Serum C-reactive protein and WBC count in conservatively and operatively managed bacterial spondylodiscitis

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Abstract
Purpose: C-reactive protein (CRP) and white blood cell (WBC) count are routine blood chemistry parameters in monitoring infection. Little is known about the natural history of their serum levels in conservative and operative spondylodiscitis treatment. Methods: Pre- and postoperative serum levels of CRP and WBC count in 145 patients with spondylodiscitis were retrospectively assessed. One hundred and four patients were treated by debridement, spondylodesis, and an antibiotic regime, 41 only with a brace and antibiotics. The results of the surgical group were compared to 156 patients fused for degenerative disc disease (DDD). Results: Surgery had a significant effect on peak postoperative CRP levels. In surgically managed patients, CRP peaked at 2–3 days after surgery (spondylodiscitis: pre-OP: 90 mg/dl vs. post-OP days 2–3: 146 mg/dl; DDD: 9 mg/dl vs. 141 mg/dl; \( p < 0.001 \)), followed by a sharp decline. Although values were higher for spondylodiscitis patients, dynamics of CRP values were similar in both groups. Nonoperative treatment showed a slower decline. Surgically managed spondylodiscitis showed a higher success rate in identifying bacteria. Specific antibiotic treatment led to a more predictable decline of CRP values. WBC did not show an interpretable profile. Conclusion: CRP is a predictable serum parameter in patients with spondylodiscitis. WBC count is unspecific. Initial CRP increase after surgery is of little value in monitoring infection. A preoperative CRP value, and control once during the first 3 days after surgery is sufficient. Closer monitoring should then be continued. Should a decline not be observed, therapy needs to be scrutinized, antibiotic treatment reassessed, and concomitant infection contemplated.

Keywords
antibiotics, conservative treatment, CRP, spondylodesis, spondylodiscitis, surgical management, WBC count

Introduction
The acute-phase protein C-reactive protein (CRP) first described by Tillett and Francis¹ is an acknowledged serum marker of infections and has been shown to be a feasible parameter for detecting and monitoring infections and systemic inflammatory response syndromes.²,³ Due to its rapid postoperative normalization and moderate costs, CRP has gained widespread acceptance for diagnosis of bacterial infection. Serial CRP measurements are known to be useful not only as a diagnostic tool for infection but also for monitoring the effect of treatment and for detection of relapse.⁴,⁵

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Early detection and treatment of spinal infections greatly improve results and outcome. Yet because clinical signs of acute infection can overlap with unspecific inflammatory tissue reactions related to a surgical procedure, monitoring of infection, especially after spine surgery for spondylodiscitis, can be difficult. Numerous plasma parameters have been used in monitoring spondylodiscitis. These range from simple and inexpensive tests such as erythrocyte sedimentation rate (ESR) to the very complex determination of soluble biomarkers of inflammatory response, such as quantification of cytokines, among others IL-6, procalcitonin, or triggering receptor expressed on myeloid cells (TREM)-1. While the exact value of ESR as an early detector of persistent infection is disputable, latter methods are complicated from an interpretational point. Furthermore, apart from being costly, they are not always available.

All surgical procedures, including complication-free management of the spine, influence serum inflammatory parameters. Kraft et al. could show a “physiological” temporary rise in CRP in nonseptic lumbar spinal surgery within the first 3 days, after which values gradually return to normal. Yet little is known about the dynamics of CRP and white blood cell (WBC) count in patients treated for spondylodiscitis. We therefore examined CRP and WBC count in operatively and nonoperatively managed spondylodiscitis and compared the results to patients surgically treated for degenerative disc disease (DDD).

### Materials and methods

#### Patients

We retrospectively assessed 145 patients diagnosed with spondylodiscitis in the years of 2013–2017 in our tertiary academic teaching hospital. Demographic data are presented in Table 1. All patients were diagnosed with spondylodiscitis by means of conventional X-ray and contrast-enhanced gadolinium MRI. One hundred and four patients (mean age 66; range 25–90) were surgically managed by means of local debridement, single or double level spondylodesis and a postoperative antibiotic regime. Forty-one patients (mean age 65; range 16–86) were treated conservatively, only with an orthosis (brace) and antibiotics. Antibiotic treatment in both patient groups was initially given intravenously over 2 weeks. Where possible, this was then given orally. An antibiotic treatment regime of at least 6 weeks was always followed. In some cases, depending on microbiological findings and blood chemistry response, this was continued for up to 12 weeks.

