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Erythrocyte Sedimentation Rate, C-Reactive Protein and Procalcitonin in Infections of the Spine and Infections in Spinal Cord Injury Patients

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Abstract: The most widely used inflammatory markers are erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and procalcitonin (PCT). A review of the literature was done on their application in spinal infections and spinal cord injury (SCI) patients. ESR, CRP and PCT as markers of infection have their uses in various but specific medical conditions.

SCI patients are unique because they are in a chronic state of inflammation. In these patients, CRP >50 mg/L may support the diagnosis of true UTI. In those with chronic infections of the spine/vertebrae, an ESR of >20-30 mm/h appears superior to an elevated CRP for diagnosis, although it is still preferred to do both tests. Serum PCT of ≥0.4 ng/mL was reported to be highly specific in diagnosing acute osteomyelitis, but evidence was very limited. No study on PCT for chronic osteomyelitis was found. In post-spine surgery patients, CRP is more useful than ESR, while PCT is superior to CRP in detection of post-operative infections because the former does not rise too high, even after major neurosurgery. PCT of >0.5 ng/mL is reasonable evidence to start antibiotics and further investigation, while levels <0.1 ng/mL suggest absence of infection.

CRP is inferior to PCT in diagnosing post-spine surgery infections, but it may be used when cost is an issue or when PCT is unavailable.

This is the first literature review of the most widely used biomarkers, including PCT, and their application in the diagnosis of infections of the spine and infections in SCI patients.

Keywords: CRP, ESR, injuries, injury, infections, procalcitonin, spinal, spinal cord, spine.

INTRODUCTION

The most widely used inflammatory markers are erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). ESR lost favor as a marker for distinguishing autoimmune diseases from infection after performing inconsistently in many studies. CRP has the advantage of being an early biomarker for infection and inflammation, although generally unable to distinguish between the two [1]. Because of their imperfections, ESR and CRP are frequently ordered together.

Despite its widespread use, the usefulness of CRP remains unconfirmed in the discrimination of infected from non-infected critically ill patients. One CRP value is insufficient. Checking CRP on day 2, and especially on day 4 of presentation, would be better practice, and if elevated, would be more predictive of infection [2].

In the 1990s, high procalcitonin (PCT) levels had been associated with infection, but mostly in septic patients [3, 4]. While the hormone end-product, calcitonin, remained normal or slightly elevated, PCT was significantly higher with infection. PCT was shown to be useful in detecting bacterial infection in those with fever but no localizing signs [3, 5].

PCT has also been noted to be high in some non-bacterial causes, like malaria, and may be mildly or moderately elevated in viral infections [3]. It is not a perfect marker for bacterial infections, but numerous studies have demonstrated that distinct increases allow differentiation of bacterial from viral, and even invasive fungal infections [6-8].

Microbial infection induces an increase in the expression of the gene, *calcitonin-I*, leading to the release of calcitonin precursors from all cells and tissues in the body. It is unknown whether this is due to microbial toxins or from the host response. In sepsis, the usual enzymatic processing of calcitonin precursors is bypassed, so the precursors remain high, while calcitonin levels are either normal or mildly elevated [3, 9].

Most of the studies done on PCT were in critically ill patients [2], particularly systemic conditions, like sepsis [10-12], blood stream infections/bacteremia [13] and pyelonephritis [14]. The use of PCT has been looked at in a wide range of conditions, including meningitis [15],

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community-acquired pneumonia and upper respiratory tract infections (upper RTIs) [16], arthritis [17], endocarditis [18], neutropenia [19], trauma [20], post-operative fever [21], urinary tract infection (UTI) [22], bronchitis, COPD exacerbations [23], ventilator-asssociated pneumonia [24], outpatient setting infections [25, 26], and post-operative infections [27], either as an aid in identifying bacterial infections, or as a tool in antibiotic stewardship [28, 29].

But there is limited data on its application in spinal infections and in spinal cord injury (SCI) patients, where it may find its place since the latter lack localizing symptoms, have atypical presentations, and possess unique characteristics.

Chronic SCI Patients: In a Chronic State of Inflammation

Chronic SCI patients are in a chronic state of inflammation. One study reported a mean CRP of 3 mg/L in paraplegics, while a mixed paraplegia/tetraplegia study that excluded patients with CRPs $\geq$10 mg/L, also showed a mean of 3 mg/L. Another group noted that mean CRP level was 38 mg/L, or 27% higher, in SCI *versus* non-SCI patients, although the former included patients with pressure ulcers and indwelling urinary catheters. But in general, studies agreed that CRP levels hovered around 3 mg/L [30-33]. This becomes more important since CVD has been associated with inflammation, and because high CRP (>3 mg/L) is now considered an independent risk for CVD [30, 34-36].

SCI patients with (even minor) pressure ulcers and indwelling urinary catheters have significantly higher CRP levels (higher than 10 mg/L) [32]. Also, history of UTI, high body mass index (BMI), and even the use of a motorized wheelchair were associated with higher CRP values [37].

Chronic SCI Patients: At Risk for Various Complications, Both Infectious & Non-Infectious

The number of chronic SCI patients has increased because of the improved survival of acute spinal cord patients. This has led to so much more chronic diseases, including diabetes, dyslipidemia and cardiovascular disease (CVD) [30, 38, 39], in these chronic patients. It has also been noted that the more severe the spinal injury is (e.g., tetraplegia *versus* paraplegia or complete *versus* incomplete), the higher the CVD risk [30, 37, 40, 41].

Chronic SCI patients are at risk for direct complications of SCI, including sensory, motor, and bowel and bladder dysfunction, while being prone to the so-called "secondary health conditions" that are indirectly related to the SCI. Secondary conditions include pressure ulcers, UTIs, and even poor mental health [42].

