on normalization of these serological markers may lead to an exaggerated and unnecessary time interval between stages, thus increasing patient morbidity. Ghanem et al.29 were the first to address this issue specifically. In their study including 109 infected total knee replacements treated according to the two-stage protocol, 23 patients (21%) required revision surgery for recurrence of prosthetic joint infection. There were no significant differences in mean ESR or CRP values (at the time of reimplantation) or significantly different variations of these parameters (between resection and reimplantation) when comparing both groups. These findings were later confirmed by an independent study group that studied serum ESR and CRP as well as synovial fluid white blood cell count and differential before the second stage.31 The authors were unable to identify any single, or combination of, commonly used testing modalities to reliably identify persistent infection following resection TKA for a deep periprosthetic infection. The ESR and CRP were particularly unreliable and frequently abnormal even when the infection had been controlled.

The decision regarding the exact timing for reimplantation remains difficult as it relies for the most part on the subjective clinical judgement of the treating physician. Favorable local soft tissues, such as correct wound healing and absence of local warmth, are a major factor. In this regard, the knee being a more superficial joint than the hip, allows an easier and more trustworthy clinical assessment. Favourable ESR and CRP kinetics, especially after antibiotic discontinuation, serve as an adjunct to decision, but complete normalization is neither essential nor enough to ensure a successful outcome.

The authors believe there is little role for deferring reimplantation until all serologic markers have normalized. In the case presented, good local soft tissue conditions guided the decision to go ahead with second-stage surgery despite persistent elevation of inflammatory parameters. Two years after surgery, the patient remains painless and infection free.

### Other alternatives

Several other serological markers have been studied in the context of prosthetic joint infection. Procalcitonin has been studied especially in the diagnosis of infection in the chronic setting. Although it has been shown to have a good specificity (albeit not higher than CRP), it has a low sensitivity and a negative predictive value. Interleukin-6 is another studied alternative. It has been studied in the diagnosis of chronic infection and showed excellent sensitivity and specificity when a >10 pg/mL cut-off was used.33 In the early uncomplicated postoperative period, it also shows an increase/decrease pattern much like CRP. The much faster peak and return to normal can hypothetically be advantageous and allow an earlier diagnosis. As the expected return to normal after uncomplicated arthroplasty is faster, an infection can be hypothetically detected by an earlier increase in IL-6 levels than in CRP levels.

### Table 1: Inflammatory parameter measurements between two-stage revision surgeries

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Day 2</th>
<th>Day 5</th>
<th>2 weeks</th>
<th>6 weeks*</th>
<th>2 months</th>
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<tr>
<td>ESR (mm/h)</td>
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<td>77</td>
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<td>32</td>
<td>24</td>
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<td>CRP (mg/L)</td>
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*Antibiotic therapy discontinuation at this point.

When is it safe to do a new prosthesis?

Although numerous studies report favourable outcomes after one-stage revision surgery, two-stage surgery has traditionally been considered as the gold standard for management of chronic infections. Two-stage exchange consists of debridement, resection of infected implants with or without placement of a temporary antibiotic-impregnated cement spacer and delayed reimplantation of a new prosthesis after infection is deemed to be eradicated.

Determining the appropriate timing and criteria for reimplantation that result in minimal reinfection rates remains controversial. Most surgeons prefer that ESR and CRP return to normal before proceeding with reimplantation, but there really is no solid scientific evidence to back it up. Some investigators have proceeded with reimplantation only when knee aspirate cultures were negative for bacterial growth, but the high false-negative rates of culture possibly resulting from the prolonged antibiotic treatment raise concerns.

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These alternatives are neither as extensively studied nor as widely available as ESR and CRP. The latter are simple routine laboratory tests performed worldwide that can give precious and due time information in a variety of clinical scenarios regarding prosthetic joint infections.

Conclusion
ESR and CRP tests are very useful in the management of musculoskeletal infections. Nevertheless, the information they provide is not the same in every clinical scenario and they should thus be interpreted accordingly. Diagnostic thresholds are different in the acute and chronic infected prosthetic joints and possibly also different between hip and knee replacements. Follow-up measurements during treatment are somewhat informative, but complete normalization is not a mandatory requirement for successful outcome.

Abbreviations list
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PJI, periprosthetic joint infection; TKA, total knee arthroplasty

References
Critical review


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