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Washington University Emergency Medicine Journal Club
Synovial Lactate and the Diagnosis of Septic Arthritis

Vignette

While working another crowded EM2 shift, you evaluate a 40-year old construction worker with a painful and swollen right knee. He cannot recall any injury to the knee and has no significant past medical history, including no prior crystalloid arthropathy (gout), knee surgeries, or endovascular infections (endocarditis). The knee hurt yesterday, but is exquisitely painful today with a palpable effusion and no notable overlying erythema or warmth to the touch. You note no surgical scars or overlying abrasions. He does not take any daily medications and cannot recall his last primary care physician evaluation.

His vitals are BP 140/80, P 60, RR 18, T 36.8°C, and pulse ox 100%. He is lean and muscular without any other remarkable findings on physical exam, including no genitourinary complaints. Passive or active range of motion of his right knee is extremely uncomfortable for him.

You promptly order morphine analgesia for this patient and then contemplate the differential diagnosis of a unilateral swollen and painful knee. In the absence of traumatic injury, you doubt a hemearthrosis, although he is a construction worker so you cannot exclude an occult twisting injury or overuse syndrome. However, the two primary diagnoses you consider most pertinent to rule-in or rule-out today are crystalloid arthropathies or septic arthritis. Recent debates about the American College of Emergency Physician's decision not to participate in the Choosing Wisely campaign linger in your mind as you ponder what resources exist to "choose wisely" (pros and cons) in ED diagnostic decision making (see **http://tinyurl.com/bs2vjj7**). You speculate on the diagnostic accuracy of serum tests (CBC, ESR, CRP) and ponder the risk/benefits of arthrocentesis.

After reviewing Roberts and Hedges' Clinical Procedures in Emergency Medicine 5th Edition chapter describing the methods to perform and interpret knee joint aspirations (page 980-983), you discuss the procedure with the patient. After obtaining informed consent, you prep the patient and perform a time-out before administering 7cc of 1% lidocaine. The subsequent joint aspirate, obtained without significant patient discomfort or other adverse sequelae, is a cloudy yellow hue. You send the fluid to the lab and request a synovial lactate because you read somewhere that is a valuable test to evaluate for septic arthritis. The lab calls you back 30-minutes later telling you that they have no protocol for synovial lactate and cannot run the specimen for lactate. You turn to the medical literature to explore this diagnosis further.

PICO Question

Population: Adult patients with suspected septic arthritis
Intervention: History/physical exam, sWBC, sLactate
Comparison: Unaided clinical gestalt
Outcome: Diagnostic accuracy (sensitivity, specificity, LR's)

Search Strategy

EBM has taught you that well-done meta-analyses can be high-yield products for busy clinicians. Therefore, you turn to PUBMED to conduct a diagnostic study Clinical Query using the search term "septic arthritis" and select the systematic reviews (108 citations – see **http://tinyurl.com/9822z3r**). Among the first 10 citations are two high-quality reviews, but one of the reviews derives from the other so you choose the meta-analysis on this topic which yields the remainder of the manuscripts that you review.

Article 1: Evidence Based Diagnostics: Adult Septic Arthritis, **Acad Emerg Med** 2011; 18(8):781-796. (http://pmid.us/21843213) Answer Key

Article 2: D-lactic acid in synovial fluid. A rapid diagnostic test for bacterial synovitis, **J Rheumatol** 1995; 22: 1504-1508. (http://pmid.us/7473474) Answer Key

Article 3: Synovial fluid lactic acid: A diagnostic aid in septic arthritis, **Arthritis Rheum**, 1978; 21(7):774-779. (http://pmid.us/697948) Answer Key

Article 4: Synovial fluid lactic acid in septic arthritis, **N Z Med J** 1981; 93(678): 115-117. (http://pmid.us/6943453) Answer Key

Bottom Line

The differential diagnosis for acute monoarticular arthritis presenting to the ED is broad and includes infections (bacterial, fungal, mycobacterial, viral), crystalloid arthropathy (gout, pseudogout), rheumatoid arthritis, and trauma. Based upon the sole ED-centric systematic review available on this topic, the best estimate pre-test probability for septic arthritis in the ED is 27%. This means that among all ED patients in whom the clinician believes that septic arthritis is sufficiently likely to merit an arthrocentesis, 27 in 100 will actually have non-gonococcal septic arthritis. Most experts agree that this is an overestimate, but there is currently no better estimate of pre-test probability to facilitate Bayesian reasoning.

