Acta Neurochirurgica (2021) 163:1583–1592
https://doi.org/10.1007/s00701-020-04628-8

ORIGINAL ARTICLE - INFECTION

Interleukin-6 as inflammatory marker of surgical site infection following spinal surgery

Markus Lenski[1] · Joerg-Christian Tonn[1] · Sebastian Siller[1]

Received: 14 July 2020 / Accepted: 22 October 2020 / Published online: 29 October 2020

Abstract

Background In order to elucidate whether serum inflammatory markers identify patients with local surgical site infection(SSI) as underlying disease for recurrent or new symptomatology following spine surgery, we evaluated the diagnostic potential of interleukin-6(IL-6) as a marker of SSI. The diagnostic significance of IL-6 was compared to the standard serum inflammatory markers C-reactive protein(CRP) and white blood cell count (WBCC).

Method Ninety-eight consecutive patients with readmission due to recurrent or new symptomology after spinal surgery of degenerative spine disorders entered the study. Baseline patients' characteristics and the abovementioned inflammatory markers were collected, and arithmetical means with standard deviation, area under the curve (AUC), thresholds, sensitivity, specificity, positive(+)likelihood ratio (LR), and negative(−)LR with corresponding 95% confidence interval(95%CI) were calculated and correlated with presence or absence of SSI.

Results Nine patients suffered from a SSI, whereas the remaining 89 patients had a recurrent/adjacent-segment degenerative disorder without evidence of infection. The most significant parameter for diagnosing a SSI was serum IL-6 (cut-off value > 15.3 pg/ml, AUC = 0.954, SE = 85.7%, SP = 97.3%), followed by CRP (cut-off value = 0.8 mg/dl, AUC = 0.916, SE = 88.9%, SP = 84.5%)

Conclusions In the case of recurrent or new symptomatology following spinal surgery, serum IL-6 has the highest diagnostic potential for diagnosing spinal SSI.

Keywords Spine surgery · Surgical site infection · Inflammatory marker · Interleukin-6 · IL-6 · C-reactive protein

Introduction

Despite all careful precautionary measures to avoid surgical site infections (SSI) following spinal surgery, the incidence of SSI after decompressed laminectomy is about 3% and even higher in association with fusion and instrumentation surgery with up to 12% [13]. Discitis occurs in 0.2 to 2.7% and is therefore a rare complication of spine surgery [13]. Further, different surgical techniques with individual level of invasiveness may explain the difference in the reported incidence of spinal SSIs [8, 31, 46]. In a meta-analysis, SSI was the most common cause of re-admission after spinal surgery [5]. Severe infections causing significant morbidity and mortality occurred in up to 1% of spinal surgeries, leading to profound complications such as readmission, long antibiotic therapy, reoperation, poor outcome with persistent neurological deficits, and increased health care costs [23]. Hence, early diagnosis and treatment of SSI are desirable to prevent aggravation [21, 34, 42].

If there is clinical suspicion of a SSI, an examination of the infection markers in the blood is carried out first. If the suspicion of a SSI is substantiated here, imaging is sought next (contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI)) and, if available, in selected cases 18-fluorodeoxyglucose positron emission tomography for accurate diagnosis [19, 23].

Standard serum laboratory markers to screen for SSI are C-reactive protein (CRP), peripheral white blood cell count (WBCC), and erythrocyte sedimentation rate (ESR). WBCC, CRP, and ESR have been used for detecting and monitoring postoperative infections [9, 23, 42]. However, these markers are affected by surgery-associated factors such as operative

This article is part of the Topical Collection on *Infection*

Presentation at a conference: 71st annual meeting of the German society for neurosurgery 2020.

✉ Markus Lenski
Markus.Lenski@med.uni-muenchen.de

[1] Neurosurgical Clinic, Clinic of the University of Munich (Ludwig Maximilians University), Campus Grosshadern, Marchioninistrasse 15, D-81377 Munich, Germany

time, intraoperative blood loss, number of operative segments, and invasiveness of the surgical approach [22]. Hence, current research focuses on detecting more reliable laboratory markers which enable the detection of SSIs following spine surgery with higher diagnostic accuracy.

Interleukin 6 (IL-6) is a peptide, which consists of 185 amino acids, and is an interleukin that acts as a pro-inflammatory cytokine [47]. The concentration of IL-6 in plasma in healthy individuals is approximately 1–6 pg/ml and can rise to 1000 pg/ml in severe systemic infections [15]. It is an important mediator of fever and it is responsible for stimulating acute phase protein synthesis such as CRP, as well as the production of neutrophils in the bone marrow. For this reason, the IL-6 increase in blood is significantly earlier measurable as the CRP increase, a fact that saves time in diagnosis and therapy initiation [15, 47] and qualifies IL-6 as an useful inflammatory marker for detecting bacterial infections at an early stage [29].

Despite the potential advantages of IL-6 compared to the traditional serum laboratory markers (like WBCC, CRP, and ESR), the role of IL-6 in diagnosing SSI following spine surgery in daily clinical routine is still not determined. The aim of this study was, therefore, to compare the diagnostic potential of IL-6 to the aforementioned markers by using receiver operating characteristic (ROC) curves and to clarify its importance in diagnosing spinal SSI.

Methods and materials

Between November 2011 and April 2016, 633 patients underwent an elective dorsal decompressive surgery at the Neurosurgical Department, University of Munich (LMU, Germany) due to degenerative disorders of the cervical, thoracic, or lumbar spine. Out of these, 98 patients were readmitted due to recurrent or new symptomatology. We prospectively evaluated these 98 patients as described below. Study approval was granted by the local Institutional Review Board (AZ17-168 and AZ18-259). This study was performed in line with the principles of the Declaration of Helsinki of 1964 and its later amendments.

