Title: Sensitivity Of C-Reactive Protein Cut-Off Values For Pyogenic Spinal Infection In The Emergency Department

Running Title: CRP for spinal infection

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Abstract

Objectives: To derive and internally validate a sensitive, elevated C-reactive protein (CRP) cut-off value among emergency department (ED) patients with neck or back pain concerning for pyogenic spinal infection (PSI).

Methods: We prospectively enrolled a convenience series of adults presenting to a community ED with neck or back pain in whom ED providers had concern for PSI during 2004-2010 (derivation) and 2010-2018 (validation). The validation cohort included only patients with PSI. We analyzed diagnostic test characteristics of various CRP cut-off values.

Results: We enrolled 232 patients and analyzed 201. The median age was 55 years, 43.8% were male, 4% had history of intravenous drug use, and 20.9% had recent spinal surgery. In the derivation cohort, 38 of 159 patients (23.9%) had PSI. Derivation sensitivity and specificity of CRP cut-off values were >3.5 mg/l (100%, 24.8%), >10 mg/l (100%, 41.3%), >30 mg/l (100%, 61.2%), and >50 mg/l (89.4%, 69.4%). Validation sensitivities of CRP cut-off values were >3.5 mg/l (97.6%), >10 mg/l (97.6%), >30 mg/l (90.4%), and >50 mg/l (85.7%).

Conclusions: CRP cut-offs beyond the upper limit of normal had high sensitivity for PSI in this adult ED population. A cut-off of 30 mg/l requires validation in other settings.

Introduction

Pyogenic spinal infection (PSI) includes spinal epidural abscess (SEA), vertebral osteomyelitis (VO), septic facet joint and paravertebral abscess.[1,2] Clinicians frequently miss the diagnosis of PSI on initial presentation.[1] Delays in diagnosis are associated with worse neurologic outcomes.[3] Cited reasons for diagnostic failure include that PSI is an uncommon disease; spinal epidural abscess (SEA) was present in one of every 255 patients presenting to the emergency department (ED) with neck or back pain in one prospective study.[3] Another reason for diagnostic delay is the fact that clinical findings alone lack adequate sensitivity to identify PSI among the many ED patients presenting with the common chief complaints of neck or back pain.[4–8] The time from symptom onset to diagnosis of PSI averages 2 to 4 months.[1]

C-reactive protein (CRP) is an acute phase reactant which may be used in conjunction with the history and physical exam to identify patients in need of advanced spinal imaging to evaluate for PSI.[1,9–11] Published diagnostic cut-offs for CRP to prompt spinal MRI range from 3 to 100 mg/l, but no particular threshold value has yet gained widespread acceptance.[3,9,12,13] The most commonly cited CRP diagnostic cut-off in ED literature is any elevation beyond the upper limit of normal, approximately 3 mg/l.[3,14] This diagnostic cut-off has very high sensitivity for PSI at the expense of lower specificity.[12] Providers face a difficult challenge of reducing missed diagnosis of PSI without over-utilizing MRI resources as one ED study found that 93% of spinal MRI for evaluation of spinal infection were negative.[15] The optimal threshold must then balance both the priorities of sensitivity and specificity.

The objective of this study was to derive and internally validate an optimal CRP cutoff to identify ED patients requiring urgent or emergent spinal MRI among adults presenting to the ED with neck or back pain concerning for possible PSI per the ED provider evaluation.

Methods

Study design and population

This single-center, prospective cohort study included a convenience sample of adults (≥17 years old) presenting to the ED with neck or back pain in whom the ED provider had a clinical suspicion for PSI. The study setting was a southwestern United States community ED with an annual census of approximately 50,000 patients during the investigation period. Treating ED physicians contacted the Principal Investigator (PI) by phone upon recognizing the possibility of PSI for patient enrollment. Enrollment depended upon the availability of the PI. During the derivation phase (January 2004 to March 2010), the PI enrolled both patients with and without spinal infection. During the validation phase (April 2010-August 2018), the PI only enrolled patients with spinal infection. Enrolled patients received routine care at our institution. We did not blind the physicians to CRP results and they used these values in clinical

decision making as per usual care at our institution. We previously published additional details of enrollment procedures and variable definitions.[16]

