Indicators for Detection of Septic Arthritis in the Acutely Swollen Joint Cohort of Those Without Joint Prostheses

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abstract

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Differentiating septic arthritis from culture-negative, acute atraumatic joint effusion is difficult. Studies have attempted to elucidate factors that herald infection, but, due to overlap, most conclude that the diagnosis ultimately relies on clinical judgment. Furthermore, studies are limited by broad inclusion criteria. The current retrospective case study sought to examine (1) which markers differentiate a culture-positive septic joint from culture-negative effusion in patients suspicious for infection despite no growth on Gram stain and without previous surgery in the affected joint and (2) whether threshold values of these markers exist that predict septic arthritis. The study was performed by reviewing records of those who underwent operative irrigation and debridement involving the shoulder, elbow, wrist, hip, knee, and ankle. Patients were included if they were older than 18 years and had an acutely swollen/painful joint and no organisms on initial Gram stain. Exclusion criteria were lack of serum markers or synovial fluid aspirate, antibiotics within 1 week, adjacent wound or skin infection, recent trauma to the joint, and previous joint infection or surgery to the joint. Several clinical, serological, and synovial parameters were collected and analyzed using paired t test with Bonferroni correction. Serum C-reactive protein was the only significantly different variable between groups. Serum C-reactive protein greater than 10.5 mg/dL was predictive of infection. In those suspicious for infection despite no growth on Gram stain and without previous surgery in the affected joint, C-reactive protein greater than 10.5 mg/dL is suspicious for joint sepsis and should warrant consideration for urgent irrigation and debridement.

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eptic arthritis presents with joint pain, swelling, warmth, and restricted movement in 78% to 85% of cases and accounts for 10% to 27% of acutely swollen joints.\textsuperscript{1,2} However, the differential diagnosis of an acute, atraumatic joint effusion is broad and includes gout, rheumatoid arthritis, reactive arthritis, exacerbation of osteoarthritis, and Lyme disease, among others. Furthermore, each of these conditions has their own distinct therapy, which often does not include surgical intervention. For those with septic arthritis, surgical irrigation and debridement combined with antibiotics should be started immediately to reduce the potential morbidity and 7% to 11.5% mortality rate associated with septic arthritis.\textsuperscript{3-5} A delay in time to surgical intervention has been correlated with the number of surgeries required to eradicate the infection and with functional outcome.\textsuperscript{6-8} Therefore, prompt recognition of a septic joint can reduce potential joint destruction and limit the number of unnecessary surgeries in aseptic effusions.

Currently, clinical findings, such as acute-onset effusion, pain, decreased range of motion, and fever, raise suspicions for a septic joint and often prompt serological and synovial fluid analysis to confirm the diagnosis. Elevated serum white blood cell (WBC) count and erythrocyte sedimentation rate (ESR) as well as synovial WBC counts greater than 50,000 cells/mm with a 90% or greater polymorphonuclear cell ratio are commonly used parameters to suggest the presence of infection.\textsuperscript{1,2} However, many studies have demonstrated the lack of sensitivity and specificity of each parameter.\textsuperscript{2,3,8,9} Multiple reviews have concluded that accurate diagnosis of septic arthritis relies more on the acumen of the experienced physician than any single laboratory marker.\textsuperscript{2,10} In addition, most studies have limited exclusion criteria (ie, patients with recent joint infections and previous surgery involving the affected joint) and contain study populations, such as those with prosthetic implants in the affected joint, that are analyzed and treated differently from those with a native joint.

Therefore, the goal of the current study was to predict the presence of septic arthritis in those with a high index of suspicion for infection despite no organisms on initial Gram stain. The study sought to examine (1) which markers differentiate a culture-positive septic joint from culture-negative effusion in patients suspicious for infection despite no growth on Gram stain and without previous surgery in the affected joint and (2) whether threshold values of these markers exist that predict septic arthritis.

\section*{Materials and Methods}
This study was approved by the authors’ institutional review board.