All patients with recurrent or new symptomatology were clinically examined (including a wound review) and blood samples were collected to define the concentration of CRP (reference range ≤ 0.5 mg/dl), IL-6 (reference range ≤ 6.3 pg/ml), and the WBCC on readmission. Serum CRP and IL-6 concentrations were determined in the SSI group on the day of diagnosis of SSI in the emergency department prior to surgical revision. This corresponds to the day of admission of all spinal SSI patients. Also in the aseptic group, the determination of infection markers was performed preoperatively in the emergency department. Serum IL-6 was measured using Elecsys® IL-6 on a Cobas E 601 analyzer (Roche diagnostics). Magnetic resonance imaging (MRI) was consecutively added, immediately with contrast and diffusion sequences whenever a SSI was suspected. Indication for surgery was in superficial SSI purulent drainage from the superficial incision or wound dehiscence and in deep SSI purulent drainage from the deep incision, spontaneous dehiscense, or an abscess/spondylodiscitis/discitis was detected on imaging.

In case of suspected SSI, a revision operation was carried out without time delay and included multiple smear tests for microbiological-bacteriological testing and antibiogram as well as histology. After obtaining of smear tests, an empiric intravenous antibiosis with vancomycin/meropenem (and additional rifampicin in case of severe sepsis) was immediately started in case of spondylodiscitis or abscess formation, while cefuroxime or clindamycin was the therapy of choice in case of a mere superficial SSI. The antibiotic regime was adapted according to the microbiological-bacteriological findings/antibiogram and continued for 4–6 weeks in case of spondylodiscitis or abscess formation (followed by an additional oral antibiosis for further 2–4 weeks after a follow-up MRI for therapeutic response) and for 2 weeks in case of a mere superficial SSI.

SSI event was defined according to the Centers for Disease Control and Prevention (CDC) criteria [7, 9, 23]. A superficial SSI was diagnosed if the event involved only skin and subcutaneous tissue of the incision and the patient had at least one of the following: (a) purulent drainage from the incision; (b) organism identified from an aseptically obtained specimen from the incision or subcutaneous tissue by a culture or PCR-based microbiological testing; (c) patient had at least one of the following symptoms: localized pain, tenderness, localized swelling, erythema, or heat and superficial incision that was deliberately opened by a surgeon; or (d) diagnosis of a SSI by a physician [7]. Criteria for a deep SSI were involvement of deep soft tissues along the incision (fascia, muscle, dura, disc, vertebral body) and at least one of the following: (a) purulent drainage from deep incision; (b) a deep incision that spontaneously dehiscenses or is deliberately opened or aspirated by a physician and patient had at least one of the following signs or symptoms: fever (< 38 °C), localized pain, and tenderness; (c) an abscess or other evidence of infection involving the deep incision that was detected on imaging [7]. An early SSI after spinal surgery was defined as infection after 29 days or less following surgery [13]. If an infection occurred later, it was defined as late SSI [13].

In the case of a recurrent or adjacent-segment degenerative disorder (e.g., re-stenosis, re-prolapse of the pulpous nucleus, postoperative bleeding, and space occupying seroma), patients were transferred for re-surgery during the first 3 days after readmission in an semi-elective manner if indicated.

Blood samples for monitoring of the concentration of CRP, IL-6, and the WBCC were carried out in all patients after re-surgery during the in-patient stay and at discharge.

The spine procedures were all performed by the same spine surgeon team of the Department of Neurosurgery which was blinded to the study. Concentrations of inflammatory markers were measured by the Department of Laboratory Medicine, and quantification of inflammatory marker levels was performed according to the manufacturer's instructions; no blood specimen was obtained solely for the purpose of this study.

Statistical analysis was performed by SPSS 17.0 (SPSS Inc., Chicago, Illinois, USA) and 23.0 for Windows. Differences were statistically significant if the p value was < 0.05. For comparison of groups for differences, the Student's t test was used for numeric values, Mann-Whitney Rank Sum test for ordinal variables and χ^2 test resp. Fisher's exact test (in case of 2×2-contingency tables) for nominal variables. For evaluation of the diagnostic potential of inflammatory parameters, ROC curves with corresponding area under the curve (AUC) were determinded. Parameters with an AUC > 0.9 have a very good and those with an AUC > 0.8 a good diagnostic potential. Optimal thresholds were calculated by maximizing specificity and sensitivity (Youden's J statistics). Thresholds lead to false negative and false positive test result, which is problematic for diagnosing SSIs. Therefore, we provide positive likelihood ratios (LR) and negative LRs. LRs are more useful than sensitivity and specificity for clinical bedside application [16]. LRs can be used to estimate the change from pretest to post-test probability of a disease. A LR higher than 1 increases and a LR lower than 1 decreases the post-test probability of a disease. A LR of 5 increases the post-test disease probability + 30%, a LR of 10 increases it + 45%, whereas a LR of 0.5 decreases the post-test probability − 15%, a LR of 0.1 decreases it − 45% [32]. The positive LR gives the change from pretest to post-test probability for a positive test result, the negative LR gives the change for a negative test result.

Results

Patients' characteristics

With 98 patients being readmitted due to recurrent or new symptomatology, the readmission rate was about 15% in a population of altogether 633 patients undergoing an elective dorsal decompressive surgery at the Neurosurgical Department, University of Munich (LMU, Germany) due to degenerative disorders of the cervical, thoracic, or lumbar spine. Out of these, 89 patients (91%) suffered from a recurrent or adjacent-segment degenerative disorder and other post-operative complications, while 9 patients (9%) had a SSI.

Baseline characteristics of both cohorts are displayed in Table 1. There were no significant differences between both cohorts.

Pathogens causing SSI

Nine patients suffered from a SSI, 7 of whom showed bacterial growth in the microbiological culture (77.8%). Five patients (55.6%) had evidence of gram positive cocci in histology, all 9 patients (100%) showed the histological appearance of acute florid granulocytic inflammatory infiltration (Table 2). The prevailing pathogens causing spinal SSIs were *Staphylococcus epidermidis* ($n = 4$), followed by *Staphylococcus aureus* ($n = 2$) and *Propionibacterium acnes* ($n = 2$). In one patient, two bacterial species were identified, in another patient, three pathogens were detected. Infection sites were the cervical spine in 2 cases (22.2%), the thoracic spine ($n = 1$, 11.1%), and most frequently the lumbar spine ($n = 6$, 66.7%). Five patients (55.6%) suffered from an early SSI infection, four patients (44.4%) experienced a delayed SSI. Eight patients (88.9%) developed a deep infection and one patient (11.1%) a superficial wound infection.