We excluded patients presenting to the ED less than 5 days after spinal surgery given persistent elevation of inflammatory biomarkers during that period regardless of whether infection is present.[17,18] We excluded patients diagnosed with tuberculous or fungal spinal infections to allow comparison of our data to other literature evaluating PSI. We excluded patients with missing CRP data. The hospital institutional review board approved the study protocol and all patients provided verbal consent as per the waiver for documentation of informed consent. We adhered to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines in our research design, reporting, and analysis.[19]

Diagnosis of pyogenic spinal infection

PSI included spinal epidural abscess, vertebral osteomyelitis, paravertebral abscess, and septic facet joint.[2] We defined PSI as present if one of three criteria were met: 1) MRI evidence of PSI per neuroradiologist report, 2) operative evidence of PSI per operative report, or 3) culture on CT-guided aspiration consistent with PSI. The use of multiple reference standards reflects the multiple diagnostic modalities used in clinical practice and provided the most accurate categorization of subjects. All patients analyzed as negative for PSI had either a negative spinal MRI or at least 6 months of follow up through the medical record showing no evidence of PSI or new neurologic deficits. We excluded patients without PSI who did not have spinal MRI or at least 6 months of follow up in the medical record.

Microbiologic evaluation

CRP measurements were obtained using commercially available Dimension RXL Chemistry analyzer (Dade Behring, Illinois, United States) from 2004 to 2013 and Dimension Vista 1500 AG autoanalyzer (Siemens, Washington, D.C., United States) from 2013 to 2019. CRP measurements were reported in units of mg/l. The lower reporting level of CRP at our institution coincided with our upper limit of normal. This value was 3.5 mg/l from 2004 to 2009, and 3.1 mg/l from 2009 to 2019.[20] ED physicians did not routinely obtain erythrocyte sedimentation rate (ESR) to allow reporting of this measurement.

Statistical analysis

We derived a highly sensitive cut-off value for CRP by constructing a receiver operating characteristics (ROC) curve and calculating a value to maximize sensitivity with the highest possible specificity.[21] We validated the sensitivity of this cut-off in a separate cohort which only contained patients with PSI present. We compared the diagnostic test characteristics of this derived cut-off to the upper limit of normal for CRP at our institution and the optimal diagnostic cut-off on the ROC according to Youden's J statistic.

Results

Patient characteristics

We enrolled 232 patients between 2004 and 2018 and excluded 31 patients from analysis (Figure 1). The most common reason for exclusion was missing CRP data (n=22). Thirty-eight of 159 analyzed patients enrolled between January 2004 and March 2010 in the derivation phase had PSI, and 25 of these patients (15.7%) had SEA. The most common diagnosis among patients without PSI was nonspecific back pain (52%), followed by non-spine diagnoses (10.7%) such as pneumonia or pyelonephritis (Table 1).

The median age was 55 years (IQR 40 to 66) for the derivation cohort and 56 years (IQR 51 to 63.5) for the validation cohort. In the derivation cohort, 39.0% of patients were male and 22.6% of patients had spinal surgery within the 90 days prior to enrollment (Table 2). Among patients with spinal infection, a minority had intravenous drug use (IVDU) history (7.9% in the derivation cohort and 11.9% in the validation cohort) or presented with fever in the ED (36.8% in the derivation cohort and 14.3% in the validation cohort). *Staphylococcus* sp. was the most commonly isolated pathogen in both the derivation (55.2%) and validation (57.1%) cohorts (Appendix table 1).

CRP findings

Median CRP values in the derivation cohort were 120 mg/l (IQR 67.7 to 172.5 mg/l) among patients with spinal infection versus 14 mg/l (IQR 3.8 to 78 mg/l) among patients without spinal infection (Figure 2). In the derivation cohort, the area under the ROC curve for CRP was 0.825 (Figure 3). The diagnostic cut-off for maximizing sensitivity and specificity with CRP was >49 mg/l per Yuoden's index.

