Sp39—What blood tests, if any, are useful in diagnosis of pyogenic spinal infections? (Complete total and differentiated blood counts, Erythrocyte Sedimentation Rate, C-Reactive Protein and Procalcitonin)

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Recommendation: Based on the available data, ESR and CRP have the largest body of literature to support their routine use in the setting of suspected spinal infection. They have good sensitivity and specificity compared to more traditional tests like CBC. Predictive value of CRP, in particular, is best when it is more markedly elevated (as opposed to the lower range of abnormal values). ESR and CRP are also recommended to be trended to evaluate for resolution of spinal infection during treatment. Next generation laboratory tests such as procalcitonin and IL-15 are gaining support, but further work is needed before they can be universally recommended for diagnosis and prognosis of spinal infection.

Strength of recommendation: Strong

Delegate Vote:

Rationale:

Pyogenic spinal infections (PSI) are an increasingly common problem amongst patients presenting with either back pain or neurologic complaints. Prompt diagnosis of spinal infections is crucial, because delays are associated with a high rate of permanent neurologic deficits and mortality.[1] Unfortunately, they represent a diagnostic challenge due to their variable, and often subtle, initial presentation. Consequently, laboratory values are increasingly being utilized as a way to provide early diagnostic information.[1,2] Introduction of novel decision guidelines combining demographic risk factors with bloodwork such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been associated with reduced diagnostic delays.[1]

One of the challenges of using laboratory values to identify PSI after spine surgery is disambiguating the impact of infection versus the normal inflammatory response after surgery. A retrospective analysis was performed by Hoeller et al. to determine the postoperative kinetics and peak value of CRP after open reduction and posterolateral fusion for either degenerative spondylolisthesis or traumatic spine fractures.[3] The authors noted that patients who subsequently developed a surgical site infection had a significantly higher CRP peak on day seven and eight postoperatively. Second peaks and/or failure to decline after this point were predictive of infection.[3] Further work is needed to establish normative laboratory values and kinetics both after primary spine infection and especially after surgery.

Complete Blood Count

Complete blood count (CBC) is a commonly used lab test in almost all patients when infection is suspected. However, several studies indicate that leukocytosis is inconsistently present in patients with pyogenic spinal infections. For instance, although white blood cell (WBC) counts are often

elevated in bacterial infections, many patients with conservatively or operatively managed bacterial spondylodiscitis may present with normal WBC values.[4] Therefore, normal WBC count does not reliably exclude a spinal infection, especially when the infection is localized or subacute in nature. Postoperative studies have further illustrated the limitations of relying solely on the CBC for diagnostic purposes. While an elevated WBC count could support the presence of infection, its absence was not sufficient to rule out postoperative infectious complications.[5]

With that said, CBC has historically been important – although it has now mostly been superseded by other markers for predicting pyogenic spondylitis. However, values from the CBC are being incorporated into many different machine learning models – many of which are aimed at differentiating pyogenic spondylitis from other types of infections such as tuberculosis spondylitis.[6–8] Generally, these models have high receiver operator characteristics (ROC), accuracy, and predictive values – especially when combined with imaging such as computed tomography (CT).[6–8] Therefore, while the CBC is a cost-effective and rapid screening tool, its diagnostic sensitivity and specificity are limited, necessitating its use as part of a broader diagnostic strategy that includes other inflammatory markers and imaging studies.

C-Reactive Protein

C-reactive Protein (CRP) is a widely used inflammatory marker to predict infection. CRP is elevated in patients who underwent spinal surgery that became infected – compared with those who did not become infected.[9] This was observed specifically for deep infections; whereas superficial infections did not have a difference.[9] CRP elevation over four times the normal limits was shown to be a strong predictor of spinal vertebral infection. Additionally, prior literature has suggested combining CRP values with imaging data such as changes in bone CT attenuation for even more predictive accuracy.[2,10] In contrast, more modest CRP elevation lacks specificity for spinal infection.[11] Given the low incidence of pyogenic spondylitis and high cost of imaging, CRP has been suggested as a screening tool for spinal infection in order to avoid unnecessary MRIs; if CRP is normal, then infection is unlikely.[11] Therefore, elevated CRP may have significant specificity above four times normal – with higher sensitivity in the case of normal findings.

CRP is commonly combined with erythrocyte sedimentation rate (ESR), another inflammatory lab value. In combination, CRP and ESR, are being integrated into large machine learning models to differentiate pyogenic spondylitis from diseases like tuberculosis spondylitis with high predictive characteristics – on the order of 0.85.[7] Both CRP and ESR are significantly associated with prognosis.[9,12] In patients being treated for pyogenic sypondylodiscitis, they are used as a measurement of treatment effectiveness.[13] In particular, a reduction in ESR is significantly associated with a good prognosis in treating pyogenic spondylitis.[12]

Procalcitonin

Procalcitonin (PCT) has gained prominence as a biomarker for bacterial infections due to its ability to distinguish bacterial infections from viral infections or noninfectious inflammatory conditions. PCT is elevated in patients with infection following spinal surgery.[9] In some cases, these

differences were seen in postoperative days 3 and 7 – while no difference was seen at postoperative day 1.[9] This suggests that PCT, although it elevates acutely, may be more predictive within a week following surgery – and not immediately. This was applicable for deep infections – but not for superficial. PCT has been evaluated in combination with additional markers such as IL-15. IL-15 is elevated in patients who underwent spinal surgery that became infected – compared with those who did not become infected.[9] This was observed for superficial and deep infections; at 3 days and 5 days postoperatively. IL-15 is also significantly associated with prognosis.[9] Other studies have combined PCT with the length of fever – such as fever beyond 3 days postoperatively or fever for more than four days total – to strongly predict postoperative infection.[5] However, in other cases, PCT levels were able to be reliably used to predict postoperative infection within one day – demonstrating high ROC metrics.[14]

Despite these promising attributes, the sensitivity of PCT in detecting localized spinal infections is not as high as that of CRP. This limitation is likely due to the localized nature of many spinal infections, which may not elicit a sufficiently robust systemic inflammatory response to drive PCT levels markedly higher.[15] Postoperative PCT levels differ between different populations of patients. Patients with type II diabetes have significantly higher levels of postoperative PCT – suggesting that they may be at an increased risk of infection.[16] PCT may play a role in the emergency setting; PCT of >0.11 ng/mL was used as a red-flag predictor of pyogenic spondylodiscitis in the emergency setting – especially when combined with other measurements such as blood urea nitrogen, creatinine, and lactate dehydrogenase levels.[15] Finally, changes to PCT have been correlated with prognosis after spinal infection.[9]

Future of Modeling and Markers

A variety of genetic and other markers are being used to diagnose pyogenic spinal infections. Newer markers such as sCD14-ST are currently being used with predictive values and ROC characteristics higher than PCT.[14] While traditionally ESR and CRP downtrends have been used to predict resolution of infection, new markers are currently being combined with deep neural networks trained on decades of data to better predict resolution with higher accuracy.[17] These markers include using 18 F-fluorodeoxyglucose positron emission tomography and traditional blood inflammatory markers. Future work will likely uncover additional markers in combination with other predictive variables, such as imaging techniques, in order to create tuned models to best diagnose and prognosticate pyogenic spinal infection.

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