Diagnostic potential of inflammatory markers

Serum IL-6 had a higher diagnostic potential for diagnosing a SSI than serum CRP on admission (d0 = day 0). Mean serum Il-6 level during SSI was 56.2 ± 39.1 pg/ml and was significantly higher than in aseptic revision surgeries with mean serum levels of 7.8 ± 3.6 pg/ml ($p = 0.02$). The mean concentration of IL-6 in serum was 66.6 ± 40.7 pg/ml during an early SSI and 42.4 ± 39.9 pg/ml during a late SSI. Serum IL-6 had the highest diagnostic potential with an AUC of 0.954 (Fig. 1) revealing an optimal threshold of 15.3 pg/ml with a SE of 87.5% and a SP of 97.3% (Table 3). The calculation of the likelihood-ratio showed that serum IL-6 concentrations above 15.3 pg/ml led to a substantial increase of the post-test probability of SSI (+ LR = 31.7), whereas concentrations below 15.3 pg/ml decreased the post-test probability of SSI (− LR = 0.15) considerably (Table 3).

The mean CRP concentration in patients with SSI was statistically significantly increased with 10.0 ± 9.4 mg/dL compared to 0.5 ± 0.7 mg/dL in non-infected patients ($p = 0.02$). The determined AUC of CRP was 0.916 (Fig. 1), leading to an optimal cut-off value of 0.8 mg/dL with a SE of 88.9% and a SP of 84.5%(Table 3). The post-test probability of SSI increased at CRP concentrations of 0.8 mg/dl or higher (+LR = 5.7), lower CRP concentrations decreased it (− LR = 0.13) drastically (Table 3). Serum WBCC did not differ significantly in patients with or without SSI (Table 3).

Serum IL-6 levels of patients with SSI were reduced by an average of about 50% of the baseline concentration 4 days after revision surgery and start of antibiotic therapy. CRP

Table 1 Baseline characteristics at revision surgery*

Characteristics	Patients with reoperation due to		*p* value
	Recurrent/adjacent-segment degenerative disorder ($n = 89$)	SSI ($n = 9$)	
Gender, male/female	60/29	7/2	0.530
Median age, years (range)	70.6 (23–87)	73.7 (56–79)	0.522
Mean ± SD time between index and revision surgery, days	374.9 ± 527.9	48.0 ± 72.8	0.068
Recurrent symptoms, no. (%)			
Neck/back pain	35 (39.3)	5 (55.5)	0.813
Radicular pain	71 (79.8)	4 (44.4)	0.324
Sensory disturbances	51 (57.3)	2 (22.2)	0.530
Paresis	50 (56.2)	2 (22.2)	0.777
Vegetative disorders	1 (1.1)	2 (22.2)	1.000
Meningismus	0 (0.0)	0 (0.0)	1.000
Pos. Spurling's/Lasègue's test	21 (23.6)	1 (11.1)	0.906
Comorbidities, no. (%)			
Cardiovascular diseases	43 (48.3)	6 (66.7)	0.777
Diabetes mellitus	12 (13.5)	4 (44.4)	0.906
History of smoking	4 (4.5)	1 (11.1)	1.000
Alcohol abuse	0 (0.0)	1 (11.1)	1.000

*Mean values are presented ± standard deviation (SD)

levels on the fourth postoperative day still showed a mean serum concentration similar to that at diagnosis. The time course of inflammatory markers in SSI prior and after revision surgery is depicted in Table 4 and Fig. 2.

Discussion

This study evaluated the diagnostic potential of the inflammatory markers IL-6, CRP, and WBCC in serum for detecting spinal SSIs as underlying disease for recurrent or new symptomatology following spine surgery. Thereby, IL-6 had the highest diagnostic potential for diagnosing spinal SSIs, followed by CRP and WBCC. In addition, IL-6 was more useful than CRP for monitoring the therapeutic success of spinal SSIs. In line with previous studies about SSIs following spine surgery, the incidence for SSI in this study was 1.4% (9 SSIs out of 633 spine surgeries) [4]. Compared to other inflammatory marker studies [24, 45], we were able to prospectively include a larger study population and ultimately a higher number of SSIs [23, 24, 26]. In a further inflammatory marker study with a noticeably higher infection rate of 6.5%, a similar high number of SSIs could be included, but in contrast to our cohort, over 75% of cases were superficial SSIs [2]. As in preliminary studies on inflammatory markers, there was a tendency towards slightly higher mean age in the SSI group; the difference did not reach significance neither in our study nor in the previous studies [23, 42]. The mean age and the proportion of patients with diabetes mellitus of our cohort matched the range of previous reports [23, 24, 42]. Unlike the other studies, this series included a very high proportion of men [23, 24, 42]. The patient population in this study is therefore comparable to the patient cohort of other inflammatory marker studies in spinal SSI.

Localized symptoms such as swelling, redness, tenderness, pus discharge, and wound dehiscence, as well as fever, are recognized clinical screening parameters for SSI [30, 42, 43]. However, any symptom may be missing in the postoperative course of patients with spinal SSI, and surgeons have to be aware that postoperative fever can frequently occur without SSI [23, 40]. These points listed above are the reason why it is difficult to diagnose a SSI in everyday clinical practice. Due to the clinical uncertainty, clinicians in the next step refer to the determination of inflammatory markers in the blood. It has already been demonstrated that interleukin-6 improves infection identification when added to physician judgment during evaluation of potentially septic patients [17]. Also for CRP, the usefulness for making the diagnosis of a spinal SSI could be proven [24, 45]. Traditionally, several serum inflammatory markers have been used as indicators of spinal SSI because of their objectivity and convenience [3, 23, 42]. The most frequently used laboratory markers for diagnosing SSI after spinal surgery are the erythrocyte sedimentation rate (ESR), the