We examined the sensitivity of CRP cut-offs from 3.5 mg/l to 100 mg/l in the derivation and validation cohorts (Figure 4). We further analyzed 4 diagnostic cut-offs for CRP (Table 3). Detectable CRP (>3.5 mg/l) and mildly elevated CRP (>10 mg/l) are commonly cited cut-off values.[3,22,23] CRP >30 mg/l was selected as a cut-off maximizing sensitivity with an easily remembered value of 10 times the upper limit of normal (3.1 mg/l) on many analyzers. CRP >50 mg/l was the rounded value of the Youden's index cut-off. CRP >30 mg/l had 100% sensitivity in the derivation cohort, and 90.4% sensitivity in the validation cohort (Table 3).

Four patients in the validation cohort had spinal infections with elevations of CRP ≤30 mg/l. Two patients were on antibiotics at the time of ED arrival and three had abnormal findings on neurologic examination (Appendix table 2).

Discussion

Current expert opinion for obtaining urgent or emergent spinal MRI in ED patients to evaluate for PSI relies on historical risk factors, physical exam, and inflammatory biomarkers, including CRP.[10,11,24] The usual recommended cut-off value for CRP is the upper limit of normal, commonly >3.1 mg/l, which has high sensitivity but poor specificity.[3] An elevated CRP cut-off of >30 mg/l, approximately 10 times the upper limit of normal, increased specificity while

maintaining high sensitivity for diagnosis of PSI in this adult ED population with a low prevalence of IVDU.

Our findings are consistent with multiple recent studies finding that CRP concentrations in PSI are usually elevated well beyond 3 mg/l. A recent prospective cohort of 88 patients with VO had a mean CRP of 140 mg/l.[12] An RCT of 351 patients with VO had a mean CRP of 122 mg/l and 91% of patients had CRP> 10 mg/l.[23] A retrospective cohort of 166 patients with SEA found that 81% of patients had CRP >3 mg/l.[22] CRP may be less sensitive for PSI associated with IVDU with one study finding a 72% sensitivity for CRP greater than the upper limit of normal.[25]

Clinicians cannot use CRP indiscriminately or in isolation as many conditions cause elevated CRP.[26] Our study examined a patient population with clinical concern for PSI, and application of CRP in the broader population of back pain would decrease specificity. Multiple conditions, such as recent use of antibiotics or cirrhosis, may contribute to less elevated CRP levels in the setting of PSI.[27–29] Clinicians should consider use of lower CRP cut-offs in patients with these conditions. In our cohort, half of the patients with PSI and relatively low CRP (≤30 mg/l) results were on antibiotics prior to arrival, and the majority of these cases had abnormalities on neurologic exam.

Close attention to units is necessary when interpreting CRP reports both clinically and in the literature. Our institution had an upper limit of normal of 3.1 mg/l for the majority of the study period, but many institutions report an upper limit of normal of 0.3 mg/dL. The recommendation to use a cut-off of 10 times the upper limit of normal can be easily and consistently applied in various clinical settings reporting different units.

Limitations

Our study represents a convenience sample, and we lack data describing patients with back pain during the study period who did not have a diagnostic work up for spinal infection. Thus, our study is subject to spectrum bias by potentially missing patients with less severe disease. We collected data at a single center, so the generalizability of our findings to other settings is unknown. We collected data over an extended period of time to collect a sufficient number of cases, but changing practice patterns, patient characteristics, or pathogen characteristics may have led to evolution of the cohort over time. Our study population had a low prevalence of IVDU, so the applicability of our findings to settings with the majority of spinal infections related to IVDU is unknown. Also, we did not systematically collect data regarding recent antibiotic use prior to ED presentation.