Clinicians are able to deduce the etiology of acute nontraumatic joint pain/swelling within 3-days in most cases, but in an era of "overdiagnosis" and "overtreatment" ED providers lack the luxury of a 3-day admission for most monoarticular arthritis patients. ED physicians' clinical decision making often skews to the "rule out worst case scenario" model, which in the case of an acutely painful/swollen joint includes septic arthritis. About 50% of septic arthritis cases involve the knee, but any synovial space can be infected. Septic arthritis management options include surgical drainage and systemic antibiotics, although needle aspiration has also been evaluated in select cases. Short-term mortality for *treated* septic arthritis ranges from 3% to 11% (Cooper 1986, Deesomchok 1990, Kaandorp 1995, Gupta 2001).

As is true with the majority of emergency medicine diagnoses (and medicine/surgery diagnoses), there is a paucity of diagnostic research to illuminate best-evidence practices for history, physical exam, clinical gestalt, and lab testing for septic arthritis. In fact, diagnostic studies of history and physical exam to evaluate septic arthritis in *any* setting are virtually non-existent. We identified two studies assessing historical risk factors and found none that evaluated physical exam. None of the studies (including the lab test studies) adheres to the STARD criteria in design or intent. Therefore, the available evidence may provide skewed estimates of diagnostic accuracy because of various biases, including spectrum bias, double-gold standard bias, and incorporation bias.

Nonetheless, the available evidence for historical risk factors identified just three factors with a likelihood ratio > 3: prosthetic joint with overlying skin infection (LR+ 15), joint surgery within the preceding 3-months (LR+ 6.9), and age > 80 (LR+ 3.5). The absence of risk factors does not significantly reduce the probability of septic arthritis (the range of LR- was 0.64-0.93). To make this diagnosis even more challenging, commonly available serum tests (WBC, ESR, CRP) for septic arthritis are inaccurate and probably worthless acutely (see below). Eliminating these serum tests from the lexicon of reflexive ED testing for septic arthritis is an attractive target to "Choose Wisely"(see Bukata essay 1 and essay 2) in reducing unhelpful, potentially expensive laboratory testing. During Journal Club, Orthopedic surgery opined that serial assessment of ESR and CRP is anecdotally helpful for the longitudinal diagnosis and prognosis in the evaluation of suspected septic arthritis. However, nobody could identify any evidence to support this practice. Although serum procalcitonin and tumor necrosis factor (as does PCR testing to identify the specific infecting organism within 3-hours) have promising positive likelihood ratios, these tests are not commonly available in the ED.

	LR+	LR-
WBC*	1.4-1.7	0.28-0.84
ESR*	1.3-7.0	0.17-2.4
CRP*	1.1-4.5	0.3-0.7
Procalcitonin	5-∞	0.3-0.7
TNF	∞	0.7
IL-6	1.5	0.9
IL-β	3.2	0.8

The suboptimal diagnostic test characteristics for history, physical exam, and serum tests leaves synovial testing as the standard of care diagnostic strategy to evaluate for septic arthritis. The sole systematic review noted that the risk of arthrocentesis includes post-procedural iatrogenic infections with a range of 0.01% in healthy populations to 0.05% in immunocompromised patients. During this Journal Club, Orthopedic surgery noted that:

1. They would prefer to perform the first and only arthrocentesis for suspected post-op joint infections to avoid iatrogenic complications (i.e. arthrocentesis-related infections)
2. Prosthetic joints typically yield less pronounced (lower) synovial leukocytosis than do native joint infections.

