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Brief Report

Utility of point-of-care synovial lactate to identify septic arthritis in the emergency department

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ABSTRACT

Background: Synovial lactate is a promising biomarker to distinguish septic from aseptic arthritis. If available as a point-of care test, synovial lactate would be rapidly available to aid the emergency provider in clinical decision making. This study assesses the test characteristics of synovial lactate obtained using an EPOC© point-of-care (POC) analyzer to rapidly distinguish septic from aseptic arthritis in the emergency department.

Methods: We enrolled a convenience sample of patients with possible septic arthritis presenting to the emergency department at a large urban academic center between October 2016 and April 2018. Enrolled patients underwent arthrocentesis based on the clinical judgment of the treating provider. We obtained synovial lactate levels (SLL) from the POC device. Standard laboratory analysis, synovial fluid culture, emergency and hospital course, operative procedures, antibiotics, and discharge diagnosis were abstracted from the electronic medical record.

Results: Thirty-nine patients undergoing forty separate arthrocentesis procedures were enrolled in this study over the two-year period. The sensitivity and specificity of SLL ≥ 5 mmol/L was 0.55 and 0.76 respectively, with +LR 2.3 and −LR 0.6. The sensitivity and specificity of SLL ≥ 10 mmol/L was 0.27 and 0.97 respectively, with +LR 7.9 and −LR 0.8; SLL ≥ 10 mmol/L performed similarly to overall synovial WBC ≥ 50,000/μL by conventional laboratory testing.

Conclusion: It is feasible to obtain a synovial lactate level using the EPOC© POC device. In our study, POC SLL performs similarly to other markers used to diagnose septic arthritis. Further study with larger sample sizes is warranted.

1. Introduction

Septic arthritis remains a relatively rare diagnosis, with roughly 16,000 cases seen in the Emergency Department (ED) per year, or 0.01% of annual ED visits in the United States [1]. It is difficult to distinguish septic from aseptic arthritis, since both frequently present with a similar clinical picture. Prior research suggests that physicians are able to accurately diagnose the etiology of acute non-traumatic monoarticular arthritis at approximately 3 days [2]. ED physicians do not have the luxury of this timeline, and inadequate or delayed treatment of septic arthritis can lead not only to increased morbidity from joint destruction in up to 50% of cases [3], but also to mortality in >10% of cases [4].

Classic signs and symptoms of septic arthritis, such as non-traumatic acute monoarticular joint pain, swelling, erythema, or micromotion tenderness to palpation, are not sufficiently sensitive nor specific for the diagnosis of septic arthritis [5]. Adding to the complexity of making an accurate diagnosis, there is not a clear diagnostic gold standard [4,6,7], with case definitions based on one of four criteria: (1) isolation of pathogenic organism from affected joint, (2) isolation of pathogenic organism from another source (i.e. blood) in the context of a suspicion of joint infection, (3) typical clinical features and turbid joint fluid in joint previously treated with antibiotics, or (4) postmortem features suspicious of septic arthritis [4]. Because synovial fluid culture is only 75–95% sensitive for septic arthritis [8], and time to culture limits timeliness of diagnosis, accurate and fast diagnostic laboratory markers are necessary to identify septic arthritis.

Though laboratory markers such as C-reactive protein (CRP) and peripheral white blood cell count (pWBC) have been used to distinguish between the two types of arthritis, several studies have shown that these markers do not differ significantly between septic and aseptic joints [9,10]. The classically taught synovial WBC (sWBC) ≥ 50,000/μL also does not adequately distinguish between these two disease processes [4,11]. Other biomarkers, such as laboratory-measured synovial

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glucose and uric acid were also considered but found to be inferior in accuracy to synovial lactate level (SLL) [9]. A few studies have been done on the potential of laboratory-measured SLL to serve as a diagnostic marker to identify bacterial etiologies of arthritis, but the overall quality of evidence is relatively low with the majority of studies being retrospective [2,9].

A limitation in the potential usefulness of SLL in the emergency department is the ability of the clinical laboratory to process the synovial sample and obtain rapid lactic acid values for the clinician's use. Many emergency departments, including the authors', may lack the ability to quickly obtain a SLL. In such a setting, a point of care test is clearly desirable. Given how promising laboratory-measured SLL is in the rapid identification of septic joints, this study was designed to assess the usefulness of EPOC© point of care (bedside) lactate values as a tool to rapidly distinguish between septic and aseptic joints.

