# Critical Review Form

## Diagnostic Test

D-lactic acid in synovial fluid. A rapid diagnostic test for bacterial synovitis, *J Rheum* 1995; 22:1504-1508

**Objectives:** **To evaluate "the usefulness of measuring D-lactic acid in SF (synovial fluid) as part of the early diagnosis of BA (bacterial arthritis)." (p. 1504)**

**Methods:** **Single-center (Hospital Clinic in Provincial, Barcelona Spain) Rheumatology clinic-based, case-control study over an unspecified 3-year period. Cases included 20 septic arthritis (defined as bacterial growth from synovial fluid) specimens from 17 patients all obtained within 72-hours of symptom onset and before antibiotics were started. The control group consisted of 99 synovial fluid specimens from patients with the following diagnoses: rheumatoid arthritis (29), crystalloid arthropathy (26), osteoarthritis (9), psoriatic arthritis (7). B27 associated arthropathy (7), amyloid arthropathy (2), Behcets (2), Sjögren's syndrome (1), polymyalgia rheumatica (2), and undifferentiated rheumatism (14).**

**D-lactic acid was measured from specimens frozen at -40º C until the assay. The frozen supernatant (0.2 ml) was mixed with 0.8 ml of glycine buffer pH 9.2 (0.6 M glycine, 0.5 M hydrazine and 1.3 mg/ml of NAD) and 0.01 ml of 5 mg/ml D-lactate dehydrogenase. The mixture was incubated at 35º C for 1-hour and then the absorbance at 340 mm was measured using a 8452A diode array spectrophoto-meter. The investigators reported sensitivity, specificity, PPV, and NPV for synovial fluid, synovial WBC, and % PMN in synovial fluid. They dichotomized synovial fluid based upon their ROC curve. They also dichotomized sWBC and sPMN based upon a literature review. The following thresholds defined "abnormal": D-lactate ≥ 0.05 mMole/L, sWBC ≥ 50000, sPMN ≥ 90%.**

| Guide | | Comments |
|---|---|---|
| **I.** | **Are the results valid?** | |
| **A.** | **Did clinicians face diagnostic uncertainty?** | Yes, clinicians were unaware of the diagnosis (culture results) at the time that the synovial fluid was obtained. |
| **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. "Routine cultures were performed in all SF samples and additional grams stains in those with suspected bacterial infection." (p. 1505) |

<table>
<tr><td>C.</td><td>Did the results of the test being evaluated influence the decision to perform the gold standard?<br>(Ascertainment Bias)</td><td>No, because D-lactate levels are not routinely obtained and the experimental assay was not available while the patient was treated.</td></tr>
<tr><td>II.</td><td>What are the results?</td><td></td></tr>
<tr><td>A.</td><td>What likelihood ratios were associated with the range of possible test results?<br><br>
<table>
<tr><th></th><th>+ BA</th><th>-BA</th></tr>
<tr><td>D-lactate (mMole)</td><td></td><td></td></tr>
<tr><td>≥0.05</td><td>17</td><td>4</td></tr>
<tr><td>< 0.05</td><td>3</td><td>95</td></tr>
</table></td><td>
<ul>
<li>Synovial D-lactate levels are significantly higher in BA than in controls (0.130 ± 0.14 vs. 0.013 ± 0.023, p < 0.001).</li>
<li>Based upon the 2x2 table to the left which labels an abnormal synovial D-lactate as ≥ 0.05mMole, the following measures of diagnostic accuracy were obtained using this website:<br>Sensitivity 85% (95% CI 66%-95%)<br>Specificity 96% (95% CI 92%-98%)<br>LR+ 21 (95% CI 8-48)<br>LR- 0.16 (95% CI 0.05-0.37)</li>
<li>The D-lactate AUC was 0.90.</li>
<li>Although note reported by the authors, based upon Figure 1 interval likelihood ratios (iLR) can be computed for synovial D-lactate:</li>
</ul>
<table>
<tr><th>Synovial D-lactate range</th><th>iLR</th></tr>
<tr><td>0-0.05</td><td>0.16</td></tr>
<tr><td>0.05-0.1</td><td>9.9</td></tr>
<tr><td>0.1-0.15</td><td>∞</td></tr>
<tr><td>>0.15</td><td>20</td></tr>
</table>
<ul>
<li>In comparison, synovial WBC and synovial PMN had inferior diagnostic accuracy.</li>
</ul>
<table>
<tr><th>Test</th><th>Sen</th><th>Spec</th><th>AUC</th><th>LR$^+$</th><th>LR$^-$</th></tr>
<tr><td>sWBC≥50</td><td>56</td><td>94</td><td>80</td><td>9.3</td><td>0.47</td></tr>
<tr><td>sPMN≥90%</td><td>73</td><td>73</td><td>76</td><td>2.7</td><td>0.37</td></tr>
</table></td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care?</td><td></td></tr>
<tr><td>A.</td><td>Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?</td><td>Uncertain since the D-lactate assay is not readily available.</td></tr>
</table>

| | | |
|---|---|---|
| **B.** | **Are the results applicable to the patients in my practice?** | No, these are Rheumatology patients. Future studies will need to assess synovial D-lactate prospectively in a consecutive sample of ED patients in order to define the diagnostic accuracy in our patient population. 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. Of course, none of these studies are necessary if a rapidly available synovial D-lactate test is not available and no such test currently exists. |
| **C.** | **Will the results change my management strategy?** | Not based upon this study alone because of the methodological limitations (case-control design, lacking of blinding, no clear gold standard) and uncertain external validity (Rheumatology clinic), and contemporary lack of availability of D-lactate assays. |
| **D.** | **Will patients be better off as a result of the test?** | Possibly, if the above uncertainties (i.e., potential forms of research bias) and barriers are addressed by future research. |

## Limitations

1) **Case-control design (increased risk of bias per QUADAS-II criteria)**

2) **Limited external validity because this was a single-center design *and* a Rheumatology clinic population – not an ED. Test accuracy may vary from one setting to another (see also Leeflang 2009).**

3) **Lack of blinding of outcome assessors.**

4) **Uncertain/poorly defined gold standard for bacterial arthritis vs. non-bacterial arthritis.**

5) **Not pragmatic since D-lactate assays are currently unavailable.**

6) **Multiple elements of STARD criteria ignored, albeit because STARD did not exist in 1995. For example, failure to report likelihood ratios or interval likelihood ratios.**

## Bottom Line

**Synovial fluid D-lactate offers a promising new diagnostic test to differentiate non-gonococcal bacterial arthritis from non-bacterial arthritis with interval LR's ranging from 0.16 (D-lactate 0-0.05) to 20 (D-lactate >0.15). 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 BA. Future research should assess the diagnostic accuracy of synovial fluid D-lactate in consecutive ED patients with suspected septic arthritis. A major barrier to using synovial D-lactate is that no quick assay is readily available. Currently, synovial D-lactate assays are a 3-day mail out test to Mayo Clinic.**