Critical Review Form

Diagnostic Test

Synovial fluid lactic acid: A diagnostic aid in septic arthritis, *Arthritis Rheum* 1978; 21:774-779

Objectives: **"…to study synovial fluid lactic acid concentration in 84 cases of acute, monoarticular arthritis to see if this test could be of value in the rapid diagnosis of septic arthritis." (p. 775)**

Methods: **Patients with previously untreated, acute monoarticular arthritis admitted between August 1976 and March 1977 to one of three California hospitals: Wadsworth Hospital Center, VA Hospital, or UCLA Medical Center. Synovial fluid was obtained via joint aspiration before any antimicrobial therapy was administered. Fluids that were grossly bloody were not included in the analysis.**

Lactic acid (the authors fail to define whether D-lactate or L-lactate was the target assay) was measured using gas liquid chromatography. Synovial fluid was preserved in 0.1 mL of 50% sulfuric acid in 0.9 mL of SF before being frozen at -20º C until analysis.

Patients were divided into one of three groups. Group A were septic arthritis cases defined by positive synovial fluid bacterial cultures. This group included 13 gram positive cocci (GPC), 13 gram negative rods (GNR), 1 fungi, and 12 gonococcal arthritis cases. Group B and C were inflammatory and degenerative arthritis cases defined by synovial fluid bacterial cultures without any growth, and lacking any biochemical evidence of a specific arthritis. This group included 16 rheumatoid arthritis, 8 gout, 4 colitis, 3 miscellaneous, 8 osteoarthritis, and 4 trauma cases.

The authors do not provide any details on blinding outcome assessors, how they identified patients, or the statistical analysis plan.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Probably, although the authors do not clearly state that clinicians were blinded to the synovial fluid lactate results, this is implied because the synovial lactate assay is not routinely available and the specimens were frozen until the time of analysis.
B.	**Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group?** **(Confirmation Bias)**	Yes, all patients had synovial fluid cultures obtained but it is unclear whether outcome assessors (who labeled the synovial fluid cultures as positive or negative) were blinded to the synovial lactate measurements.
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard?** **(Ascertainment Bias)**	No, all patients had a synovial fluid culture.
II.	**What are the results?**	
A.	**What likelihood ratios were associated with the range of possible test results?** * To convert lactate mg/dL to mMol/L divide by 9. To convert lactate mMol/L to mg/dL multiply by 0.111. **TABLE** Diagnosis / Total Protein Mean (range) / Glucose Mean (range) / SWBC Mean (range) / % PMN Mean (range) / S Lactic acid Mean (range) Non-GC SA: 5.5 (4-7) / 20 (3-36) / 103261 (31,000-202,000) / 97 (86-99) / 1170 (48-2500) GC: 4.7 (3-6) / 30 (2-69) / 26800 (1020-74,000) / 85 (70-94) / 27 (18-50) Inflammatory: 3.2 (2-5) / 83 (27-125) / 4845 (150-33,500) / 51 (4-86) / 39 (8-62) Degenerative: 2.5 (1-4) / 93 (81-109) / 787 (111-14,582) / 27 (0-40) / 16 (5-28)	• 84 patients were studied, although only 70 are reported in Fig 2 (unexplained exclusions). • Mean age was 45 years. • All patients with gonococcal arthritis (n = 12) had synovial fluid lactate < 50 mg/dL* (average 27 mg/dL) whereas the mean SF lactate for GNR was 1587 mg/dL and for GPC 555 mg/dL. These equate to 3mM, 176 mM, and 17 mM, respectively.* • The mean SF lactate for inflammatory cases ranged from 18-47 mg/dL (2-5 mM/L) and degenerative arthritis cases ranged from 14-17 mg/dL. • **SF lactate can differentiate non-gonococcal septic arthritis from both GC septic arthritis and inflammatory/degenerative arthritis, but it cannot differentiate GC septic arthritis from inflammatory/degenerative arthritis.** • SF glucose, protein, WBC, and % PMN varied widely and significantly overlapped between groups (see Table to left). • The authors do not report any measures of diagnostic accuracy, but they can be