2. Methods

We prospectively enrolled patients undergoing arthrocentesis for the evaluation of a swollen or painful joint in the ED at the University of California San Francisco Fresno campus, a large urban academic center, between October 2016–April 2018. Arthrocentesis was performed at the discretion of treating providers according to standard practices. Synovial fluid was sent to the main laboratory for analysis and desired fluid studies were ordered by the treating physicians. The study protocol did not affect whether or not joint aspiration occurred, nor did it dictate which laboratory studies each treatment provider ordered. If the provider completing the aspiration was able to obtain at least 1 mL of additional synovial fluid in a separate sterile syringe, the patient was able to be enrolled in our study. The study sample was then analyzed promptly using the point of care EPOC© blood gas analysis system by Alere using the standard test card. Point of care (POC) SLL was recorded, in addition to joint location, fluid characteristics, and patient identifiers.

From the electronic medical record, investigators then abstracted data including sWBC and cell count with differential, synovial gram stain and culture. Investigators also reviewed the patient's ED and hospital course, any operative procedures done, antibiotics given, and final discharge diagnosis. Since synovial fluid culture itself is an imperfect diagnostic measure [8], we defined septic arthritis as patients with (1) synovial fluid culture positive or (2) septic arthritis diagnosed by our orthopedists with surgical intervention and IV antibiotics given during the hospital stay, even if cultures were ultimately negative. We also included in our final analysis a small number of patients who had fluid samples from septic bursitis and were treated with antibiotics.

Statistical analysis was done using Excel® (Microsoft Office 2016) and SPSS© (IBM, version 24). Sensitivity and specificity for each diagnostic test was analyzed using the chi-squared analysis, Fisher's exact test, and linear regression modeling. ROC curves were calculated using both parametric and non-parametric analyses. The C-statistic (area under the ROC curve) for each test was obtained using the parametric analysis. The positive and negative likelihood ratio for each test was calculated using the chi-squared table, and values were confirmed with the non-parametric ROC analysis.

3. Results

During the study period, 39 patients were enrolled with 40 arthrocenteses performed (one patient had the procedure on bilateral knees). Eleven (28%) of the 39 patients were female. Mean patient age was 51 years, ranging from 16 to 85 years. There was no significant difference in diagnosis of septic joint by gender ($p = 0.82$) or age ($p = 0.60$).

Of the 40 separate joints sampled, there were 29 knees (73%), 6 elbows (15%), 3 ankles (8%), 1 wrist (2%) and 1 shoulder (2%). Eleven (27.5%) joints were ultimately diagnosed as septic arthritis or infected bursitis, with 6 (15%) undergoing operative intervention [Table 1]. The diagnoses for patients without septic joints were simple effusion ($n = 15$, 37%), crystal arthropathy including gout or pseudogout ($n = 9$, 22%), and inflammatory arthritis ($n = 6$, 15%).

The sensitivity and specificity of a SLL ≥ 5 mmol/L was 55% [95% CI 32–94%] and 76% [95% CI 62–93%] respectively, with LR+ 2.3 and LR− 0.6. The sensitivity and specificity of a SLL ≥ 10 mmol/L was 27% [95% CI 10–72%] and 97% [95% CI 79–99%] respectively, with LR+ 7.9 and LR − 0.8. The sensitivity of the commonly used physical examination findings and laboratory tests to evaluate septic joints was poor in our study [Table 2]. The specificity of sWBC ≥50,000/μL, sWBC ≥100,000/μL, and WBC differential of polymorphonuclear neutrophils ≥90% all performed well in ruling in septic arthritis, though they were all poorly sensitive in ruling it out.