Determining the Cause of Fever is More Problematic in SCI Patients

Another distinct feature in chronic SCI patients is the occurrence of fever. Fever arises frequently in SCI patients, and infectious causes are foremost, with UTIs and RTIs being the most common. Fever in these patients is considered an early sign of morbidity [43-48], and since other localizing symptoms are usually not found in these patients, it becomes even more important. Fever may also be the only manifestation [46], which highlights the difficulty in distinguishing the cause as infectious or non-infectious. Non-infectious causes may include adverse reaction to blood products, phlebitis [44], but also a fatal fever in acute cervical SCI with tetraplegia and high level injury paraplegics. This entity is also known as "quad fever or SCI fever", an idiopathic extreme increase in core body temperature caused by impaired thermoregulation from the SCI [45, 46, 49].

All the above points, plus the fact that SCI patients deteriorate rapidly if not treated promptly, underscore the importance of accurate diagnostic tools that will benefit them. And so this study was done to seek out, review and analyze the evidence on the use of the widely used biomarkers for inflammation/infection (ESR and CRP), and determine whether PCT has a role in the diagnosis of infections of the spine and infections in SCI patients.

METHODS

References were identified through PubMed using the terms *procalcitonin*, *spinal infections*, *spine*, *erythrocyte sedimentation rate*, *ESR*, *C-reactive protein*, *CRP, infection*. Additional studies were gathered from the references of the journal articles. Non-English journal articles were excluded.

Prospective and retrospective studies were primarily collected, but studies with other designs (such as review papers and a consensus statement) were included as they were found to be useful. The articles included in this traditional literature review (and some notable information about the studies) can be found in Tables **1-3**, and were focused on the use of ESR, CRP and PCT in spinal infections and infections in SCI patients.

PRESENT EVIDENCE ON THE USE OF ESR AND CRP

For Urinary Tract Infections in Spinal Cord Injury Patients

In a small study involving 16 acute SCI patients undergoing urinary catheter drainage, condom drainage and normal bladder function, a majority had elevated CRP levels on admission. Episodes of symptomatic bacteriuria/acute UTI were associated with very high CRP levels, ranging from 50-210 mg/L, and decreased significantly with antibiotic treatment, becoming normal in almost all cases within 14 days. In contrast, most episodes of asymptomatic bacteriuria were associated with CRP levels <10 mg/L, although some had levels >20 mg/L that fell to normal in the absence of antibiotic therapy within 14 days [50]. The study, though, was published in 1986, and the results have not been reproduced to the best of our knowledge.

Bacteriuria is very common in SCI patients. However, because of their sensory abnormalities, they do not present with usual UTI symptoms. Instead, they have back or abdominal discomfort, worsening spasticity, malaise, lethargy, or cloudy urine and/or change in odor of the urine [44, 51].

Osteomyelitis

In vertebral or spinal osteomyelitis, the authors of a comprehensive review stated that available data was difficult to generalize because of the different definitions of elevated

Table 1. Studies on ESR or CRP in relation to spinal infections & infections in spinal cord injury patients.

Paper	Type	Patients	Results	Comments/ Limitations
Serial concentrations of CRP as an indicator of urinary tract infection in patients with SCI (Galloway, *et al*., 1986).	Prospective	16 patients between September 1982 & May 1983	12 episodes of clinical UTI all had CRP>50 mg/L, & returned to normal after treatment. 96 episodes of asymptomatic bacteriuria had CRP<10 mg/L. 13 episodes of asymptomatic bacteriuria had CRP>20 mg/L, and only 3 of the 13 had CRP>50 mg/L.	Non-randomized study.
The prevention & management of urinary tract infections among people with spinal cord injuries (National Institute on Disability & Rehabilitation Research Consensus Statement, 1992).	Consensus Statement	N/A	N/A	Not a trial but deemed useful for this review paper
Review article: How useful are laboratory investigations in the ED evaluation of possible OM (Harris, *et al*., 2011)?	Review article	N/A	N/A	Not a trial but deemed useful for this review paper
Pyogenic vertebral OM: identification of microorganisms & laboratory markers used to predict clinical outcome (Yoon, *et al*., 2010).	Retrospective	45 cases with clinical diagnosis of hematogenous or post0operative non-TB OM between May 2003 & December 2007	Microorganism was identified in 75.6% of the cases. 10 cases in the negative-culture group were treated successfully without recurrence. Microorganism identification made no significant difference on treatment outcome, duration of antibiotic given or normalization of laboratory values.	Single institution.
Prospective evaluation of a clinical decision guideline to diagnose SEA in patients who present to the ED with spine pain (Davis, *et al*., 2011).	Prospective cohort analysis	55 patients with SEA in the 9-year control period & 31patients with SEA in the 5-year study period	Sensitivity & specificity of ESR in patients with risk factor: 100% & 67%, respectively. Receiver operating characteristic curve better for ESR than CRP.	Comparison was done with a historical cohort group. Single institution study. Some patients diagnosed to not have SEA did not undergo imaging.
Cervical pyogenic spinal infections: are they more severe diseases than infections in other vertebral locations (Urrutia, *et al.,* 2013)?	Retrospective	102 patients with pyogenic spinal infections during a 14-year period (between January 1999 & May 2013)	Cases with cervical pyogenic spinal infections had significantly more neurological involvement, needed more surgical treatment, & higher mortality rates. The percentages of ESR>30 mm/h & CRP>10 mg/L were not significantly different between cervical (elevated ESR in 89.5%; elevated CRPin 89.5%) and non-cervical infections (elevated ESR in 77.1%; elevated CRP in 88%).	Mortality rate in this study was higher than other published literature. Single institution study.
Spondylodiscitis (disc space infection)associate with negative microbiological tests: comparison of outcome of suspected disc space infections to documented non-tuberculous pyogenic discitis (Bhagat, *et al*., 2007).	Retrospective	69 patients diagnosed with discitis for the period 1995 to 2000.	Cases with positive culture were more likely to have fever, neurologic deficit and be dependent in terms of mobility. Mean CRP at presentation were 157 mg/L & 96 mg/L (significantly different), in the culture-positive & -negative groups, respectively. Mean ESR at presentation were 88 mm/h & 69 mm/h (significantly different) in the culture-positive & -negative groups, respectively.	Single institution study. 26 of the 69 patients were culture-negative.