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<td>* To convert lactate mg/dL to mMol/L divide by 9. To convert lactate mMol/L to mg/dL multiply by 0.111.</td>
<td>computed by reconstructing a 2x2 table from Figure 2, excluding the GC cases:

Non-GC Septic Arthritis
<table>
<tr><th></th><th>+ SA</th><th>- SA</th></tr>
<tr><td>Synovial lactate</td><td></td><td></td></tr>
<tr><td>≥ 50</td><td>26</td><td>7</td></tr>
<tr><td>< 50</td><td>1</td><td>36</td></tr>
</table>
From this 2x2 table the following diagnostic accuracy estimates are obtained:
Sensitivity 96% (95% CI 83%-100%)
Specificity 84% (95% CI 75%-86%)
LR+ 5.9 (95% CI 3.3-7.1)
LR- 0.04 (95% CI 0.002-0.23)

• More importantly, one can calculate interval LR's from Figure 2

<table>
<tr><th>Range of synovial lactate</th><th>Interval LR</th></tr>
<tr><td>0-50 (0-5.5 mM)*</td><td>0.0568</td></tr>
<tr><td>50-100 (5.5-11.1 mM)*</td><td>0.91</td></tr>
<tr><td>100-150 (11.1-16.7 mM)*</td><td>∞</td></tr>
<tr><td>>150 (> 16.7 mM)*</td><td>∞</td></tr>
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<td>III.</td>
<td>How can I apply the results to patient care?</td>
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<tr>
<td>A.</td>
<td>Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?</td>
<td>Uncertain. Is this D-lactate or L-lactate?</td>
</tr>
<tr>
<td>B.</td>
<td>Are the results applicable to the patients in my practice?</td>
<td>Uncertain, since there are multiple potential design biases and pragmatic barriers to applying this evidence. Are these ED patients? What is the prevalence of septic arthritis? How quickly can the synovial lactate be available? Furthermore, diagnostic accuracy is only the second-tier in the proposed hierarchy of diagnostic research (see also Leeflang 2009). Higher levels of evidence would also assess diagnostic thinking efficacy, therapeutic efficacy, patient outcome efficacy, and societal (i.e. cost-effectiveness) efficacy.</td>
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C.	**Will the results change my management strategy?**	No, because it is uncertain what stereoisomer form of lactate was measured. Also, readers are left uncertain why the range of synovial lactates in septic arthritis varied by ten-fold compared with Gratacós' study. Finally, gas liquid chromatography is not available at our hospital (or at most hospitals around the world) so this is a 3-work day turnaround mail out test which is *not* diagnostically useful in the ED.
D.	**Will patients be better off as a result of the test?**	Possibly, if further research confirms the diagnostic accuracy of synovial lactate and synovial lactate testing is feasible within a reasonable timeframe from the ED. It is noteworthy that in contrast to the Gratacós study, two cases of partially treated septic arthritis in this manuscript had non-elevated synovial lactate.

Limitations

1) **Uncertain whether D-lactate or L-lactate was assessed.**

2) **No details about how patients were identified (Rheum Clinic vs. ED, consecutive vs. case-control). This is one of the STARD criteria and essential to delineate since test accuracy may vary from one setting to another (see also Leeflang 2009).**

3) **Unexplained exclusion of 14 patients from the analysis.**

4) **No blinding of outcome assessors.**

5) **No assessment of diagnostic accuracy. For example, failure to report likelihood ratios or interval likelihood ratios.**

Bottom Line

Whereas synovial WBC, synovial protein, and synovial glucose values overlap significantly between non-gonococcal SA and other forms of acute monoarticular arthritis, synovial lactate is an accurate test to discriminate these etiologies. At a

threshold of 50 mg/dL the synovial lactate LR^+ is 5.9 and LR^- 0.04. More importantly, the interval LR for 0-50 mg/dL is 0.06 and for >100 mg/dL 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 bias. Further studies are needed in ED settings with real-time D-lactate assays evaluating consecutive patients with acute monoarticular arthritis to be more confident about the diagnostic accuracy of synovial lactate.