The C-statistic for SLL ≥ 10 mmol/L was 0.69 [Fig. 1]. (A C-statistic of 0.5 represents a tool no better than chance, >0.7 a good model, >0.8 a strong model, and 1.0 is a model with perfect prediction.) Similar or poorer C-statistic values were obtained for all of the commonly used

Table 1
Patients diagnosed with septic arthritis

Patient number	Age (years)	Gender	Joint	Synovial lactate (mmol/L)	Synovial WBC (leukocytes/ml)	PMNs (%)	Gram stain	Synovial culture	Operative intervention	Blood culture	Diagnosis
1	63	M	Knee	1.27	750	79	Neg	*Staphylococcus aureus*	No	Micrococcus Species	Septic joint
2	57	M	Knee	16.87	40,000	84	Pos	*Staphylococcus aureus*	Yes	No Growth	Septic joint
3	16	F	Knee	1.17	5622	86	Neg	No growth	Yes	No Growth	Septic joint and osteomyelitis
4	53	M	Ankle	5.76	100,800	86	Neg	No growth	Yes	N/A	Septic joint and gout
5	52	M	Elbow	4.41	1650	87	Neg	*Staphylococcus aureus*	No	N/A	Infected bursitis
6	58	M	Knee	7.28	1935	88	Neg	*Staphylococcus aureus*	Yes	No Growth	Septic joint with cellulitis
7	33	M	Knee	4.25	15,390	93	Neg	*Staphylococcus aureus*	No	Staphylococcus aureus	Multiple septic joints, bacteremia
8	55	F	Elbow	4.74	80,750	94	Neg	No growth	Yes	N/A	Septic joint and gout
9	55	M	Elbow	11.79	133,750	95	Neg	*Staphylococcus aureus*	No	N/A	Infected bursitis
10	85	F	Shoulder	11.61	18,117	96	Neg	*Escherichia coli*	Yes	No Growth	Septic joint
11	64	M	Knee	9.27	47,520	97	Pos	Group B *Streptococcus*	No	N/A	Infected bursitis

Table 2
Test Characteristics of synovial lactate and fluid characteristics used in the diagnosis of septic joints

Test	*p* value	Sensitivity	Specificity	C-Statistic	LR+	LR−
Synovial lactate ≥5	0.075	0.55 [0.32, 0.94]	0.76 [0.62, 0.93]	0.68	2.3	0.6
Synovial lactate ≥10	0.056	0.27 [0.10, 0.72]	0.97 [0.79, 0.99]	0.69	7.9	0.8
Cloudy synovial fluid	0.578	0.45 [0.24, 0.87]	0.52 [0.36, 0.74]	0.48	0.9	1.1
Warmth or erythema	0.183	0.64 [0.40, 0.99]	0.59 [0.43, 0.80]	0.62	1.5	0.6
WBC ≥ 50 K	0.056	0.27 [0.10, 0.71]	0.97 [0.79, 0.99]	0.69	7.9	0.8
WBC ≥ 100 K	0.071	0.18 [0.05, 0.64]	1	n/a	10	0.8
PMN ≥ 90%	0.467	0.45 [0.24, 0.87]	0.62 [0.47, 0.82]	0.54	1.2	0.9
Positive gram stain	0.071	0.18 [0.05, 0.64]	1	n/a	10	0.8
Micromotion tenderness	0.196	0.27 [0.10, 0.72]	0.9 [0.72, 0.97]	0.62	2.6	0.8

tests and physical exam findings used to distinguish septic from non-septic joints [Table 2].

4. Limitations

The EPOC© point of care analyzer and cartridges were not developed for use in analyzing synovial fluid, nor are they approved for this indication. Furthermore, we were unable to compare POC SLL to a laboratory value as our hospital does not process these samples. We did not measure time from sample collection to analysis but did request that samples be analyzed as soon as possible after collection. This was a small, single-center study, and our data did not reach statistical significance, likely secondary to the small sample size and low incidence of disease within our population. Given our small sample size, our sensitivity and specificity data have wide confidence intervals. A large multicenter, prospective study would better elucidate whether POC SLL provides adequate sensitivity and specificity in the diagnosis of septic arthritis.

5. Discussion

In our present study, POC SLL ≥ 10 mmol/L performed similarly with the classic diagnostic marker of sWBC ≥50,000/μL with poor sensitivity at 27% and near perfect specificity at 97%. Our results reflect similar sensitivity and specificity as prior studies measuring sWBC for the diagnosis of septic arthritis, with wide ranges for both measures (sensitivity: 31–70% with cutoff at 50,000/μL and 6–31% at 100,000/μL; specificity 74–97% with cutoff at 50,000/μL and 94–100% at 100,000/μL) [2,7,11,12]. Though POC SLL and sWBC had similar test characteristics in our small study, the advantage of bedside POC SLL is a shorter time to diagnosis. The additional cost of the test was also not burdensome, at approximately $3.40. This is in comparison to a cost of approximately $6.80 for the formal laboratory cell count and differential [13].