Exclusion criteria were any type of neurologic impairment, necessity for revision surgery, superficial or deep wound infection, evidence of further bacterial infection (i.e. endocarditis, pulmonary, or urinary tract infection), or significant further nonorthopaedic complications, such as cardiac decompensation or sudden onset renal decompensation, which may have an added effect on CRP values and enhanced the confounding bias. Only patients who were dismissed to rehabilitation and outpatient treatment were included in the study. Patients initially treated conservatively with secondary transition to surgical management were excluded from the study.

To evaluate the influence of surgical trauma on the CRP and WBC dynamics, 156 nonspondylodiscitis patients, receiving mono- or bi-level lumbar fusion surgery for DDD with a screw/rod system and intervertebral cage implantation acted as a control group.

#### Table 1. Demographic data.

|                | Average (minimum–maximum/median) (years) | Gender (Female/Male) | Localization* (%) |
|----------------|------------------------------------------|----------------------|-------------------|
| Spondylodiscitis (n = 145) | 66.5 (16–90/79) | 60/85 | 15.86% (n = 23) | 29.65% (n = 43) | 63.45% (n = 92) |
| DDD (n = 156) | 54.8 (16-83/59) | 76/80 | N/A | N/A | 100% |
| Spondylodiscitis | | | | | |
| Conservative therapy* (n = 41) | 65.4 (16–86/69) | 15/26 | 24.39% (n = 10) | 26.82% (n = 11) | 60.97% (n = 25) |
| Surgical management* (n = 104) | 66.9 (25–90/69) | 46/58 | 12.50% (n = 13) | 30.76% (n = 32) | 64.42% (n = 67) |

DDD: Degenerative disc disease.

*Thirteen patients had affection of two areas of the spine. Of these, five were treated conservatively, eight were surgically managed at both sites.

Blood chemistry parameters

We evaluated the CRP and WBC count kinetics during therapy. In all patients, blood specimens were obtained on admission to hospital. For surgically treated patients, this was mostly the day prior to surgery (n = 101). In 31 cases, surgery was performed on the day of admission, due to epidural empyema. Baseline presurgery blood chemistry was also always available in these patients. Further blood chemistry controls in all patients were performed after starting specific spondylodiscitis therapy. As this was not always performed on identical days in all patients, we assessed values on days 2 or 3, 4–7, 8–14, 15–21, and 22–28 days, so as to get comparable results.
Comorbidity as well as the American Society for Anesthesiology (ASA) score, physical examination, and antibiotic regime were correlated to blood chemistry findings. We also evaluated the region of spinal surgery and microbiological findings. In surgically managed patients, microbiological assessment was done on six intraoperatively gained tissue specimens, swabs, and aspiration of local fluid. In all patients, independent of the treatment method, blood cultures were obtained on the day of hospital admission and on the consecutive day.

Statistical analyses

Distribution of categorical and ordinal data were described by relative prevalence. We used the Shapiro–Wilk test to describe the spread of metric variables of independent groups, hereby assessing whether the random sample survey had a normal distribution. Provided the assumption of normal distribution was not declined (p value ≤ 0.1), comparison was performed using the t-test. If the assumption of normal distribution was declined, the Mann–Whitney U test was used. The context of two categorical variables was examined using the Fisher’s exact test. Due to the explorative character of this study, all p values are descriptive.

Results

Localization of spondylodiscitis and patient comorbidity

In 63.5% (n = 92), the lumbar spine was the primary area of manifestation, followed by the thoracic (29.7%; n = 43) and the cervical spine (15.9%; n = 23). Only 5% of patients had an affection of the sacrum (Table 1). In 13 patients (9.0%), we found a simultaneous manifestation in two areas of the spine. The most prevalent comorbidity was arterial hypertension in 46.2% (n = 67). Moreover, 27.5% (n = 40) of all patients had a known history of diabetes mellitus, and 26.2% (n = 38) a history of malignancy. Renal insufficiency with the necessity of dialysis therapy was found in 10.3% (n = 15). Occasionally, obesity was an issue, yet did not predominate. The mean body mass index of patients was 26.4 kg/m².