Abbreviations: CRP - C-reactive protein; ED - Emergency Department; ESR - erythrocyte sedimentation rate; N/A - not applicable; OM - osteomyelitis; SCI - spinal cord injury; SEA - spinal epidural abscess; TB - tuberculosis; UTI - urinary tract infection; & - and.

Table 2. Summary of Data on CRP and/or ESR after spinal surgery.

Paper	Type	Patients	Results	Limitations
ESR and WBC counts after spinal surgery in early post-operative period (Kuhn MG, *et al*., 2012).	33-month retrospective study.	75 pts who had spinal instrumentation & fusion.	Peak ESR at POD 3 or 7 (1 pt had a peak at 1 month). Majority had high ESR at 1 and 3 months. WBC counts had similar trend.	Retrospective. No comparison to cohort that had infection. Small study.
Surgical site infection in spinal surgery: based on serial CRP (Kang B, *et al*., 2010).	8-month prospective study.	348 pts who had spinal surgery.	CRP peaked on POD 1 or 3. Mean CRP: 14.9 mg/L on POD 1 & 15.4 mg/L on POD 3. CRP normalized in less than half by POD 5. Half of pts with abnormal CRP were infection-related. ESR peaked in POD 5 on ave. CRP (>4.0 mg/L) for SSI: Sn 83.3%, (100% for early onset), Sp 96.8%. ESR (>9 mm/h in women & >15 mm/h in men) for SSI: Sn 100%, Sp 53.6%.	
Cervical spinal infections: more severe than in other vertebral locations? (Urrutia J, *et al*., 2013).	14-year retrospective study.	102 patients with pyogenic spinal infections.	Less than 1/5 had cervical infections. 89.7% had vertebral osteomyelitis and discitis. 68.4% had neurologic deficits. Significantly more of those with cervical infections had neurologic deficits, needed surgery & higher mortality. 89.5% had ESR>30 mm/h & CRP >10 mg/L.	Did not focus on inflammatory biomarkers. Descriptive study. Retrospective.
Normal range of inflammation-related laboratory findings & predictors of postoperative infection in spinal posterior fusion surgery (Lee J, *et al*., 2012).	99-month retrospective study.	608 pts who had spinal posterior fusion with pedicle screw fixation.	At POD 2-3, CRP, ESR, WBC & ANC were similar. Significant difference in ESR only in POD 12-14. CRP decreased significantly at POD 4-7, then increased again at POD 8-11. But CRP (>42.7 to 47.1 mg/L) & ANC (>5,898.5/uL) significantly higher starting POD 4 in group with infection, esp. at POD 8-11.	Retrospective.
Early-phase enhanced inflammatory reaction after spinal instrumentation surgery (Takahashi J, *et al*., 2001).	44-month prospective study.	73 pts who had spinal posterior decompression surgery without instrumentation or spinal posterior decompression & fusion surgery with instrumentation.	CRP rose more steeply in surgery with instrumentation. CRP peaked at POD 2, declined steeply & normalized in 4 weeks without instrumentation & still high in with instrumentation at 6 weeks. ESR similar to CRP behavior. ESR much higher in with instrumentation group at POD 42. 2^{nd} rise in CRP esp. a CRP on day 7>day 4 may be infection (WBC trend followed CRP, while ESR remained high after day 4)	
CRP after neurosurgery: prospective study (Al-Jabi Y, *et al*., 2009).	18-month prospective study.	100 pts who had neurosurgical procedures (including discectomy with laminectomy).	For post-operative infection, CRP trend (rising on POD 5): Sn 100%, Sp 93.1%; ESR trend (rising on POD 5): Sn 100%, Sp 57.5%. Higher CRP with severity of procedure. CRP peaked on POD 2. CRP higher in POD 5 *vs* POD 2 in 100% with infection (lower in without). ESR still increasing on POD 5, but more significant increase when with infection.	All the infections in this study occurred in non-spinal procedures (only in post-craniotomy patients).
Presentation, Incidence, Etiology, and Treatement of SSIs After Spinal Surgery (Pull ter Gunne AF, *et al*., 2010).	114-month retrospective study.	3,174 adult pts who had orthopedic spine surgery.	Wound drainage most frequent sign in SSI (67.9% in deep and 64.6% in superficial). CRP, ESR, WBC high in $\geq$94.4%. at diagnosis. CRP (>5.0 mg/L): Sn 96.8% for deep & 100% for superficial SSI; ESR (>30 mm/h): Sn 94.4% for deep & superficial SSI; WBC (>11,000/cu mm or <4,500/cu mm): 43.7% for deep & 57.9% for superficial SSI. Most common causative organism after deep & superficial spinal surgery: *S. aureus*.	Retrospective study. Some missing information from EMR. No Sp calculated.

(Table 2) contd…..