Table 2 Pathogens causing spinal surgical site infections

Case no.	Culture	Pathology	Type of infection	Time from surgery to diagnosis in days
1	Negative	Gram positive cocci Florid granulocytic inflammatory infiltration	Deep infection, Discitis	60 Delayed infection
2	*Staphylococcus aureus*	Florid granulocytic inflammatory infiltration	Superficial infection	36 Delayed infection
3	*Propionibacterium acnes*	Gram positive cocci Florid granulocytic inflammatory infiltration	Deep infection, epidural abscess	33 Delayed infection
4	*Staphylococcus epidermidis*, Propionibacterium acnes	Gram positive cocci Florid granulocytic inflammatory infiltration	Deep infection, epudiral abcess	13 Early infection
5	Staphylococcus epidermidis	Florid granulocytic inflammatory infiltration	Deep infection, Discitis	237 Delayed infection
6	*Pseudomonas aeruginosa*, *Enterococcus faecalis*, Staphylococcus epidermidis	Florid granulocytic inflammatory infiltration	Deep infection, epidural abscess	20 Early infection
7	Staphylococcus epidermidis	Florid granulocytic inflammatory infiltration	Deep infection, discitis	13 Early infection
8	Staphylococcus aureus	Gram positive cocci Florid granulocytic inflammatory infiltration	Deep infection, epidural abcess	12 Early infection
9	Negative	Gram positive cocci Florid granulocytic inflammatory infiltration	Deep infection, discitis	8 Early infection

Superficial spinal infection, skin and subcutaneous tissue with no fascial involvement; deep spinal wound infection, fascia, muscle, discitis, osteomyelitis, and epidural abscess [11, 40]; early infection < 29 days after spinal surgery, delayed infection ≤ 29 days after spinal surgery [11]

WBCC, and CRP level [2, 9, 23, 24, 42]. These laboratory values can be obtained in many medical institutions all over the world [23]. Previous reports showed that serum CRP concentrations were a reasonable prized [25] and useful marker of SSI following spine surgery [21, 23, 24, 41] and even more useful than the ESR [23]. CRP screening has been proven to be a valuable tool especially in the detection of early postoperative spinal SSIs [24, 33, 35]. In accordance with prior studies, we found CRP levels to be useful for diagnosing SSI after spinal surgery. Furthermore, we were able to show that CRP concentrations in serum have a good diagnostic potential for diagnosing SSI after spinal surgery. This is of high clinical relevance due to its widespread availability.

Correct and timely diagnosis plays a key role in spinal infections, as it improves patient outcome [27]. To expedite early diagnosis and treatment, sensitive and reliable inflammatory serum markers which peak at an early stage of disease are needed. Ideally, an inflammatory marker should have a very high diagnostic accuracy and be able to differentiate between infection and aseptic course at a very early stage of the disease. As an inducer of the acute phase proteins, serum IL-6 could be a useful tool herein. The raise of serum IL-6 directly induces the acute phase protein CRP, which peaks 24 to 48 h later and reaches its maximum concentration when IL-6 already drops [11, 18]. Hence, IL-6 peaks and normalizes quicker than CRP and prolonged elevation of IL-6 levels might indicate an inflammatory process at an earlier stage. As IL-6 increase precedes that of CRP in infection, a somewhat earlier diagnosis of infection may be achieved with IL-6 measurements, so far, the diagnostic power of serum Il-6 levels in SSI following spinal surgery has not been investigated.

In this study, serum IL-6 showed to be a very good marker for diagnosing SSIs with excellent diagnostic accuracy. In our series, increased serum IL-6 concentrations were significantly associated with SSI in patients with new or recurrent symptoms following spine surgery. According to our study results, interleukin-6 would be the most accurate marker for diagnosis. Therefore, IL-6 concentrations above 15.3 pg/ml should direct the surgeon's attention to SSI. Subsequently, imaging with contrast-enhanced CT, contrast-enhanced MRI, or positron emission tomography CT should then be performed [23].

Serum IL-6 was found to have high process-related costs, including extended analysis times, but improved diagnostic accuracy [1]. The measurement of IL-6 by Enzyme-Linked Immunosorbent Assay is widely available around the world [39] and does not take much longer than for CRP. In fact, the Elecsys® IL-6 on a Cobas E 601 analyzer (Roche diagnostics)

Table 3 Inflammatory markers in surgical site infections after spinal surgery

	n	AUC	Cut-off	Mean ± SD infection	Mean ± SD aseptic	*p*	SE	SP	+ LR	− LR
IL-6 (pg/ml)	82	0.954	15.3	56.2 ± 39.1	7.8 ± 3.6	0.02	85.7% (0.487–0.974)	97.3% (0.861–0.995)	31.7 (4.48–224.43)	0.15 (0.02–0.90)
CRP (mg/dL)	86	0.916	0.8	10.0 ± 9.4	0.5 ± 0.7	0.02	88.9% (0.565–0.980)	84.5%, (0.731–0.916)	5.7 (3.0–10.9)	0.13 (0.02–0.84)
WBCC ($\times 10^3/\mu L$)	89	0.745	9.7	11.7 ± 6.6	7.4 ± 2.1	0.09	66.7% (0.354–0.879)	86.2% (0.751–0.928)	4.8 (2.2–10.7)	0.39 (0.15–0.98)

IL-6 interleukin-6, *CRP* C-reactive protein, *WBCC* serum white blood cell count, *n* number, *AUC* area under the curve, *SD* standard deviation, *SE* sensitivity, *SP* specificity, + *LR* positive likelihood radtio, − *LR* negative likelihood ratio; values in brackets, 95% confidence interval

needs 18 min to measure serum IL-6 levels [12]. Therefore, measuring IL-6 could already today enable a faster and even more reliable diagnosis of SSI. This is important because IL-6 could reduce the risk of misdiagnosis or delayed diagnosis. Delayed diagnosis is a serious event and has a negative impact on patient outcome including prolonged hospitalization, permanent disability, and mortality as well as increased health care costs and loss of working days [4, 6, 27]. In fact, the critical question must be asked whether the slightly higher diagnostic potential of IL-6 justifies the significantly higher additional costs of determining this inflammatory marker. In this context, it should also be considered that a therapy response and also therapy failure, especially of antibiotic therapy, can be better monitored in the further clinical course with IL-6 than with CRP [14, 44]. This is a particular advantage of IL-6 in the daily clinical routine. Although the results suggest that serum IL-6 has a high diagnostic potential for diagnosing SSIs after spine surgery, physicians must be aware that serum IL-6 is also frequently increased after various inflammatory stimuli and conditions, such as major surgery, trauma, meningitis, arthritis, systemic infections, and sepsis [10, 28, 36, 37]. Furthermore, older patients (over 60 years) have significantly higher serum IL-6 concentrations than younger patients after instrumented lumbar spine fusion [38]. The correct interpretation of serum IL-6 therefore requires a work-up of the entire patient's medical history.