So how well does the synovial fluid distinguish non-gonococcal bacterial arthritis from other acute joint problems? Synovial gram stain has sensitivity 29% - 65% with an undefined specificity (Argen 1966, Goldenberg 1976, McCutchan 1990, Faraj 2002, McGillicuddy 2007). A synovial WBC > 100,000 cells/mm^3 has an interval LR of infinity, whereas a synovial WBC 0-25,000 has interval LR of 0.33.

Our review of the synovial lactate data in conjunction with Laboratory Medicine and Orthopedic Surgery for this Journal Club suggests that synovial lactate is a promising test for the future ED evaluation of suspected acute septic arthritis. Unfortunately, two of the three studies did not distinguish whether they assessed D- or L-lactate! Bacteria, not humans (with rare exceptions such as short gut syndrome), produce D-lactate. On the other hand, humans, not bacteria, produce L-lactate. Laboratory Medicine believes that D-lactate is biologically plausible as a diagnostic marker of bacterial arthritis, but no commercially available laboratory test currently exists for D-lactate. D-lactate is a 3-day mail out test to Mayo Clinic. On the other hand, Laboratory Medicine hypothesizes that L-lactate is correlated with the synovial white blood cell count with higher sWBC counts producing more L-lactate. This hypothesis has not been tested. In fact, none of the synovial lactate studies evaluated the L- or D-lactate real-time. Instead, specimens were frozen and tested in batches long after the patient care episode was past. Here is the study-by-study synopsis of the available data.

Gratacós 1995

This is the only study to specify which form of lactate they assessed (D-lactate). Interval LR's range from 0.16 (D-lactate 0-0.05 mmol/L) to 20 (D-lactate >0.15 mmol/L). This test is superior to synovial WBC $\geq$ 50,000 cells/mm^3 (LR^+ 9.3, LR^- 0.47) or sPMN > 90% (LR^+ 2.7, LR^- 0.37) and may be particularly useful for partially treated septic arthritis.

Brook 1978

At a threshold of 5.5 mmol/L (note 10-fold higher than Gratacós' study which may indicate that Brook was studying L-lactate) the synovial lactate LR^+ is 5.9 and LR^- 0.04. More importantly, the interval LR for 0-5.5 mmol/L is 0.06 and for >16.7 mmol/L it is infinity. Unfortunately, the authors do not describe whether they evaluated D-lactate or L-lactate and by failing to adhere to STARD criteria, the authors leave open the possibility for significant biases, most of which skew estimates of sensitivity and specificity upwards.

Moss 1981

Based on this case-control, single-center, Rheumatology clinic study, synovial lactate assays (probably L-lactate based on the investigator's discussion) using the Calbiochem-Behring Rapid Lactate Kit accurately discriminates non-GC septic arthritis from other etiologies of acute monoarticular joint pain/swelling. At a threshold of 10 mmoL/L (which is nearly two-fold the 5.5 mmoL/L threshold proposed by Brook 1978) the LR^+ is 22 and the LR^- is 0. Using the Brook 5 mmoL/L threshold, Moss demonstrates LR^+ 2.7 and LR^- 0 (compared with 5.9 and 0.04 for Brook, respectively) for lactate. The interval LR for 0-10 mmol/L is zero versus 17.2 for 10-20 mmoL/L and infinity for synovial lactate >20 mmoL/L.

In summary, Lab Medicine, Ortho, and EM agreed that the available data on synovial lactate is insufficient to change the diagnostic management of these patients. However, all agreed that sufficient clinical equipoise exists to justify additional research. Future studies should assess diagnostic accuracy in a consecutive sampling of ED patients with monoarticular arthritis in whom there is sufficient suspicion of non-GC septic arthritis to perform an arthrocentesis. It will be essential for these future studies to follow the STARD criteria and to report interval LR's. If these "level 2" diagnostic accuracy studies confirm synovial lactate as a useful adjunct to synovial WBC, the logical progression in research would be to assess the impact of awareness of synovial lactate on clinician decision-making.