Paper	Type	Patients	Results	Limitations
CRP After Spinal Surgery (Mok JM, *et al*., 2008).	9-month prospective study.	149 pts who had spinal surgery.	CRP: post-operative peak 165.8 mg/dL (mean) on POD 2.68 (mean). ESR: post-operative peak 67.9 mm/h (mean) on POD 4.20 (mean). For predicting infectious complication, 2nd rise of CRP: Sn 53%, Sp 76%; ESR: 64%, Sp 72%.	Low number of pts who met inclusion criteria. Blood tests not daily. Exclusion of pts with diseases known to cause high CRP (but probably at higher risk for infection too).
CRP and leukocyte count after lumbar spine surgery: fusion *vs* nucleotomy (Kraft CN, *et al*., 2011).	4-year retrospective study.	1,320 pts who had spine surgery.	CRP peaked on POD 2-3 in the majority, then a rapid fall in all. Post-operative infections mostly showed a steady increase in CRP, usually with symptoms or deviation from normal trend. WBC count does not show typical and interpretable trend even if complication-free. Antibiotics did not influence CRP, WBC count profile.	Retrospective study.
Acute phase response in pts undergoing spinal surgery: modulation by perioperative naproxen and famotidine (Munoz M, *et al*., 2004).	Prospective study on consecutive pts.	40 pts who had elective instrumented spinal fusion.	Treatment group (received naproxen & famotidine) had lower post-operative temperatures, asked for less analgesics & tolerated them well. CRP significantly lower in treatment group.	Observational study. Small number of pts.
Comparison of post-operative CRP in minimally invasive & open lumbar fusion surgery (Houten JK, *et al*., 2011).	18-month prospective study.	74 pts who had lumbar fusion with instrumentation (minimally invasive or open surgery).	CRP significantly lower in minimally invasive surgery (13.5 mg/L *vs* 21.3 mg/L, p<0.01). Peak of CRP (mean): 2.9 days (no difference between groups)	Data collected according to protocol only in 40% because many had missing specimens (lack of rigid adherence). Small number of pts.

Abbreviations: ave. - average; BSI - bloodstream infection; CTD - connective tissue disease; esp. - especially; EMR - electronic medical record; FMF - familial Mediterranean fever; GI - gastrointestinal; IBD - inflammatory bowel disease; MI - myocardial infarction; OM - osteomyelitis; PCT - procalcitonin; PJI - prosthetic joint infection; POD - post-operative day; pt - patient; *S. aureus* - *Staphylococcus aureus*; SLE - systemic lupus erythematosus; SCI - spinal cord injury; Sn - sensitivity; Sp- specificity; SSI - surgical site infection; TIA - transient ischemic stroke; UTI - urinary tract infection; *vs* - *versus*; VTE - venous thromboembolism; 2nd - second; > - more or greater than.

values for ESR and CRP. "Elevated" ESR levels were seen from 82-90% of patients, but the range is a result of various cut-offs, including 30, 50 and 60 mm/h. The same was seen in CRP, wherein the levels were "high" in 63-100% of patients, but the cut-offs used were very variable (as low as 0.8, 30 to as high as 100 mg/L). The mean values of ESR ranged from 57-85 mm/h, and the mean value of CRP of 62 mg/L. Given the limitations inherent to the evidence, the authors proposed doing ESR and CRP together, stressing that a low level of suspicion for osteomyelitis and a normal ESR and low CRP (<5 mg/L) should be reassuring for the absence of osteomyelitis. On the contrary, low values for ESR and CRP do not rule out osteomyelitis in those who are highly suspected to have it, and that those with unexplained high levels of the biomarkers (especially, ESR>30mm/h and CRP>30mg/L) should undergo further work-up [52].

A retrospective study of 45 cases with pyogenic, non-tuberculous vertebral osteomyelitis revealed that in 75% of cases, a microorganism was isolated, with the largest proportion being *S. aureus* (20% methicillin-resistant *S. aureus* and 16% methicillin-susceptible *S. aureus*. ESR and CRP levels were not distinctly different between culture-positive and -negative groups when done on the 1st, 2nd and 3rd weeks of treatment. Even on the 4th week of treatment, when the predictive ability of treatment failure seemed best based on Receiver Operating Characteristic (ROC) curve analysis, the authors concluded that the absolute values of the two tests (ESR >50 mm/h with a sensitivity of 43%/specificity 87% and CRP 28 mg/L with sensitivity of 71%/specificity 87%) cannot be used to predict cure or recurrence of infection, but they can contribute to the overall assessment of treatment response [53].

In Spinal Epidural Abscess

In adults, ESR and CRP have been used as part of a decision guideline for Emergency Department (ED) diagnosis of spinal epidural abscesses, after eliciting spine pain, non-progressing neurologic deficits, or radicular pain. The study found that elevated ESR (>20 mm/h) appeared better than elevated CRP (>10 mg/L), *via* ROC curve analysis, with an area under the curve of 0.96 for ESR, and just 0.81 for CRP, but showed that they were both highly specific and moderately specific, respectively, for diagnosis [54]. This underscores the superiority of ESR over CRP in non-acute conditions, such as spinal epidural abscess.

For Pyogenic Spinal Infections

A retrospective study on 102 patients with pyogenic spinal infections showed that the majority had vertebral osteomyelitis with adjacent discitis. Sixty three percent showed one-segment involvement, and that cervical involvement, particularly, C5-C6 was most common. In those with cervical pyogenic spinal infections, neurologic abnormalities were more frequently found, and the need for surgery was almost 2 times more frequent. In these patients,

Table 3. Summary of data on procalcitonin in spinal/skeletal infections with or without CRP and/or ESR.