Prior studies revealed that the WBCC was not a reliable screening marker for SSI after posterior lumbar decompression surgery [23] or routine elective spinal procedures [2]. Also in this study, the mean WBCC did not differ significantly in the SSI and non-infectious group. In consequence, the WBCC is not a suitable screening parameter for the presence of spinal SSI.

One of the strengths of this study is the good study design: only inflammatory markers of patients with readmission and with symptoms consistent with an SSI were prospectively examined. An innovation is the calculation of AUCs and the introduction of cut-off values with corresponding likelihood ratios in the research area of spinal SSIs.

We acknowledge that this clinical study is limited by several factors. First, the number of SSIs included was relatively small. Hence, there was the possibility of type 2 error due to the relatively small amount of SSI cases. Moreover, other less studied and seldomly used inflammatory markers such procalcitonin [2], serum amyloid A [9], and presepsin [26] were not available. The quantitative and proportional determination of the lymphocyte subpopulation is not part of our standard procedure in cases of suspected SSIs. Therefore, we could not compare our inflammatory markers to the lymphocyte count. There is no reference in the literature that lymphopenia is as well or even better than serum IL-6 for diagnosing SSIs [20–23]. On the contrary, previous studies have shown that lymphopenia represented a immunodepression status after

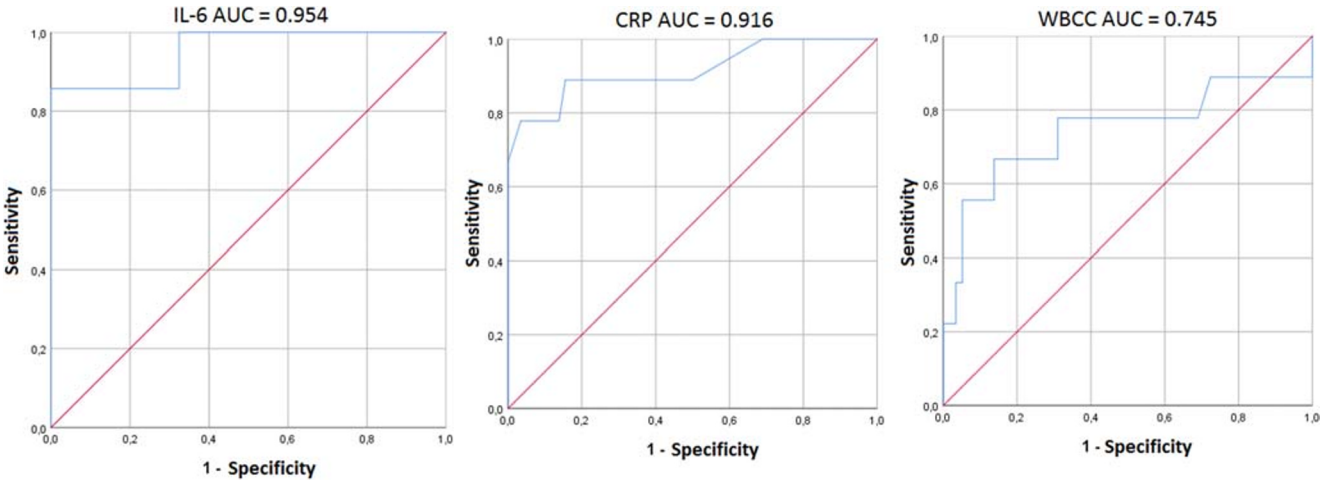

Fig. 1 ROC curves of inflammatory markers for diagnosing surgical site infections after spinal surgery. IL-6, interleukin-6; CRP, C-reactive protein; WBCC, white blood cell count; ROC curves, receiver operating characteristic curves; AUC, area under the curve

surgery, thus indicating the increased susceptibility to infection, which may lead to the development of a postoperative infection [42]. Therefore, the lymphocyte count and percentage on day 4 [21, 23] and the white blood cell differential [42] cannot be considered a replacement for serum IL-6 in routine diagnostics according to current studies. With this study, we aimed to investigate the clinically relevant and widespreadly available inflammatory markers; thus, we concentrated on those which are in our tool kid of everyday practice. However, we believe that we have captured the inflammatory

Table 4 Time course of inflammatory markers in SSI prior and after revision surgery

	n	Span	Minimum	Maximum	Mean	SD	Variance
CRPd0	9	27,20	,20	27,40	10,0222	938,120	88,007
CRPd1	6	24,20	6,60	30,80	14,5667	877,557	77,011
CRPd2	7	19,20	5,30	24,50	13,2429	781,193	61,026
CRPd3	8	21,20	3,00	24,20	99,375	758,945	57,600
CRPd4	8	17,70	3,50	21,20	10,0250	601,777	36,214
CRPd5	7	17,00	1,60	18,60	85,000	643,221	41,373
CRPd6	5	15,90	1,00	16,90	64,200	633,774	40,167
CRPd7	6	15,00	2,00	17,00	68,333	627,460	39,371
IL6d0	9	110,40	3,60	114,00	50,3500	39,91,212	1592,977
IL6d1	6	72,70	18,00	90,70	47,7500	31,64,091	1001,147
IL6d2	7	39,50	17,00	56,50	42,9286	14,47,880	209,636
IL6d3	7	68,00	10,40	78,40	37,9857	21,21,591	450,115
IL6d4	7	82,10	4,90	87,00	30,8429	29,56,884	874,316
IL6d5	7	56,60	2,90	59,50	25,6571	22,20,584	493,100
IL6d6	4	24,90	8,80	33,70	19,5750	11,59,235	134,383
IL6d7	5	33,50	3,80	37,30	14,2800	14,08677	198,437
WBCCd0	9	21,70	2,40	24,10	11,6578	664,071	44,099
WBCCd1	6	31,30	6,80	38,10	15,2833	11,79,414	139,102
WBCCd2	7	14,70	8,20	22,90	12,3571	556,353	30,953
WBCCd3	8	16,80	2,60	19,40	10,3125	517,589	26,790
WBCCd4	6	5,90	4,90	10,80	82,833	215,724	4654
WBCCd5	6	6,60	4,90	11,50	87,667	238,300	5679
WBCCd6	5	11,30	2,40	13,70	70,800	417,337	17,417
WBCCd7	6	10,00	3,00	13,00	82,000	387,195	14,992