Microbiological findings

In only 58.6% (n = 85) of all patients, microbiological culturing was successful. In surgically treated cases, we had positive findings in 67.3% (70/104), whereas in conservative cases, positive findings were found only in 36.5% (15/41). In cases where bacteria were isolated, we found Staphylococci in 76.5%, followed by Gram-negative bacteria in 12.9% and Enterococci in 12.9%. In rare cases, patients showed more than one bacteria (9.4%). In all cases, we performed microbiological and immunological assays to rule out tuberculous spondylodiscitis. Histological workup of specimens obtained from all surgical cases and some conservatively managed patients did not show granulomas or signs of caseous necrosis.

CRP kinetics in surgically managed patients

The preoperative mean value of CRP of surgically managed patients was 90.2 mg/l (6.1–492.2 mg/l). Independent of the spondylodiscitis localization, mean values increased to 106.8 mg/l (16.7–394.4 mg/l) the first day after surgical treatment and peaked between days 2 and 3 with 146.2 mg/l (36.1–484.0 mg/l). Mean values then decreased between days 4 and 7 to an average of 103.7 mg/l (Table 2). Between days 8 and 14, we observed a further decrease of values below preoperative CRP levels (mean: 69.9 mg/l (0.9–361.4 mg/l)).
Interestingly, CRP values of surgically treated patients with lumbar spondylodiscitis ($n = 60$) and those of patients with lumbar DDD ($n = 156$) showed a similar course (Table 3). The preoperative mean CRP value of latter patients was 9.0 mg/l and increased the first day after operation to 73.3 mg/l. Peak CRP values were reached between days 2 and 3 after surgery. Maximum average CRP values increased up to 141.1 mg/l and reached comparable values of spondylodiscitis patients on days 2–3 after surgery (144.6 mg/l). Four to seven days postoperatively average CRP values of DDD patients noticeably declined to 58.9 mg/l, while mean values of spondylodiscitis patients remained comparatively high with 109.7 mg/l (Figure 1).

| Days | Therapy | Mean | SD | Minimum | 25% Percentile | Median | 75% Percentile | Maximum | $p$ value<sup>a</sup> |
|------|---------|------|----|---------|---------------|--------|---------------|---------|----------------|
| −3, −2, −1 | DDD 156 | 9.01 | 16.28 | 0.2 | 1.8 | 3.5 | 8.0 | 125.0 | <0.001 |
| | Spondylodiscitis | 46 | 8049 | 98.38 | 0.7 | 17.5 | 41.6 | 85.9 | 428.4 |
| 0 | DDD | 4 | 25.35 | 39.87 | 0.2 | 2.9 | 8.2 | 47.8 | 84.8 | 0.057 |
| | Spondylodiscitis | 19 | 114.72 | 119.66 | 6.2 | 30.9 | 48.7 | 175.6 | 411.8 |
| 1 | DDD | 92 | 73.34 | 36.07 | 9.6 | 45.9 | 69.3 | 93.3 | 167.0 | 0.085 |
| | Spondylodiscitis | 33 | 97.22 | 58.25 | 20.8 | 60.5 | 73.0 | 132.6 | 254.3 |
| 2, 3 | DDD | 38 | 141.08 | 60.41 | 19.3 | 94.4 | 148.0 | 191.0 | 300.0 | 0.718 |
| | Spondylodiscitis | 39 | 144.61 | 88.98 | 36.1 | 78.4 | 122.9 | 211.0 | 365.8 |
| 4–7 | DDD | 136 | 58.87 | 47.82 | 5.8 | 24.2 | 41.8 | 80.1 | 228.0 | <0.001 |
| | Spondylodiscitis | 50 | 109.68 | 89.37 | 8.5 | 43.3 | 86.6 | 170.0 | 358.6 |
| 8–14 | DDD | 131 | 21.69 | 35.76 | 0.2 | 6.4 | 14.6 | 22.0 | 307.0 | <0.001 |
| | Spondylodiscitis | 46 | 65.38 | 62.97 | 0.9 | 21.1 | 43.8 | 94.7 | 327.6 |

CRP: C-reactive protein; DDD: Degenerative disc disease; SD: standard deviation.

<sup>a</sup>$p$ value of Mann–Whitney U tests.

**Figure 1.** CRP kinetics after lumbar spondylodesis for spondylodiscitis ($n = 64$) and DDD ($n = 160$). CRP: C-reactive protein; DDD: degenerative disc disease.