Paper	Type	Patients	Results	Limitations
PCT a sensitive & specific marker in diagnosis of septic arthritis and acute osteomyelitis (Maharajan K, *et al*., 2013).	18-month prospective study.	82 pts (adults & pediatric) with suspected acute osteomyelitis & septic arthritis.	PCT for differentiating confirmed pyogenic from presumed & non-infective cases at cut-off of 0.04 ng/mL: Sn 85.2%, Sp 87.3%; *vs* traditional cut-off 0.5 ng/mL: Sn 66.7%, Sp 91%.	Low sample size. Unknown if acute osteomyelitis cases included vertebral osteomyelitis. Not specific for spinal/vertebral infections.
PCT for differentiation of infectious & non-infectious fever after orthopedic surgery (Hunziker S, *et al*., 2010).	17-month prospective, observational study.	103 post-orthopedic surgery patients with new-onset fever.	PCT for infection on days 1 (& 3) of fever had best results. At cut-off 0.1 ng/mL: Sn 91% (85%), Sp 16% (32%); Sp 16%; at cut-off 0.25 ng/mL: Sn 66% (62%), Sp 47% (85%); at cut-off 0.5 ng/mL: Sn 47%, (31%), Sp 76% (91%); at cut-off 1.0 ng/mL: Sn 38% (23%), Sp 91% (91%). CRP & WBC did not correlate well with underlying infections	Observational design. Moderate sample size so study had limited power. Various surgical procedures (includes spine surgery) and types of infections analyzed. Not specific for spinal/vertebral infections.
Comparison of CRP & PCT after spine surgery (Chung YG, *et al*., 2011).	12-month retrospective study.	103 patients who had elective spine surgery.	PCT peaked (mean: 0.17 ng/mL) at POD 1>POD 3 & dropped below 0.05 ng/mL by POD 5 (except for 2 pts). CRP peaked (mean: 26.7 mg/L) at POD 3 (except underweight pts) & not normal at POD 5. ESR still increasing on POD 5 (mean: 14.32 mm/h).	Not case-controlled study. Sn & Sp not calculated. Relatively low sample size. Short follow-up. Antibiotics given until POD 4.
Dynamics of PCT in pts after major major neurosurgery (Laifer G, *et al*. 2005).	5-month prospective study.	50 pts who had major neurosurgery.	After major neurosurgery, PCT remained <o.2 ng/mL *vs* WBC count, ANC, CRP, which peaked on POD 1.	Not a specific study for spinal/vertebral infections. Small study.
PCT for the diagnosis and follow-up of post-operative infections (Yasmin D, *et al*., 2006).	8-month retrospective study.	21 pertrochanteric hip fractures who had surgery.	PCT for systemic complications at cut-off 0.5 ng/ mL: Sn 100%, Sp 100% at POD 1 and Sn 100%, Sp 50% at POD 2. PCT peaks at POD 1; low at POD 5. CRP peaks at POD 2; low at POD 21. ESR low at POD 43.	Only on pertrochanteric hip fractures and did not include spinal/vertebral fractures. Small study so insufficient statistical power.
PCT as early predictor of post-operative infections in pts with acute SCI (Nie H, *et al*., 2011).	33-month prospective, non-randomized study.	339 acute SCI patients who had surgery.	PCT for post-operative infections at cut-off 0.1 ng/mL: Sn 92%, Sp 32%, at cut-off 0.5 ng/mL: Sn 88%, Sp 74%, at cut-off 2.0 ng/mL: Sn 23%, Sp 94%.. Lower Sn & Sp of CRP at all cut-off values.	Markers taken once after surgery. Some infections that did not meet criteria were not included. "Relatively small" study.

Abbreviations: ave. - average; BSI - bloodstream infection; CTD - connective tissue disease; esp. - especially; EMR - electronic medical record; FMF - familial Mediterranean fever; GI - gastrointestinal; IBD - inflammatory bowel disease; MI - myocardial infarction; OM - osteomyelitis; PCT - procalcitonin; PJI - prosthetic joint infection; POD - post-operative day; pt - patient; *S. aureus* - *Staphylococcus aureus*; SLE - systemic lupus erythematosus; SCI - spinal cord injury; Sn - sensitivity; Sp- specificity; SSI - surgical site infection; TIA - transient ischemic stroke; UTI - urinary tract infection; *vs* - *versus*; VTE - venous thromboembolism; 2nd - second; > - more than.

mortality was almost 6 times higher than those with non-cervical pyogenic spinal infections. Data on ESR and CRP was limited to reports stating that 90% of patients had ESR levels >30 mm/h and CRP >10 mg/L [55]. In this group, these biomarkers act only as supportive evidence or additional clues in the diagnosis, which will be made using imaging, followed by cultures.

In Spondylodiscitis

Sixty-nine cases of spondylodiscitis were retrospectively studied, and 62% were culture-positive. Fever was found more often (2 times more frequently) in the culture-positive patients, as well as neurologic deficits and being mobility-dependent (3 times more). *S. aureus* was the most common microbiologic cause that was isolated, then streptococci, followed closely by coagulase negative staphylococci, then *Escherichia coli*, with one case that grew *Bacteroides fragilis*. Significantly more CRP and ESR elevations were present in those with positive-cultures, with CRP attaining a much better correlation with positive microbiology than ESR. Mean CRP in the culture-positive group was 157 mg/L (range: 22-400 mg/L) which was much higher than the culture-negative group with a mean CRP of 96 mg/L (range: 23-280 mg/L). Mean ESR in the culture-positive group was 88 mm/h, while in the culture-negative group, the mean was 69 mm/h (range: 30-127 mm/h). The authors theorized that the lower ESR and CRP levels, and the poorer correlation of the biomarkers in culture-negative patients, may be due to these cases being localized infective processes without bacteremia [56].

As Markers for Post-Spine Surgery Infections

CRP as a screening test for post-operative infections after neurosurgery (including craniotomies, brain biopsy and discectomies) was studied. CRP levels after discectomy first peaked on day 2, on average, with mean values of around 102 to 138 mg/L. A second rise after the first peak of CRP was 100% sensitive and 93% specific in the early detection of post-operative infections [57]. Another study on early infection after micro-discectomy, produced very similar sensitivity and specificity values. The studies agree that CRP can be a useful marker for post-spine surgery infections [58, 59].

A retrospective study of 132 patients focused on surgical site infections after spine surgeries, including discectomy, decompression, uninstrumented fusion, osteotomy and hardware removal. CRP (mean: 116 mg/L) and ESR (mean: 77 mm/h) were elevated in 98% and 94% of patients, respectively. CRP was more useful than ESR since the former had already normalized by day 15 after the operation, while ESR was still peaking, particularly in spine fusion patients. The study provided good insight into the microbiology of post-spine surgery infections. Most of the surgical site infections yielded a positive culture (78%), with 73% monomicrobial and the rest polymicrobial. Over 90% were Gram-positive bacteria, with *S. aureus* making up 72% (of which 17% were methicillin-resistant), followed by *Enterococcus faecalis*, then *E. coli*. Based on presentation, ESR, CRP, imaging and cultures, patients who had surgical site infections ended up receiving antibiotic treatment for an average of 33 days, with deeper infections getting treated longer (mean of 41 days, *versus* 20 days for superficial infections). Surgical debridement was done in almost 90% of deep infections, with primary retention of spinal hardware in 73%. Lastly, majority of the patients that needed surgical intervention needed just one procedure, and 33% did not require surgery at all [57].