A retrospective case study was performed by reviewing the electronic medical records of Hershey Medical Center from January 1, 2003, through April 1, 2011. Participants were identified by scanning the computerized medical records for the CPT codes 23030, 23044, 23930, 24000, 24100, 24101, 24102, 25028, 25100, 25101, 25105, 26990, 27050, 27052, 27054, 27301, 27310, 27330, 27331, 27334, 27335, 27603, 27610, 27620, 27625, 29805, 29820, 29821, 29822, 29823, 29843, 29830, 29835, 29836, 29837, 29838, 29871, 29895, 29897, 29898, 29905, and 29906 (all codes for operative irrigation and debridement performed open or arthroscopically). Only codes involving the shoulder, elbow, wrist, hip, knee, and ankle were considered. Patients were selected for the study if they underwent operative irrigation and debridement performed open or arthroscopically. Exclusion criteria included (1) lack of serum inflammatory markers or synovial fluid aspirate, (2) antibiotic use within 1 week of presentation, (3) laceration or wound including or adjacent to the affected joint, (4) history of recent trauma to the affected joint, (5) local skin infection, (6) history of joint infection, or (7) previous surgical intervention involving the affected joint. Several clinical, serological, and synovial parameters were collected for each patient who qualified (Table 1).

Statistical analyses were conducted in 2 stages. First, a $t$ test (assuming unequal variances for each group) was used to compare variables between culture-positive and culture-negative groups. Second, the Bonferroni correction was applied to each $P$ value to hold the overall type I error rate (false-positive rate) at 5%. Only the following continuous variables were ana-

\begin{table}[h]
\centering
\caption{Variables Collected}
\begin{tabular}{|l|}
\hline
Clinical factors \hfill \\
\hline
Sex \hfill \\
Age at presentation \hfill \\
Temperature at presentation \hfill \\
Joint involved \hfill \\
Delay between presentation and surgery \hfill \\
Diagnosis of diabetes mellitus \hfill \\
Diagnosis of inflammatory arthritis (gouty and/or rheumatoid arthritis) \hfill \\
Methotrexate use \hfill \\
Ethanol or intravenous drug abuse \hfill \\
Intra-articular corticosteroid injection in affected joint \hfill \\
\hline
Serologic values \hfill \\
WBC count with neutrophil percentage \hfill \\
Erythrocyte sedimentation rate \hfill \\
C-reactive protein \hfill \\
\hline
Synovial values \hfill \\
Final culture growth \hfill \\
Gram stain finding \hfill \\
WBC count with neutrophil percentage \hfill \\
Presence of crystals \hfill \\
\hline
Abbreviation: WBC, white blood cell.
\end{tabular}
\end{table}
lyzed: age, temperature, serum C-reactive protein (CRP), serum ESR, serum WBC count and percentage of neutrophils, and synovial WBC count (log-transformed before analysis) and percentage of neutrophils. Categorical variables were not analyzed due to a small sample size.

**RESULTS**

A total of 1906 patients underwent operative joint irrigation and debridement during the study period. After reviewing inclusion and exclusion criteria, 17 patients were found to be suitable for the study. The study cohort included 12 men and 5 women with a mean age of 60.4 years (range, 25-92 years). The culture-positive group comprised 9. Average temperature at presentation was 37.2°C (range, 35.6°C-39.4°C). The knee was affected in 7 patients, the elbow in 4, the ankle and shoulder in 2 each, the hip in 1, and both the elbow and knee in 1. Average delay from presentation to surgical intervention was 0.93 days (range, 0-4 days). Three patients, including 2 in the culture-positive group, received a corticosteroid injection in the affected joint, whereas 1 of the 2 patients with rheumatoid arthritis (both in the culture-negative group) were taking methotrexate. The culture-negative group included 3 patients with diabetes mellitus vs 1 in the culture-positive group. One patient reported chronic ethanol abuse, and no patient was an intravenous drug abuser.

Table 2 depicts serologic and synovial values for each patient. In 1 patient, synovial WBC count and neutrophil percentage could not be calculated due to a concentrated specimen.

Statistical comparisons between culture-positive and culture-negative patients are shown in Table 3. Serum CRP was the only significantly different variable between the groups after Bonferroni adjustment. Culture-negative patients tended to have smaller serum CRP values than culture-positive patients. Furthermore, serum CRP greater than 10.5 mg/dL appeared to be predictive of infection (Figure). In identifying joint infection, the sensitivity and specificity of serum CRP greater than 10.5 mg/dL were 75% and 100%, respectively.

Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>WBC, K/µL</th>
<th>% PMN</th>
<th>ESR, mm/hr</th>
<th>CRP, mg/dL</th>
<th>WBC, cells/µL</th>
<th>% PMN</th>
<th>Crystals</th>
<th>Operative Culture Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>13.8</td>
<td>74</td>
<td>38</td>
<td>2.8</td>
<td>49,368</td>
<td>92</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>14.1</td>
<td>76</td>
<td>47</td>
<td>10.4</td>
<td>60,460</td>
<td>92</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>12.6</td>
<td>80</td>
<td>12</td>
<td>1.1</td>
<td>71,992</td>
<td>95</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>14.6</td>
<td>79</td>
<td>25</td>
<td>7.1</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>15.7</td>
<td>85</td>
<td>129</td>
<td>1.5</td>
<td>64,788</td>
<td>98</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>F</td>
<td>13.5</td>
<td>71</td>
<td>56</td>
<td>7.2</td>
<td>93,570</td>
<td>97</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>G</td>
<td>16.3</td>
<td>78</td>
<td>18</td>
<td>3.5</td>
<td>58,724</td>
<td>94</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>H</td>
<td>10.6</td>
<td>80</td>
<td>65</td>
<td>3.8</td>
<td>505</td>
<td>82</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>15.7</td>
<td>65</td>
<td>17</td>
<td>2.5</td>
<td>107,222</td>
<td>95</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>J</td>
<td>13.0</td>
<td>89</td>
<td>49</td>
<td>27</td>
<td>63,824</td>
<td>87</td>
<td>0</td>
<td>Pasteurella</td>
</tr>
<tr>
<td>K</td>
<td>9.2</td>
<td>80</td>
<td>30</td>
<td>6.7</td>
<td>159,000</td>
<td>90</td>
<td>0</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>L</td>
<td>13.5</td>
<td>81</td>
<td>61</td>
<td>18.1</td>
<td>88,448</td>
<td>93</td>
<td>0</td>
<td>Streptococcus viridans</td>
</tr>
<tr>
<td>M</td>
<td>11.5</td>
<td>68</td>
<td>89</td>
<td>27</td>
<td>59,338</td>
<td>93</td>
<td>0</td>
<td>Haemophilus</td>
</tr>
<tr>
<td>N</td>
<td>11.7</td>
<td>80</td>
<td>91</td>
<td>27</td>
<td>50,191</td>
<td>96</td>
<td>0</td>
<td>S aureus</td>
</tr>
<tr>
<td>O</td>
<td>13.7</td>
<td>74</td>
<td>101</td>
<td>27</td>
<td>29,718</td>
<td>96</td>
<td>0</td>
<td>S aureus</td>
</tr>
<tr>
<td>P</td>
<td>11</td>
<td>78</td>
<td>25</td>
<td>2.6</td>
<td>75,757</td>
<td>94</td>
<td>0</td>
<td>S aureus</td>
</tr>
<tr>
<td>Q</td>
<td>13.5</td>
<td>91</td>
<td>9</td>
<td>14.6</td>
<td>94,710</td>
<td>70</td>
<td>0</td>
<td>Salmonella</td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; N/A, not available; PMN, polymorphonuclear leukocytes; WBC, white blood cell.
**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Culture-negative Group (n=9)</th>
<th>Culture-positive Group (n=8)</th>
<th>Nominal P</th>
<th>Bonferroni-adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, y</td>
<td>55.2±12.07</td>
<td>66.6±21.79</td>
<td>.22</td>
<td>1.00</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>4.4±3.13</td>
<td>18.8±9.97</td>
<td>.004</td>
<td>.032</td>
</tr>
<tr>
<td>Serum WBC, K/µL</td>
<td>14.1±1.77</td>
<td>12.1±1.58</td>
<td>.029</td>
<td>.23</td>
</tr>
<tr>
<td>Synovial WBC (log-transformed)</td>
<td>10.5±1.76</td>
<td>11.2±0.49</td>
<td>.37</td>
<td>1.00</td>
</tr>
<tr>
<td>Serum neutrophil, %</td>
<td>76.4±5.85</td>
<td>80.1±7.43</td>
<td>.28</td>
<td>1.00</td>
</tr>
<tr>
<td>Synovial neutrophil, %</td>
<td>93.1±4.97</td>
<td>89.9±8.58</td>
<td>.37</td>
<td>1.00</td>
</tr>
<tr>
<td>ESR, mm/hr</td>
<td>45.2±36.45</td>
<td>56.9±34.34</td>
<td>.51</td>
<td>1.00</td>
</tr>
<tr>
<td>Preop temperature, ºC</td>
<td>37.1±1.26</td>
<td>37.3±1.01</td>
<td>.71</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; preop, preoperative; WBC, white blood cell.