There are also several limitations in our dataset related to laboratory studies. ED physicians used CRP in the clinical decision-making process. Thus, patients with elevated CRP values may have been more likely to undergo additional spinal imaging and hence more likely to have infections diagnosed. We had strict criteria for excluding spinal infection, included a prolonged follow up period, to address this limitation. We lack sufficient ESR data to compare

the diagnostic characteristics of ESR versus CRP. Some studies report ESR is more sensitive than CRP in diagnosing SEA,[3,25] but recent literature challenges this claim.[11]

Conclusion

CRP cut-off values above the upper limit of normal had excellent sensitivity for PSI in this adult ED population with low prevalence of IVDU. Clinicians should not apply elevated CRP cut-offs in patients with IVDU or conditions associated with decreased CRP values, such as cirrhosis or recent antibiotic use. A CRP cut-off of >30 mg/l to increase specificity with acceptable sensitivity requires validation in other settings.

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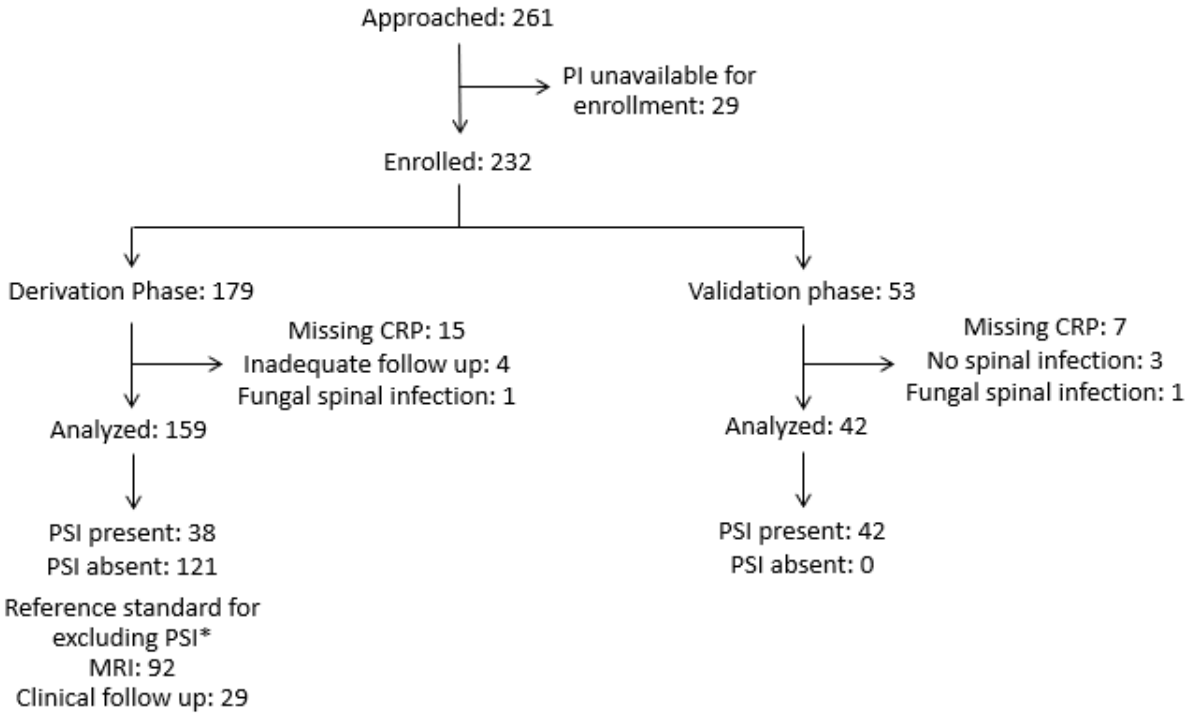
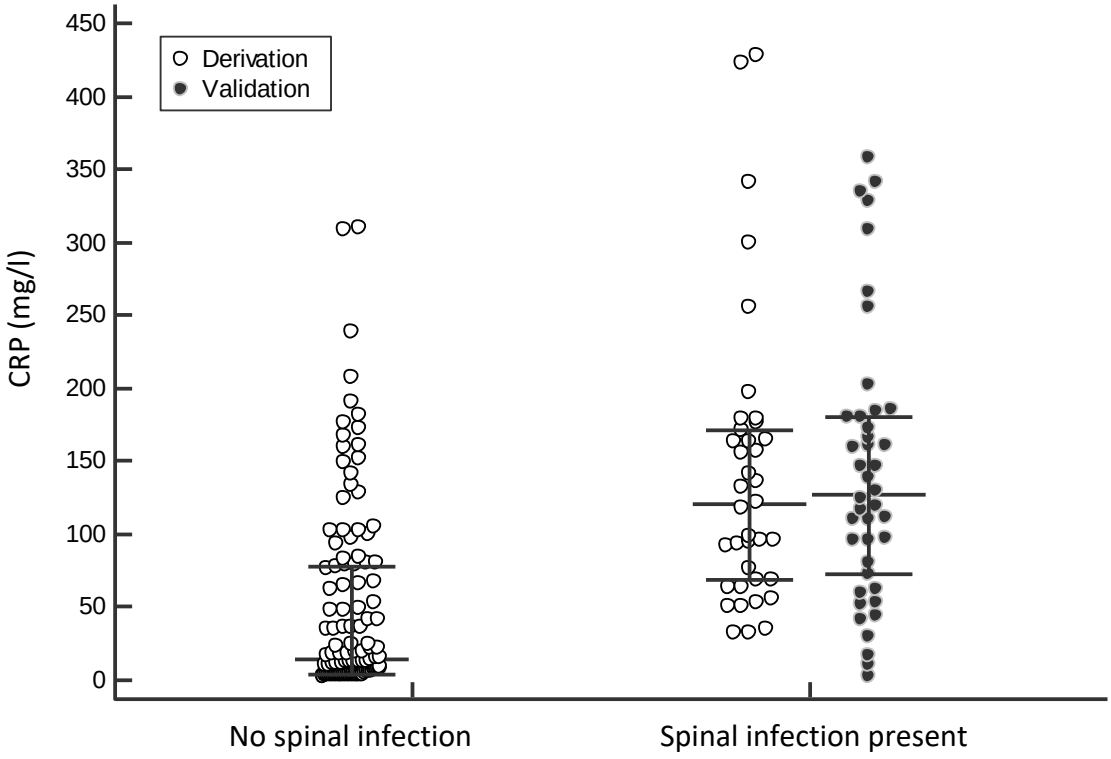
Figure 1. Patient flow diagram.