Another retrospective study of 347 post-spine surgery (fusion and nucleotomy) patients showed similar results for CRP, peaking at days 2-3 after surgery, rapidly falling at days 4-6, before reaching near normal levels at days 10-14 [60].

A retrospective study on 608 patients who had spinal posterior fusion with pedicle screw fixation was done, checking different markers prior to the operation, 2-3 days after the operation, then 4-7 days, 8-11 days, and 12-14 days post-surgery. Patients were subdivided into groups according to the number of levels of fusion (one-, two-, multi-level), and compared to the group that had post-operative infections. The non-infection groups displayed peaks for CRP, WBC count and absolute neutrophil count (ANC) on days 2-3 after the operation, while ESR levels peaked later at days 4-7. The infection group also showed peaking of the different markers before progressively decreasing, except for ESR and CRP. ESR did not have a peak, and just continually increased until days 12-14. CRP showed an initial peak, but after that, progressively increased instead of decreasing. The problem with ESR was that there was no significant difference between values in the infection and the non-infection groups. In contrast, the presence of infection led to much higher CRP levels, in addition to the distinct upward trend already described. These findings pointed to CRP as the superior indicator for infection, especially when levels are high and rise after post-operative day 7 [61].

A prospective study of 149 patients showed less impressive findings, but agreed that CRP is much more sensitive than ESR in detecting post-operative infections after spine surgery. CRP was shown to peak, on average, at days 2-3 after the operation, and ESR on day 4. Mean level for CRP was 165 mg/L and for ESR, 68 mm/h. The sensitivity and specificity for CRP were 53% and 76%, respectively, while for ESR, the values were 64% and 72%, respectively. These appear to be similar numbers, but because CRP decreases much earlier than ESR, a second CRP peak or a deviation from its normal downward trend can be useful in detecting infection in 78% of patients, compared to only 48% if ESR is used, because ESR declines to normal much later, sometimes remaining elevated up to a year post-surgery [62-64].

Another prospective study on 73 patients who had spinal decompression surgery without instrumentation or spinal posterior decompression and fusion surgery with instrumentation demonstrated that CRP values do peak on day 2 post-surgery, decreasing on day 4, but with post-operative infections, increased again on day 7. The authors recommended that a post-operative CRP be done between days 4-7, for the early detection of infection. Another notable finding was that the use of implants in spinal surgery was seen to enhance the acute inflammatory response immediately after the operation, as indicated by the distinctly higher levels of CRP and ESR in those who had instrumentation, although they still progressively declined over time [65].

Another prospective study on 348 patients who had spinal surgery (single- and multi-level decompression, and surgery with implantation) were followed with serial CRP and ESR done on days 1, 3, 5 and 7 after surgery. Compared to the other studies, the CRP peak was recorded on either day 1 or 3. Forty three percent of the patients' CRP levels normalized in 5 days. Sixteen patients showed an abnormal CRP trend which included a rise after the initial peak. But only 50% were diagnosed with infections, 62% of which were related to the surgery. The sensitivity and specificity of CRP that was computed as a predictor for surgical site infection were 83% and 97%, respectively. But for early wound infections, sensitivity and specificity of CRP were much better at 100% and 97%. In contrast, ESR sensitivity and specificity were 100% and 54%. But, ESR response after surgery was slow and inconsistent. Therefore, the authors considered a negative CRP value on day 5 enough to rule out a post-operative infection after short-segment decompression, and additional CRP testing on day 7 for more extensive surgeries [66].

A prospective study on 89 patients looked at the post-operative values of CRP to see if there was a difference between those who undergo open lumbar fusion surgery *versus* minimally invasive spinal surgery. The mean CRP peak level of those who had the minimally invasive procedures was much lower compared to the peak from the open and more invasive procedures, supporting the knowledge that CRP is dependent on the amount of tissue destruction-mediated inflammation that is associated with surgery [67].

There is prospective, observational evidence though that CRP levels are affected by medications, particularly the combination of naproxen and famotidine, which caused a decrease in CRP levels when post-lumbar spinal surgery patients were pre-treated with those medications. In contrast, other investigations that also included spinal surgery patients reported that post-operative CRP levels are not affected by the administration of non-steroidal anti-inflammatory drugs (NSAIDs) [68-71].

So far, we have seen that CRP performs better than ESR in post-spine surgery cases. One prospective study looked at ESR before and after (days 3 and 7, and then 1 and 3 months) spinal instrumentation and fusion in pediatric patients. ESR peaked variably, with 54% at day 3, and 43% at day 7 after the operation. ESR rapidly increases a within the first week after surgery before returning to normal. The problem was that the return to normal levels was slow in the non-infected group, with 78% still elevated at 1 month and 53% still high at 3 months post-operatively. This makes ESR much less useful than CRP in the detection of early infections post-surgery. In fact, the authors felt that WBC count may even be more useful [72]. But most researchers consider WBC count to be unreliable in the detection of surgical site infections because it may continue to be normal even when surgical site infections are present, and may be elevated in the early post-operative period even in the absence of infection [73].

PRESENT EVIDENCE ON THE USE OF PROCALCITONIN

Procalcitonin's role in the discrimination of infectious from non-infectious causes of fever has been reviewed. Procalcitonin generally displays elevated levels, much like CRP, in bacterial infections. Unlike CRP, PCT does not rise in autoimmune systemic diseases, inflammatory bowel diseases, malignancies and auto-inflammatory diseases, such as familial Mediterranean fever, tumor necrosis factor receptor superfamily 1A-associated periodic syndrome. The only exception is Still's disease where PCT was found to be high. But in general, elevated PCT levels enable the identification of bacterial infections [1].