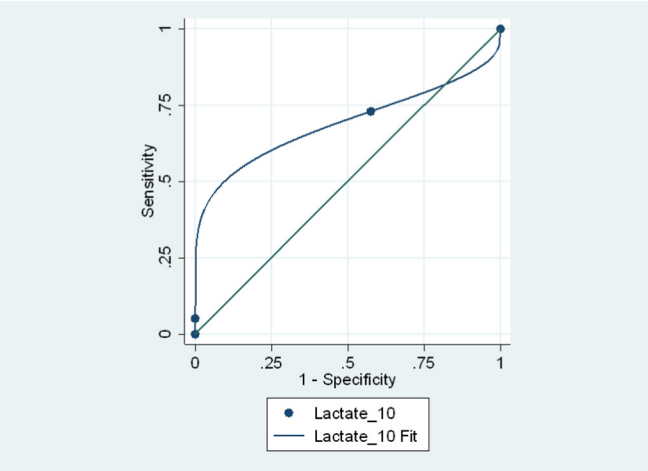

Fig. 1. ROC curve for synovial lactate level (SLL) ≥ 10 mmol/L. C-Statistic for Lactate ≥10 = 0.689704.

Of the eleven patients ultimately diagnosed with septic joints, two had positive blood cultures, though only 54% of these patients had blood cultures drawn at all. The same organism grew from the blood and synovial fluid in only one patient. Since one of our metrics for the diagnosis of septic arthritis or bursitis was synovial fluid culture growth, there may be some concern that improper cleansing of the skin led to the contamination of the sample with methicillin-resistant *Staphylococcus aureus* (MRSA), staph aureus or another cutaneous bacteria and therefore a false positive. In our study population of 40 joints, only one patient ultimately grew MRSA as part of their synovial fluid culture; an additional 5 patients had *Staphylococcus aureus* cultured from synovial fluid. However, all of these patients had additional findings to suggest a septic joint independent of the synovial fluid culture result alone. Future studies with larger sample size will need to address this clinical question.

The measurement of SLL is not a new idea and has been previously shown to correlate well with response to antimicrobial treatment [14-16], however, explicit guidelines and diagnostic cut off values still have not been clearly established. Mean SLL was 15.1 (±5.7 SD) mmol/L among non-gonococcal septic arthritis joints in one study and reportedly markedly elevated compared to gonococcal septic arthritis and non-septic arthritides [16]. Another paper reported mean SLL of 24.4 mmol/L for culture-positive and 17.3 mmol/L for culture-negative septic arthritis, whereas mean SLL for rheumatoid arthritis, crystal arthropathy, and osteoarthritis were 5.9, 2.7, and 1.8 mmol/L, respectively [15]. Neither of these early groundbreaking studies reported sensitivity, specificity, or positive/negative likelihood ratios.

In the few available studies since the 1980s, laboratory-measured SLL has shown to be nearly 100% specific at a threshold of SLL ≥ 10 mmol/L [2,9]. The only study with sensitivity, specificity, and likelihood ratios for SLL analysis that we identified showed mean SLL 11.7 and 3.5 mmol/L in septic and gouty arthritis, respectively ($p = 0.0003$) [9]. This same 2014 retrospective study found that a cutoff threshold to maximize sensitivity (89.5%) and specificity (77.3%) of SLL was ≥4.3 mmol/L, with AUC 0.901 [9]. Our study with bedside POC SLL testing did not perform as well as the 2014 paper which utilized main laboratory measurements, but this may be secondary to a very small sample size.

To our knowledge, this is the first study to prospectively assess bedside POC SLL in the ED diagnosis of septic arthritis. Our study was a proof-of-concept study with promising results. We were able to quickly obtain reasonable SLL values from the POC device. In our study, the test characteristics of POC SLL > 10 mmol/L were similar to those of sWBC > 50,000. However, due to the small sample size of our study there is not enough evidence at this time to conclusively state that POC SLL is better than classic laboratory testing and more research is necessary prior to recommending its routine usage in the diagnosis of septic arthritis.

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