**Discussion**

Differentiating septic arthritis from culture-negative, acute atraumatic joint effusion can be perplexing for the clinician. Multiple studies have attempted to best elucidate risk factors that herald infection,\(^1\)\(^3\)\(^4\)\(^8\)\(^9\) which accounts for 8% to 27% of all acute, painful effusions.\(^2\)\(^11\)\(^12\)

Various serum and synovial markers have been proposed as the best indicator for infection.\(^1\)\(^3\)\(^8\)\(^9\) The overall consensus is that, although not perfect, synovial polymorphonuclear cell count greater than 90% and WBC count greater than 50,000/mm\(^3\) are most predictive of infection.\(^1\)

However, because of significant overlap in laboratory values among those with a septic joint and those with inflammatory arthritis,\(^8\)\(^13\)\(^15\) most studies conclude that the physician must ultimately rely on clinical judgment to formulate a diagnosis.\(^6\)\(^7\)\(^14\)

Although these studies are informative, they are limited by broad inclusion criteria. More specifically, current studies include patients with a low index of suspicion for infection and a previous joint surgery, including total joint arthroplasty, in their analyses. In the current authors’ experience, many patients present with an acutely swollen knee, a history of similar episodes due to an underlying disease such as gout, and no significant signs or symptoms of infection. Thus, these patients have a low suspicion for infection and do not create as difficult a diagnostic dilemma. However, patients who have undergone previous surgery on the affected joint are often treated with a higher-than-normal index of suspicion for infection. Despite being considered by most surgeons as a different cohort from those with native joints, patients with prosthetic joints accounted for 38% of patients in studies examining septic arthritis.\(^4\)

Furthermore, patients with previous joint replacements may present differently and have a different treatment algorithm. Much research has been devoted to diagnosing infection in the cohort with a prosthetic joint,\(^16\)\(^-\)\(^19\) whereas none is available in an exclusively native group. Therefore, the current study sought to examine a select group of patients: those with a high index of suspicion for infection despite no growth on Gram stain and without previous surgery in the affected joint.

In this study, serum CRP was the only statistically significant variable between culture-negative and culture-positive patients. Culture-positive patients had an almost 4-fold greater serum CRP value than culture-negative patients. More convincing, CRP greater than 10.5 mg/dL appeared to be predictive of infection: 75% of patients with positive cultures and none with negative cultures had CRP values exceeding this threshold.

Other studies have demonstrated that an elevated CRP is a sensitive marker predicting infection,\(^15\)\(^20\) but its use has been limited by a low specificity. Unlike serum ESR and synovial WBC count, which have threshold values widely used to stratify risk of infection, no consensus threshold value for CRP has been determined.\(^2\)

Based on these results, CRP greater than 10.5 mg/dL is suspicious for a septic joint and should warrant significant consideration for urgent irrigation and debridement in a native joint.

This study has several limitations. First, the small sample size limited the ability to analyze categorical variables and may raise concerns over the validity of the primary finding. A stringent set of inclusion and exclusion criteria was largely responsible for the limited number of patients. However, the authors decided that these filters were necessary to identify a specific cohort that was incompletely addressed in previous studies. Despite the small sample size, the authors support their findings based on the rigorous method of statistical analysis. The
analysis was focused on a small number of continuous variables because the authors thought a priori may be important. They also accounted for conducting multiple statistical tests because the risk of finding false positives increases as more tests are conducted; the Bonferroni correction held the overall risk of false positive at 5%.

Second, synovial cultures were selected as the gold standard to identify joint infection, although their sensitivity ranges from 75% to 95%. However, newer methods of identification are not readily available and may not offer major advantages in detecting Staphylococcus or Streptococcus joint infections.

**CONCLUSION**

Differeniating patients with septic arthritis from those with culture-negative aspirates in a cohort of native joints with no growth on initial Gram stain can be difficult. Serum CRP level was the only significantly different factor between these 2 groups, which both included patients who were all highly suspicious for infection. A CRP level greater than 10.5 mg/dL should raise serious concerns for the presence of septic arthritis. Further multicenter studies are needed to confirm these findings.

**REFERENCES**