Most studies on PCT's use in spinal infections have so far been limited to post-spine surgery cases. A number of studies have also looked at its usefulness in acute osteomyelitis and septic arthritis in both pediatric patients and adults, but the osteomyelitis cases could not be optimally analyzed for this review because the individual papers did not separate vertebral or spinal osteomyelitis from others.

Procalcitonin in Osteomyelitis: Limited data

An 18-month prospective study of all age groups (82 pediatric and adult patients) with acute osteomyelitis and septic arthritis was done and the authors calculated the sensitivity and specificity of PCT using a cut-off of 0.4 ng/mL. In distinguishing confirmed pyogenic (27 patients) from presumed-pyogenic (21 patients)/non-pyogenic (34 patients) infections, the sensitivity and specificity of PCT were 85% and 87%, respectively. In the discrimination of confirmed-presumed pyogenic from non-pyogenic infections, PCT's sensitivity was 62.5% and its specificity was 100%, while in the diagnosis of confirmed pyogenic from non-pyogenic infections, PCT was 85% sensitive and 100% specific. The authors demonstrated that a cut-off of 0.4 ng/mL for PCT optimized its sensitivity and specificity, *versus* 0.25 ng/mL which made it sensitive but non-specific, and 0.5 ng/mL which made it specific but poorly sensitive [74].

Procalcitonin After Spine Surgery: More Data

A prospective evaluation of 103 adults who developed fever post-orthopedic surgery (including 7 post-spine surgery cases) supported the moderate diagnostic accuracy of PCT in identifying an underlying infection, demonstrating that PCT levels were significantly higher in those with infections on days 0, 1 and 3 of the new-onset fever than those without infections. Sensitivity increased the lower the cut-off, reaching 89%, 91% and 85% when the cut-off of 0.1 ng/mL was used on days 0, 1, and 3, respectively. Specificity was 91% on the same days using a cut-off of 1.0 ng/mL, and using a cut-off of 0.5 ng/mL on a test done on day 3, although specificity was poorer (71% and 76% on days 0 and 1) with the lower cut-off value. The authors reported that CRP and WBC count did not correlate well with infection, and so recommended that in febrile post-orthopedic surgery patients, antibiotics may be withheld if a PCT is <0.1 ng/mL, and started for a value >0.5 ng/mL, stressing that the test would be helpful in differentiating infectious from non-infectious causes of fever in these patients [75].

A retrospective study on 103 patients characterized the trend of PCT and CRP after spine surgery. PCT generally peaked one day after surgery, and values never reached 0.1 ng/dL, except in diabetics. Also, 40 to 60 year old patients, females, hypertensives, and those with short operation times (<2 h) generally had peak PCT levels at 3 days after surgery. By day 5, PCT had gone down substantially (except for 2 patients). CRP levels generally peaked on day 3, except in underweight patients (<18.5 kg/m^2) who continued to show increasing levels on day 5. In general, CRP levels had not even dropped to half on day 5 [76]. Given the physiologic trend of PCT, with peak at day 1 and dropping significantly by day 3, it appears that the best time to use PCT in suspected post-operative infection cases would be at or 3 days after the surgery.

Similarly, a prospective study on 50 patients who had major neurosurgery (including resection of glioma, meningoma, metastases, adenoma, hemangioma, astrocytoma, aneurysm clipping, and decompression) found that after major "neuro"-surgery (where spine surgery technically falls under), PCT did not increase above 0.2 ng/mL, and so the authors proposed that levels above higher than that in post-neurosurgery may be used in the detection of bacterial infections [21].

A study on the utility of PCT in diagnosing post-operative complications after fracture surgery for pertrochanteric hip fractures (21 patients) showed that no patient developed a post-operative infection, although some got infectious complications unrelated to the surgery itself, such as upper respiratory tract infection and urinary tract infection. In this study, PCT peaked 1 day after the operation, but remained within normal limits, rapidly declined, and returned to pre-operative levels on day 5. Local wound complications like non-infected decubitus ulcers did not significantly affect PCT levels, in contrast to systemic

complications which had substantially higher levels. Notably, the sensitivity and specificity of PCT using a cut-off of ≥0.5 ng/mL were 100% and 100%, respectively, but specificity decreased to 50% when PCT was done on day 2 after the operation. These features were superior to CRP, since the latter was greatly very affected by the trauma to the surgery, as evidenced by its five-fold increase from pre-operative values, peaking at day 2, and decreasing very slowly (since levels were still four-fold higher at day 5), thereby reflecting the slower response of CRP to inflammation. The authors concluded that PCT was superior to CRP and ESR [77]. These data did not come from post-spine surgery patients, but spine surgery basically involves bone manipulation, which is very similar to what these patients underwent. Plus, the normal trend of PCT levels after operation were very similar to those from the earlier study that was done on post-spine surgery patients.

Fortunately, PCT has been studied as a predictor of post-operative infections in acute traumatic SCI. Three hundred thirty-nine patients were followed prospectively, and data showed that those who developed post-operative infections had significantly higher PCT and CRP levels than those without infections. ESR and WBC count levels did not differ between groups. PCT outperformed CRP in terms of sensitivity and specificity even with the different cut-offs (0.1, 0.5 and 2.0 ng/mL). Similar to the other studies, lower cut-off values such as 0.1 ng/mL for PCT yielded a sensitivity of 92% and specificity of 32%. At a 0.5 ng/mL cut-off, sensitivity was less at 88%, and specificity became 74%, although specificity improved to 94% with a cut-off of 2.0 ng/mL. This was a study on SCI patients who had spine surgery that clearly showed PCT's reliability and accuracy in predicting early post-operative infections compared to CRP and other inflammatory markers [78].