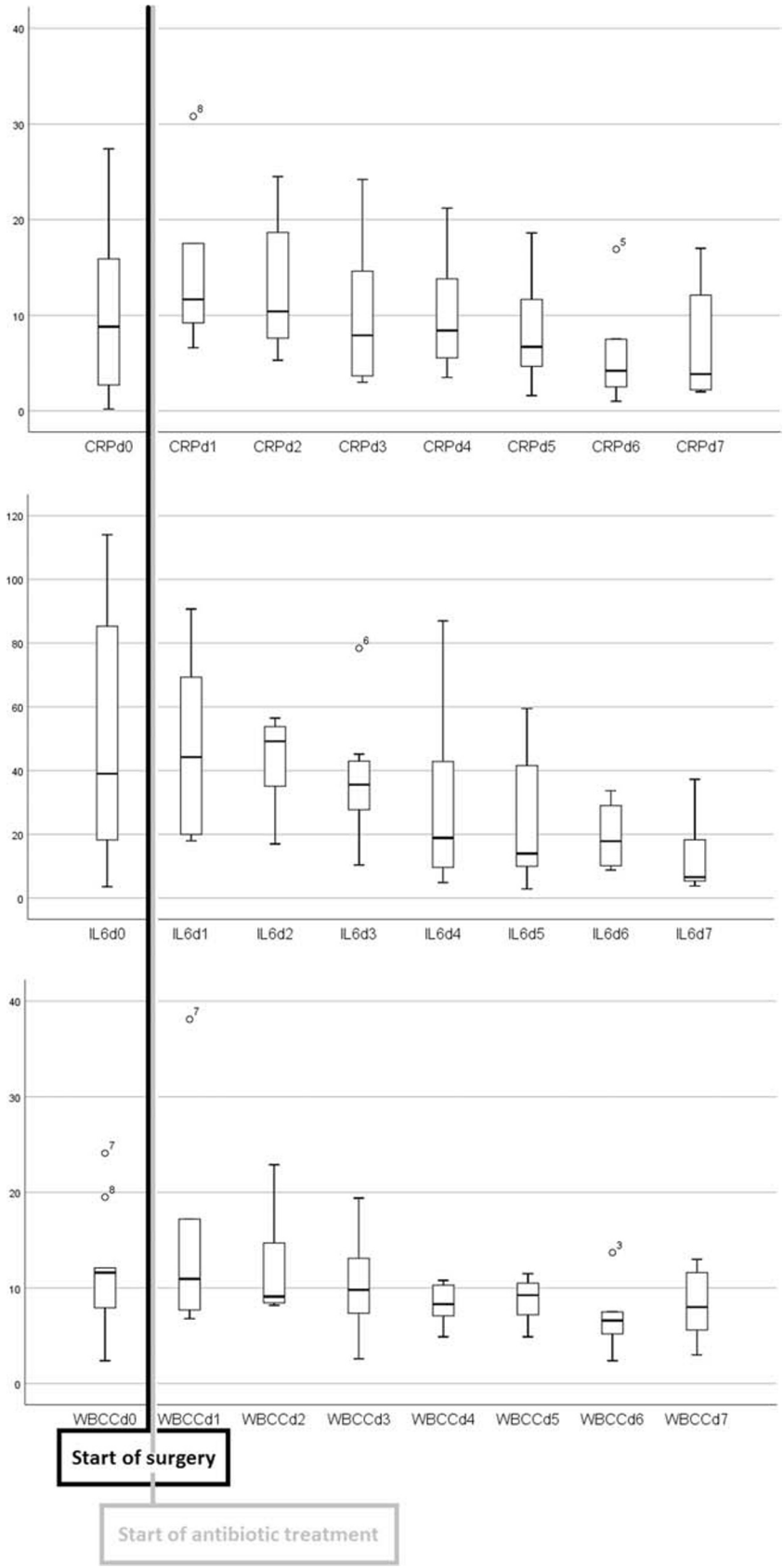

Fig. 2 The time course of inflammatory markers

marker levels in a representative postoperative spinal study population.