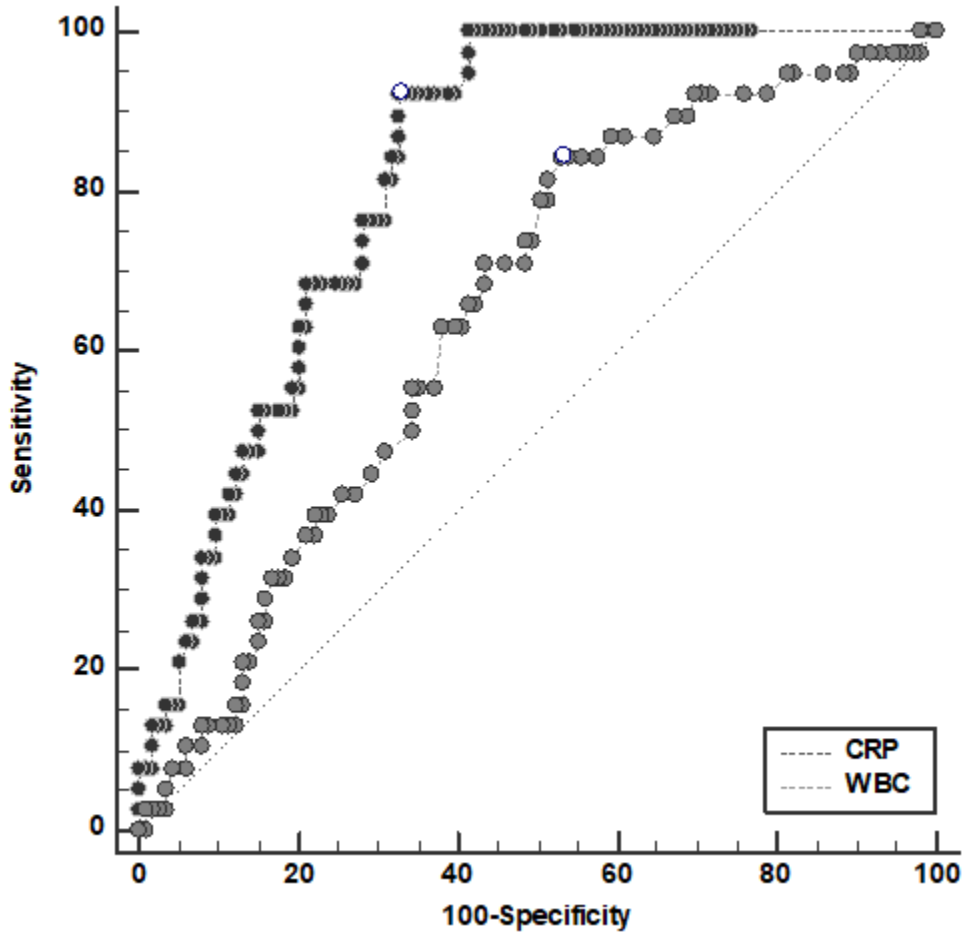
*PSI= pyogenic spinal infection. Reference standard shown for cases without infection only.