CRP kinetics in conservative therapy

Initial mean CRP value of conservatively treated patients was 95.9 mg/l (1.8–414.6 mg/l), thus higher than baseline values of surgically managed patients. In all cases, calculated antibiotic treatment was only started after taking samples for culture, which was not always possible on the day of admission. We therefore observed a peak of CRP values...
in conservative patients on the first day after admission to hospital to mean values of 157.80 mg/l (Table 2). These then declined continuously and were 144.3 mg/l on days 2–3, thereby being lower than values of operatively managed patients. Further decline was then markedly slower, and on days 4–7 CRP values were 109.52 mg/l, being higher than comparable values of surgically treated patients. On days 8–14, the mean CRP value of conservatively treated patients was 78.9 mg/l, in comparison to 69.9 mg/l for those surgically managed (Figure 2).

**CRP kinetics and microbiological findings**

In cases with positive microbiological findings (58.6%), patients received a calculated systemic antibiotic treatment. Despite this, independently of conservative or surgical management, only after approximately 3 weeks we could observe a noticeable improvement of CRP values in comparison to those patients receiving a targeted antibiotic therapy. Patients without microbiological findings, that is, those receiving calculated antimicrobial therapy, had a higher tendency to show subsequent fluctuations in their CRP values, despite having shown initial marked decrease. In conservatively treated cases, a distinct decrease between days 4 and 14 was observed if a targeted antibiotic treatment was possible, though it must be added that these were also the patients with significantly higher CRP values initially. CRP values decreased from 217 mg/l to 98 mg/l, while patients without positive bacterial findings showed a decrease from 71 to 66 mg/l, only.

**Leukocyte—Kinetics**

WBC count did not show a typical, interpretable profile in any of the patient groups. Baseline values of WBC count were very variable for patients with spondylodiscitis. Despite having a proven infectious disease, these were not always pathological (mean 13.4 G/L; SD ± 20.9 G/L). As expected, patients with fusion surgery for DDD had normal baseline WBC counts with 8.5 (SD 2.9 G/L). Reaction of WBC after beginning specific treatment (surgery and conservative) in patients with spondylodiscitis was highly variable and without any interpretable profile. In patients with surgery for DDD, leukocyte count had a characteristic pattern with a maximum usually within the first 3 days after surgery. Leukocyte counts were then back to or below preoperative values between 4–6 days after surgery.

**Discussion**

Despite dealing with an infectious entity, CRP dynamics in the first days after surgery for spondylodiscitis was not markedly different than in patients receiving fusion surgery for degenerative disease. Analogous to other surgical procedures, we observed a postoperative CRP rise and peak between days 2 and 3 after intervention, indicating a major, iatrogenic-induced inflammatory response. The intensity of
this operative peak was individual and of no prognostic relevance. Yet, while peak values varied significantly between individuals, the CRP profile had a remarkable resemblance for patients subjected to the same procedure. Mok et al.\textsuperscript{5} as well as Kraft et al.\textsuperscript{13} suggested that in varying types of spinal procedures, postoperative CRP kinetics are similar, regardless of operation, magnitude, or region. Our findings suggest that this could hold true even for surgical management of bacterial infection of the spine.

As described for noninfectious spine surgery,\textsuperscript{13} we believe that in spondylodiscitis treatment peak CRP values serve only as a reference value for assessing treatment success. If CRP levels remain persistently high at the 5–7 days control, this may be indicative of a local complication, nonrespondence to the antibiotic regime or a further, spine-independent comorbidity requiring specific workup.

The distribution of spondylodiscitis in our patient group, with manifestation primarily in the lumbar spine (almost 2/3), is congruent to reports in numerous publications.\textsuperscript{14,15} Frequently observed single or multiple comorbidities, led on by age, hypertension, diabetes, malignancy, and dialysis therapy are typical. Numerous theories exist as to why the incidence of spondylodiscitis in these patients with a latent or manifest immunodeficiency is increased. The exact pathophysiological mechanisms remain unclear.