Conclusions

In summary, we conclude that IL-6 is a useful serum marker to detect early and delayed SSI. Here it showed to be of particular importance in spinal surgery. Thus, in any case of suspected SSI, the IL-6 serum concentration can direct clinical management in patients with suspicion of SSIs. It must be critically considered that the diagnostic potential of CRP is almost as high as for IL-6, but the laboratory essay costs are significantly lower.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Markus Lenski and Sebastian Siller. The first draft of the manuscript was written by Markus Lenski and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The study was not financially or materially supported by or any income was received from a commercial sponsor or the NIH, Wellcome Trust, HHMI, or other foundations requiring open access.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Acharya A, Markar SR, Ni M, Hanna GB (2017) Biomarkers of acute appendicitis: systematic review and cost-benefit trade-off analysis. Surg Endosc 31:1022–1031. https://doi.org/10.1007/s00464-016-5109-1
2. Aljabi Y, Manca A, Ryan J, Elshawarby A (2019) Value of procalcitonin as a marker of surgical site infection following spinal surgery. Surgeon 17:97–101. https://doi.org/10.1016/j.surge.2018.05.006
3. Aono H, Ohwada T, Kaneko N, Fuji T, Iwasaki M (2007) The postoperative changes in the level of inflammatory markers after posterior lumbar interbody fusion. J Bone Joint Surg Br 89:1478–1481. https://doi.org/10.1302/0301-620X.89B11.19478
4. Atesok K, Papavassiliou E, Heffernan MJ, Tunmire D, Sitnikov I, Tanaka N, Rajaram S, Pittman J, Gokaslan ZL, Vaccaro A, Theiss S (2020) Current strategies in prevention of postoperative infections in spine surgery. Global Spine J 10:183–194. https://doi.org/10.1177/2192568218819817
5. Bernatz JT, Anderson PA (2015) Thirty-day readmission rates in spine surgery: systematic review and meta-analysis. Neurosurg Focus 39:E7. https://doi.org/10.3171/2015.7.FOCUS1534
6. Calderone RR, Garland DE, Capen DA, Oster H (1996) Cost of medical care for postoperative spinal infections. Orthop Clin North Am 27:171–182
7. Center for Disease Control and Prevention (2020) Surgical Site Infection (SSI) Event https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf. Accessed 26 March 2020
8. Chaudhary SB, Vives MJ, Basra SK, Reiter MF (2007) Postoperative spinal wound infections and postprocedural diskitis. J Spinal Cord Med 30:441–451. https://doi.org/10.1080/10790268.2007.11753476
9. Deguchi M, Shinjo R, Yoshioka Y, Seki H (2010) The usefulness of serum amyloid A as a postoperative inflammatory marker after posterior lumbar interbody fusion. J Bone Joint Surg Br 92:555–559. https://doi.org/10.1302/0301-620X.92B4.22807
10. Di Cesare PE, Chang E, Preston CF, Liu CJ (2005) Serum interleukin-6 as a marker of periprosthetic infection following total hip and knee arthroplasty. J Bone Joint Surg Am 87:1921–1927. https://doi.org/10.2106/JBJS.D.01803
11. Douraiswami B, Dilip PK, Harish BN, Jagdish M (2012) C-reactive protein and interleukin-6 levels in the early detection of infection after open fractures. J Orthop Surg (Hong Kong) 20:381–385. https://doi.org/10.1177/230949901202000325
12. Elecsys® IL-6 (Roche diagnostics) https://diagnostics.roche.com/global/en/products/params/elecsys-il-6.html. Accessed 9 Sept 2020
13. Emamhadi MGS, Nozari-Golsefid H (2018) Post-operative infections in spine procedures: a brief review. Iran J Neurosurg 4:5–12. https://doi.org/10.32598/irjns.4.1.5
14. Engervall P, Granstrom M, Andersson B, Bjorkholm M (1995) Monitoring of endotoxin, interleukin-6 and C-reactive protein serum concentrations in neutropenic patients with fever. Eur J Haematol 54:226–234. https://doi.org/10.1111/j.1600-0609.1995.tb00676.x
15. Fraunberger P, Wang Y, Holler E, Parhofer KG, Nagel D, Walli AK, Seidel D (2006) Prognostic value of interleukin 6, procalcitonin, and C-reactive protein levels in intensive care unit patients during first increase of fever. Shock 26:10–12. https://doi.org/10.1097/01.shk.0000215319.06866.bd
16. Gallagher EJ (2003) Evidence-based emergency medicine/editorial. The problem with sensitivity and specificity. Ann Emerg Med 42:298–303. https://doi.org/10.1067/mem.2003.273
17. Henning DJ, Hall MK, Watsjold BK, Bhatraju PK, Kosamo S, Shapiro NI, Liles WC, Wurfel MM (2020) Interleukin-6 improves infection identification when added to physician judgment during evaluation of potentially septic patients. Am J Emerg Med 38:947–952. https://doi.org/10.1016/j.ajem.2019.158361
18. Hollig A, Stoffel-Wagner B, Clusmann H, Veldeman M, Schubert GA, Coburn M (2017) Time courses of inflammatory markers after aneurysmal subarachnoid hemorrhage and their possible relevance for future studies. Front Neurol 8:694. https://doi.org/10.3389/fneur.2017.00694
19. Inanami H, Oshima Y, Iwahori T, Takano Y, Koga H, Iwai H (2015) Role of 18F-fluoro-D-deoxyglucose PET/CT in diagnosing surgical site infection after spine surgery with instrumentation. Spine (Phila Pa 1976) 40:109–113. https://doi.org/10.1097/BRS.0000000000000674
20. Iwata E, Shigematsu H, Koizumi M, Nakajima H, Okuda A, Morimoto Y, Masuda K, Tanaka Y (2016) Lymphopenia and elevated blood C-reactive protein levels at four days postoperatively are useful markers for early detection of surgical site infection following posterior lumbar instrumentation surgery. Asian Spine J 10:220–225. https://doi.org/10.4184/asj.2016.10.2.220
21. Iwata E, Shigematsu H, Koizumi M, Nakajima H, Okuda A, Morimoto Y, Masuda K, Yamamoto Y, Tanaka Y (2016)

Lymphocyte count at 4 days postoperatively and CRP level at 7 days postoperatively: reliable and useful markers for surgical site infection following instrumented spinal fusion. Spine (Phila Pa 1976) 41: 1173–1178. https://doi.org/10.1097/BRS.0000000000001501