Figure 2. Distribution of C-reactive protein values.



* Long horizontal bars represent medians for each group and vertical lines represent the interquartile range.

Figure 3. Receiver operating curves for C-reactive protein and leukocyte count in derivation cohort.



Area under the curve was 0.825 for CRP and 0.651 for leukocyte count (WBC).

Figure 4. Sensitivity of C-reactive protein cut-off values from 0 to 100 mg/l.

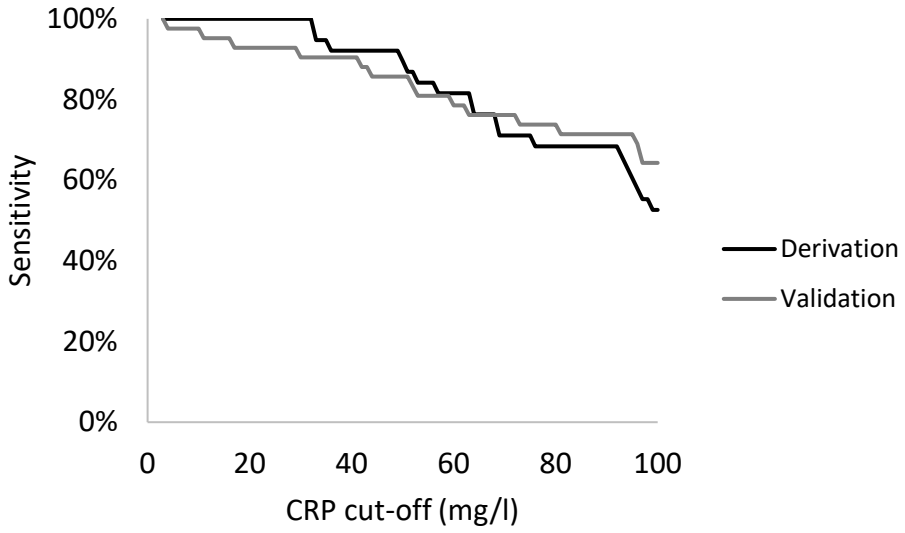


Table 1. Final diagnosis of 201 analyzed patients.

Final diagnosis	Derivation (n= 159)	Validation (n= 42)
Pyogenic spinal infection	38 (23.8)	42 (100)
Spinal epidural abscess	25 (15.7)	29 (69.0)
Vertebral osteomyelitis	21 (13.2)	26 (61.9)
Septic facet joint	3 (1.9)	10 (23.8)
Paravertebral abscess	19 (11.9)	24 (57.1)
Metastatic Cancer	7 (4.4)	
Epidural hematoma	4 (2.5)	
Central disc herniation	8 (5.0)	
Meningitis or myelitis	2 (1.3)	
Nonspecific back pain	83 (52.2)	
Non-spine diagnosis	17 (10.7)	

All data are presented as number (%).

Table 2. Baseline characteristics.