In all patients, we attempted to isolate bacteria, independent of the treatment method. This was significantly more successful in surgically managed patients, very likely due to the numerous specimens taken from the vicinity of the infectious disc and vertebra. With little more than 30% positive findings, we had a fairly low yield in identifying bacteria in conservatively managed patients, despite the fact that we did not only rely on venous blood cultures but always performed computer tomography (CT)-guided needle aspiration from the infectious area, prior to administration of antibiotics. This well-known problem in conservative management of spondylodiscitis\textsuperscript{16–18} compounds the administration of targeted antibiotics. Therefore, numerous authors propagate surgical debridement and fusion surgery, when possible. Rapid pain relief and immediate structural stability are further arguments to prefer surgery over conservative therapy.\textsuperscript{17–20}

Cases without marked structural damage to the bony spine, or patients refusing surgery, were treated with a standardized conservative regime. A nonspecific calculated antibiotic therapy with ampicillin/sulbactam was initiated, if there was no other focus. In case of penicillin allergy, cefuroxime was the antibiotic of choice. This regimen very frequently led to a marked decline of CRP values within the first days suggesting a good effectiveness. Interestingly this decline then slowed down in comparison to surgically managed patients, but did further decline over the observation period, though with marked variability in individuals. In the clinical setting, this variability can be bothersome, especially in patients where microbiological workup was unsuccessful. In these patients, there is the very understandable tendency to change and perhaps reswitch the antibiotic regime, based on fluctuating CRP values. If the patient’s general condition allows, our suggestion would be, to postpone antibiotic treatment changes till a repeated increase of CRP values over 2 or 3 consecutive days is noticed and not to react too quickly to moderate fluctuations.

Postoperative maximum CRP levels depend heavily on the region and type of surgery performed.\textsuperscript{4,8,10,21} This implies that the peak response correlates with an iatrogenic tissue injury. Yet Larsson et al.\textsuperscript{4} could not always find a connection to the magnitude of surgery and peak postoperative CRP levels. They suggested that the increase in CRP depends not only on the amount, but also on the type of tissue injured. To diminish this confounding factor, we compared spinal surgery for lumbar spondylodiscitis with surgery for lumbar DDD. Although both types of surgery incorporate an open single- or bi-level approach, implantation of titanium pedicle screws and rods, decompression of the spinal canal over partial laminectomy and discectomy, the management of the intervertebral space in both patient groups are markedly different. While we routinely placed cages into the intervertebral space (polyetheretherketone (PEEK) or titanium) in the DDD group, we did not always follow an identical regimen in spondylodiscitis patients. Some cases were only debrided, others managed with an antibiotic carrier (i.e. beads or sponges) and in rare cases, a titanium cage filled with antibiotic sponges was inserted. These management variations mirror the suggestions made in the literature for surgical treatment of spondylodiscitis.\textsuperscript{22} In our patient group, this did not have an impact on CRP dynamics, but needs mentioning for clarity sake.

Numerous factors favor CRP as a more effective laboratory test than WBC count. CRP level is stable for an individual and has a narrow normal range. It is hardly influenced by medication or common comorbidities, other than liver failure.\textsuperscript{23} WBC count on the other hand is substantially less expensive. However, especially with proven infectious complications, it is only of interpretational value in combination with ESR, body temperature, and CRP levels.\textsuperscript{6} Our data underline that in contrast to CRP, WBC count in spondylodiscitis does not show a typical and therefore interpretable profile. It is therefore only of secondary value in monitoring the course of the disease.

Apart from the obvious limitations of all retrospective studies, our data is based on a heterogeneous patient collection concerning age and comorbidities. These comorbidities may be a sort of confounding bias, and have an effect on our findings. Contrast-enhanced MRI is the gold standard in diagnosis of spondylodiscitis, yet there remains the possibility of having included false positive cases in whom increased CRP may not have resulted from the spine. Whether these findings can therefore be generalized and applied to other patients must be discussed. Nonetheless, we believe the sample size to be large enough to allow careful conclusions.
In elective degenerative spine surgery and in the surgical management of spondylodiscitis, we suggest routine serum CRP level measurements prior to surgery, on days 2–3 and on days 4–7 postoperation. With no suspicious clinical findings for complications and an effective antibiotic regimen, a marked drop in CRP values on the 4–7 postoperative days should be observed. When CRP values do not fall, a local complication, ineffective antibiotic therapy or a concomitant problem with lagging clinical signs must be considered. In conservative treatment of spondylodiscitis, a similar regimen is suggested. In cases with a calculated antibiotic therapy, fluctuations in CRP values in days 2–3 after first antibiotic administration need to be closely observed.

Authors' note

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Author contributions

All authors contributed to the study design. CvG, TK, and KE assessed patients’ clinical and MRI data. MFell and DK performed the literature review and revision of the manuscript. MFriedrich performed statistics and correction of manuscript. CNK did the critical evaluation of the data and compiled the manuscript draft.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

The study was approved by the institutional research ethics committee and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

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