Procalcitonin: A Tool for Antibiotic Stewardship

We found no studies looking into the usefulness of PCT in antibiotic stewardship in spinal infections and SCI patients with infections. We feel that it should be studied more for this indication than for diagnosis, especially in places with slow turn-around times. It could prove to be a useful guide in discontinuing antibiotics at a more "proper" and evidence-based time, especially in chronic infections being treated with long term antibiotics. If PCT-guided antibiotic therapy in intensive care unit (ICU) patients with sepsis, severe sepsis and septic shock was deemed safe [79-81], then it must be more feasible to do a similar study on more stable patients.

CONCLUSION/RECOMMENDATIONS

This is the first review of ESR, CRP and PCT and their application in diagnosing infections of the spine and infections in patients with SCI. After reviewing the evidence, it should be stressed that these biomarkers have their uses in various but specific medical conditions.

It is best to remember that SCI patients are a unique group of patients that are in a chronic state of inflammation. Their CRP level can be as high as 38 mg/L in those with decubitus ulcers or indwelling urinary catheter, although most will have a level of around 3 mg/L. When they develop infection, they may present atypically. On the other hand, they may present solely with fever, which may or may not be infectious in nature.

In SCI patients, distinguishing asymptomatic bacteriuria from a true UTI may be accomplished by demonstrating a CRP >50 mg/L, which may support the latter diagnosis (although this has not been reproduced). A repeat CRP at day 14 may be considered if there is a question of response to therapy, since most patients' CRP levels normalize with effective antibiotics at this time.

In chronic osteomyelitis and spinal epidural abscess, ESR appears superior at a cut-off of >30 mm/h for the former, and >20 mm/h for the latter. In spondylodiscitis, a positive culture is associated with significantly higher CRP levels (range: 22-400 mg/L), and correlate better than elevated ESR levels (range: 30-127 mm/h). In chronic osteomyelitis, CRP levels are usually >10-30 mg/L. Given the variations, it is still preferred to do both ESR and CRP in chronic bone and spinal infections.

PCT is best used in stable and chronic patients, in whom physicians can afford to wait on starting treatment, and in whom infected sites are inaccessible for biopsy. A serum PCT of ≥0.4 ng/mL was reported to be 100% specific in the diagnosis of acute osteomyelitis, but evidence is limited and lacking in chronic osteomyelitis. Whether that value can be used as a decision tool to start antibiotics in stable patients who have not received antibiotics would be a good subject for research. Once antibiotics are started, PCT levels would be expected to decrease, but there appears to be no long term data as to the trend of PCT while on antibiotic therapy in chronic infections, and as already mentioned, whether there is a particular cut-off when antibiotics can be stopped.

In post-spine surgery patients, PCT should be used when post-operative infections are suspected, including patients who had acute traumatic SCI and had surgery. PCT is superior to CRP because it normally does not rise too high, and certainly not higher than 0.2 ng/mL, even after major neurosurgery. PCT of >0.5 ng/mL is reasonable evidence to start antibiotics and further investigation, while a PCT of <0.1 ng/mL would be reassuring to physicians that the patient is likely infection-free. A PCT between 0.2 and 0.5 ng/mL should be an indication to watch the patient closely, to see if there is a need to do work up for post-operative infection.

When PCT is used, it should be remembered that diabetics can have peaks that reach 0.1 ng/mL (in contrast to non-diabetics) after surgery, and that females, hypertensives, those with short (<2 hour) operation times, and those within the 40-60 year old age group can have later peaks of around 3 days (*versus* the usual 1 day) after the operation.

CRP is inferior to PCT in diagnosing post-spine surgery infections, but it may be used in place of PCT when cost is an issue or when PCT is unavailable. It should be kept in mind that CRP is affected by the amount of tissue damage related to the surgery, and possible pre-treatment with non-steroidal anti-inflammatory drugs (with or without an H2 blocker). When using CRP, infection can be detected by looking for a second rise in CRP level, after the initial peak that generally occurs on day 2 to 3 after the surgery. It is useful to know that underweight individuals can continue to have increasing CRP levels at day 5 after surgery.

To end, ESR, CRP and PCT, plus the evidence on these inflammatory biomarkers in spinal infections and SCI patients were reviewed, and these biomarkers have specific places of use in certain clinical conditions. These tests will never be gold standards, and they need to be used in conjunction with clinical history and physical examination, cultures, pathology or imaging. But these biomarkers are available, and some of them are being widely used.

This review examined the available evidence on ESR, CRP and PCT in spinal infections and infections in patients with SCI in order to come up with recommendations to guide clinicians on the best way to use these tests, despite their limitations, and to highlight further areas of research.

KEY ISSUES

- ESR, CRP and PCT as markers of infection have their uses in various but specific medical conditions.
- SCI patients are unique because they are in a chronic state of inflammation (CRP levels can be as high as 38 mg/L, although most will be around 3 mg/L); SCI patients with infection may present atypically; SCI patients may present with fever alone, and the cause may be infectious or non-infectious.
- In SCI patients, CRP >50 mg/L may support the diagnosis of true UTI.
- In chronic infections of the spine/vertebrae, ESR is superior for diagnosis (with a cut-off of >30 mm/h; >20 mm/h for spinal epidural abscess), although it is still preferred to do both ESR and CRP (the latter using a cut-off of >10-30 mg/L).
- Serum PCT of $\geq$0.4 ng/mL was reported to be 100% specific in diagnosing acute osteomyelitis, but based on limited data (no study on chronic osteomyelitis).
- In post-spine surgery patients, PCT is superior to CRP because it does not rise too high, and not higher than 0.2 ng/mL, even after major neurosurgery.
- PCT of >0.5 ng/mL would be adequate reason to start antibiotics and further investigation, while a PCT of <0.1 ng/mL would suggest absence of infection.
- CRP is inferior to PCT in diagnosing post-spine surgery infections, but it may be used when cost is an issue or when PCT is unavailable.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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