22. Iwata E, Shigematsu H, Okuda A, Morimoto Y, Masuda K, Nakajima H, Koizumi M, Tanaka Y (2016) Lymphopenia at 4 days postoperatively is the most significant laboratory marker for early detection of surgical site infection following posterior lumbar instrumentation surgery. Asian Spine J 10:1042–1046. https://doi.org/10.4184/asj.2016.10.6.1042
23. Iwata E, Shigematsu H, Yamamoto Y, Tanaka M, Okuda A, Morimoto Y, Masuda K, Nakajima H, Koizumi M, Tanaka Y (2018) Lymphocyte count at 4 days postoperatively: a reliable screening marker for surgical site infection after posterior lumbar decompression surgery. Spine (Phila Pa 1976) 43:E1096–E1101. https://doi.org/10.1097/BRS.0000000000002617
24. Kang BU, Lee SH, Ahn Y, Choi WC, Choi YG (2010) Surgical site infection in spinal surgery: detection and management based on serial C-reactive protein measurements. J Neurosurg Spine 13: 158–164. https://doi.org/10.3171/2010.3.SPINE09403
25. Klinger A, Buchfelder M, Schlaffer SM, Kremenevskaja N, Kleindienst A (2013) Infection surveillance in transsphenoidal pituitary surgery - comparison of lipopolysaccharide-binding-protein, interleukin 6, C-reactive protein, white blood cell count, erythrocyte sedimentation rate and body temperature. Acta Neurochir 155:2177–2182; discussion 2182. https://doi.org/10.1007/s00701-013-1875-x
26. Koakutsu T, Sato T, Aizawa T, Itoi E, Kushimoto S (2018) Postoperative changes in presepsin level and values predictive of surgical site infection after spinal surgery: a single-center, Prospective Observational Study. Spine (Phila Pa 1976) 43:578–584. https://doi.org/10.1097/BRS.0000000000002376
27. Lener S, Hartmann S, Barbagallo GMV, Certo F, Thome C, Tschugg A (2018) Management of spinal infection: a review of the literature. Acta Neurochir 160:487–496. https://doi.org/10.1007/s00701-018-3467-2
28. Lenski M, Biczok A, Neufischer K, Tonn JC, Briegel J, Thon N (2019) Significance of cerebrospinal fluid inflammatory markers for diagnosing external ventricular drain-associated ventriculitis in patients with severe traumatic brain injury. Neurosurg Focus 47: E15. https://doi.org/10.3171/2019.8.FOCUS19407
29. Lenski M, Scherer MA (2014) Synovial IL-6 as inflammatory marker in periprosthetic joint infections. J Arthroplast 29:1105–1109. https://doi.org/10.1016/j.arth.2014.01.014
30. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR (1999) Guideline for Prevention of Surgical Site Infection. Centers for disease control and prevention (CDC) hospital infection control practices advisory committee. Am J Infect Control 27:97–132 quiz 133-134; discussion 196
31. Massie JB, Heller JG, Abitbol JJ, McPherson D, Garfin SR (1992) Postoperative posterior spinal wound infections. Clin Orthop Relat Res 99–108
32. McGee S (2002) Simplifying likelihood ratios. J Gen Intern Med 17:646–649. https://doi.org/10.1046/j.1525-1497.2002.10750.x
33. Meyer B, Schaller K, Rohde V, Hassler W (1995) The C-reactive protein for detection of early infections after lumbar microdiscectomy. Acta Neurochir 136:145–150. https://doi.org/10.1007/bf01410617
34. Mok JM, Guillaume TJ, Talu U, Berven SH, Deviren V, Kroeber M, Bradford DS, Hu SS (2009) Clinical outcome of deep wound infection after instrumented posterior spinal fusion: a matched cohort analysis. Spine (Phila Pa 1976) 34:578–583. https://doi.org/10.1097/BRS.0b013e31819a827c
35. Mok JM, Pekmezci M, Piper SL, Boyd E, Berven SH, Burch S, Deviren V, Tay B, Hu SS (2008) Use of C-reactive protein after spinal surgery: comparison with erythrocyte sedimentation rate as predictor of early postoperative infectious complications. Spine (Phila Pa 1976) 33:415–421. https://doi.org/10.1097/BRS.0b013e318163f9ee
36. Pallas Beneyto LA, Rodriguez Luis O, Saiz Sanchez C, Coltell O, Bautista Rentero D, Miguel Bayarri V (2016) Prognostic value of interleukin 6 for death of patients with sepsis. Med Clin (Barc) 147: 281–286. https://doi.org/10.1016/j.medcli.2016.06.001
37. Qiao Z, Wang W, Yin L, Luo P, Greven J, Horst K, Hildebrand F (2018) Using IL-6 concentrations in the first 24 h following trauma to predict immunological complications and mortality in trauma patients: a meta-analysis. Eur J Trauma Emerg Surg 44:679–687. https://doi.org/10.1007/s00068-017-0880-9
38. Repo JP, Hakkinen AH, Porkka T, Hakkinen K, Kautiainen H, Kyrola K, Neva MH (2019) Increased interleukin-6 and C-reactive protein levels after instrumented lumbar spine fusion in older patients. J Orthop Surg (Hong Kong) 27:2309499019826406. https://doi.org/10.1177/2309499019826406
39. Roche's Elecsys IL-6 test receives FDA emergency use authorisation to help in identifying patients at high risk of severe inflammatory response https://www.roche.com/dam/jcr:a12d0dbe-0e3d-4591-8e25-386029fca684/en/roche-mediarelease-il-6-fda-eua-04062020.pdf. Accessed 26 Sept 2020
40. Seo J, Park JH, Song EH, Lee YS, Jung SK, Jeon SR, Rhim SC, Roh SW (2017) Postoperative nonpathologic fever after spinal surgery: incidence and risk factor analysis. World Neurosurg 103:78–83. https://doi.org/10.1016/j.wneu.2017.03.119
41. Takahashi J, Ebara S, Kamimura M, Kinoshita T, Itoh H, Yuzawa Y, Sheena Y, Takaoka K (2001) Early-phase enhanced inflammatory reaction after spinal instrumentation surgery. Spine (Phila Pa 1976) 26:1698–1704. https://doi.org/10.1097/00007632-200108010-00014
42. Takahashi J, Shono Y, Hirabayashi H, Kamimura M, Nakagawa H, Ebara S, Kato H (2006) Usefulness of white blood cell differential for early diagnosis of surgical wound infection following spinal instrumentation surgery. Spine (Phila Pa 1976) 31:1020–1025. https://doi.org/10.1097/01.brs.0000214895.67956.60
43. Todd B (2017) New CDC guideline for the prevention of surgical site infection. Am J Nurs 117:17. https://doi.org/10.1097/01.NAJ.0000521963.77728.c0
44. Van Asten SA, Nichols A, La Fontaine J, Bhavan K, Peters EJ, Lavery LA (2017) The value of inflammatory markers to diagnose and monitor diabetic foot osteomyelitis. Int Wound J 14:40–45. https://doi.org/10.1111/iwj.12545
45. Wang J, Xu JW, Li HP (2019) Diagnosis value of serum infection index for early infection of patients undergoing posterior cervical expansive open-door laminoplasty. Zhongguo Gu Shang 32:892–897. https://doi.org/10.3969/j.issn.1003-0034.2019.10.004
46. Weinstein MA, McCabe JP, Cammisa FP Jr (2000) Postoperative spinal wound infection: a review of 2,391 consecutive index procedures. J Spinal Disord 13:422–426. https://doi.org/10.1097/00002517-200010000-00009
47. Zetterstrom M, Sundgren-Andersson AK, Ostlund P, Bartfai T (1998) Delineation of the proinflammatory cytokine cascade in fever induction. Ann N Y Acad Sci 856:48–52. https://doi.org/10.1111/j.1749-6632.1998.tb08311.x