Author: Maja Babic

QUESTION 2: When do common blood biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or Procalcitonin normalize after spine surgery?

RECOMMENDATION: Following spinal surgery with or without instrumentation, CRP values peak on days 2-3 postoperatively and normalize within 14 days. ESR also normalizes within 14 days.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 50%, Disagree: 29%, Abstain: 21% (NO Consensus)

RATIONALE

Multiple prospective studies suggest that CRP values peak within 2-3 days postoperatively (peak levels depend on extent of surgery, levels involved, etc.) and decrease back to baseline within 14 days. A rapid decline of CRP postoperatively is interrupted if postoperative infection sets in and a secondary rise occurs [1,2]. Prospective studies have shown that ESR peaks by day four following spinal surgery and in the majority of cases normalizes by two weeks postoperatively [3]. However, monitoring of CRP level was found to be superior to that of ESR for early detection of infections after cervical spine surgery in a series of 51 cases of anterior cervical fusion [4]. A second rise of CRP and ESR or failure to decline is an indicator of potential surgical site infection [5,6]. Limited data is available on the value of Procalcitonin [7].

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Author: Maja Babic

QUESTION 3: Is there a role for the use of serum biomarker for the diagnosis of spinal surgical site infection (SSI)?

RECOMMENDATION: Yes, C-reactive protein (CRP) is a predictable, reliable and economical screening tool for early infectious complications following spine surgery. Erythrocyte sedimentation rate and white blood cell count have nonspecific kinetics that are less helpful in identifying early SSI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 67%, Disagree: 25%, Abstain: 8% (Super Majority, Weak Consensus)

RATIONALE

In a prospective study involving 348 patients who underwent decompression laminectomy, postoperative CRP was helpful in detecting early infectious complications following surgery. As a predictor for early wound infection, the sensitivity, specificity, positive predictive value and negative predictive value for abnormal CRP responses were calculated as 100%, 96.8%, 31.3% and 100%, respectively. Close observation of the surgical site is recommended in patients with abnormal CRP values at day five or seven postoperatively, namely for failure to decline or a secondary rise [1].

Of 149 patients undergoing elective spine surgery, 20 developed infectious SSI complications. Postoperative CRP kinetics were predictable and indicative of early infection where a secondary rise or lack of CRP decrease had a sensitivity, specificity, positive predictive value and negative predictive value of 82%, 48%, 41%, and 86% for infectious complications, respectively [2].

Out of 400 patients undergoing lumbar micro-discectomy over a 15-month period, 9 developed infectious complications related to surgery. CRP values were shown to be a reliable and economic screening tool in identifying the patients at risk with a sensitivity for serial CRP testing (day one and five postoperatively) calculated as 100% with a specificity of 95.8% [3].

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Author: Bryan Alexander

QUESTION 4: Is there a role for molecular techniques such as polymerase chain reaction (PCR) or next-generation sequencing (NGS) for the diagnosis of spinal surgery infection? If so, in which group of patients should this be done?

RECOMMENDATION: It is reasonable to selectively incorporate these diagnostic modalities as an adjunct to standard methodologies where there is a history or high pre-test probability for culture negative infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 71%, Disagree: 14%, Abstain: 15% (Super Majority, Strong Consensus)

RATIONALE

Successful management of periprosthetic joint infections (PJI) is significantly enhanced with a prompt and accurate microbiological diagnosis. Conventional culture methods for diagnosis of PJI can be compromised and complicated by early antibiotic treatment, heterogeneity of surgical sampling, fastidious microorganisms difficult to grow in culture and non-planktonic pathogens utilizing biofilms. Therefore, modern molecular microbiologic methods have naturally been seen as very promising for increasing diagnostic yield in these circumstances. Technologies that have more recently been applied to PJI generally include ribosomal RNA sequencing, species-specific and multiplex PCR and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).

Specifically, with respect to spinal and vertebral infections, these varied technologies have demonstrated success in leading to an etiologic diagnosis. These methods have been used to identify a variety of pathogens, including *Staphylococcus spp.* [1–3], *Streptococcus spp* [3,4], *Enterococcus spp.* [4], Enterobacteriaceae [3–5], *Brucella spp.* [6], *Mycobacterium spp.* [2], atypical bacteria (*T. whipplei*) [7], *Mycoplasma spp.*) [8], anaerobes (*Clostridium spp.*) [3], *Fusobacterium spp.*) [4,9] and fungi (*Aspergillus spp.*) [10].

By far, the most experience with these techniques for spinal infections is in the diagnosis of Pott's disease (*Mycobacterium tuberculosis*) [2,6,11–15]. These reports generally demonstrate a high sensitivity and specificity of PCR modalities, though many of these studies have been completed in tuberculosis endemic geographic areas with likely higher inoculum infections and a well-defined pre-test probability.

False positive results from dead or colonizing/contaminating bacteria is a concern with these tests, and studies evaluating the appropriate number of samples to optimize sensitivity and specificity specific to these molecular methods are limited and not specific to spinal infections [16]. Another important concern with molecular techniques for PJI diagnostics is that they do not commonly allow for susceptibility testing to appropriately target antimicrobial therapy. Certain resistance mechanisms, such as methicillin resistance in *S. aureus* [1,17,18] or rifampin resistance in *M. tuberculosis* [12], are reliably expressed if genetically detected. This is not the norm, however, as resistance expression is generally a complex phenotype determined by multiple factors. Care should be taken not to overly rely on non-susceptibility-generating techniques, as they can just as easily lead to long courses of overly-broad therapy, as can no etiologic diagnosis at all, undermining patient safety and important principles of antimicrobial stewardship. In addition, it has been noted that utilizing molecular methods as an adjunct to and in combination with standard culture methodologies often serves to improve overall diagnostic yield [3].

A few studies have attempted to establish test sensitivity and specificity data when compared to routine culture for bone and joint specimens in general [4,15,19–23], however these efforts are limited by lack of a true gold standard diagnostic method for comparison, the variety of testing methodologies clinically employed and non-standardized clinical criteria for utilization of these methods. Predictably, results vary widely, with sensitivities reported between 50–92% and specificities between 65–94% [20]. No studies investigating sensitivity and specificity of these techniques specific only to spinal post-surgical infections have yet been reported. Therefore, an evidence-based evaluation of the appropriate clinical criteria for utilization of these techniques in spinal surgery patients is not currently possible. One study proposed a strategy for routine collection and potential use of molecular diagnostics in PJI [24]. There is no data investigating the cost effectiveness for any diagnostic schema incorporating molecular methods, however given their positive proof-of-concept and the significant clinical impact of spinal post-surgical infections, it seems reasonable to selectively incorporate the use of molecular methods into situations where there is a high pre-test probability for indolent or culture-negative infection as further studies are done to standardize their use.

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