	Derivation cohort		Validation cohort
	No spinal infection (n=121)	Pyogenic spinal infection (n=38)	Pyogenic spinal infection (n=42)
Median age (IQR), y	56 (39 to 68)	51.5 (42.8 to 59)	56 (51 to 63.5)
Male sex	34 (28.1)	28 (73.7)	26 (61.9)
Historical risk factors			
IVDU history	0 (0)	3 (7.9)	5 (11.9)
Dialysis	4 (3.3)	3 (7.9)	1 (2.4)
Indwelling vascular catheter	0 (0)	4 (10.5)	6 (14.3)
Recent SSTI or bacteremia	3 (2.5)	14 (36.8)	11 (26.2)
Immunosuppression	4 (3.3)	2 (5.3)	1 (2.4)
Diabetes	39 (32.2)	16 (42.1)	17 (40.5)
Cirrhosis	0 (0)	3 (7.9)	4 (9.5)
Spinal implant present	7 (5.8)	0 (0)	2 (4.8)
Recent spinal surgery	22 (18.2)	14 (36.8)	6 (14.3)
Recent spinal injection	20 (16.5)	0 (0)	8 (19.0)
Physical exam findings			
Fever (≥38 C) in ED	23 (19)	14 (36.8)	6 (14.3)
Extremity weakness*	18 (14.9)	8 (21.1)	6 (14.3)
Extremity numbness*	11 (9.1)	6 (15.9)	3 (7.1)
Abnormal reflex exam*	4 (3.3)	4 (10.5)	4 (9.5)
Any new neurologic deficit*	24 (19.8)	13 (34.2)	12 (28.6)

*Neurologic deficits only counted as present if assessed to be acute by the principal investigator.

Table 3. Diagnostic characteristics of 4 c-reactive protein cut-off values.

	Derivation				Validation
CRP cut-off (mg/l)	Sensitivity	Specificity	Positive LR*	Negative LR*	Sensitivity
>3.5	100	24.8	1.33	0	97.6
>10	100	41.3	1.70	0	97.6
>30	100	61.2	2.57	0	90.4
>50	89.4	69.4	3.01	0.12	85.7

*LR= likelihood ratio.

Appendix Table 1. Identified pathogens for patients with pyogenic spinal infection.

	Derivation cohort (n=38)	Validation cohort (n=42)
Pathogen identified*	31 (81.6)	38 (90.5)
Gram-positive bacteria		
Staphylococcus sp.	21 (55.2)	24 (57.1)
MSSA	10 (26.3)	21 (50)
MRSA	11 (28.9)	3 (7.1)
Staphylococcus, coagulase negative	1 (2.6)	2 (4.8)
Streptococcus sp.	6 (15.8)	5 (11.9)
Enterococcus	0	2 (4.8)
Corynebacterium	0	1 (2.4)
Clostridium septicum	1 (2.6)	0
Gram-negative bacteria		
Serratia marcescens	1 (2.6)	1 (2.4)
Salmonella	0	0
Escherichia coli	1 (2.6)	1 (2.4)
Pseudomonas aeruginosa	0	2 (4.8)

*Pathogens identified on cultures of blood, needle aspirate, or operative wounds. All data are presented as number (%).

Appendix table 2. Case summaries* of patients with CRP ≤30 mg/l in the setting of spinal infection.

Case No.	Age/ Sex	Risk Factors	Recent antibiotics	Neurologic exam	CRP	Pathogen	Spinal infection
1	69 F	Diabetes	No	Extremity weakness	10.6	MRSA	Cervical VO, paravertebral abscess, SF
2	61 F	None	Yes	Extremity weakness, overflow incontinence	17	MRSA	Cervicothoracic SEA, thoracic SF
3	47 M	None	No	Normal	3.2	MSSA	Cervical VO and paravertebral abscess
4	61 F	30 days post-op, vascular catheter, recent infection	Yes	Extremity weakness and numbness, abnormal reflexes	29.7	Not identified	Cervicothoracic SEA and VO. Thoracic paravertebral abscess.

*No patient had fever ≥38^0 C either in the ED or measured prior to arrival. VO= vertebral osteomyelitis, SF=septic facet joint.