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Complications - Infection

The C-Reactive Protein May Not Detect Infections Caused by Less-Virulent Organisms

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ABSTRACT

Background: The aim of the present study was to evaluate the influence of organism type on the performance of the synovial fluid C-reactive protein (CRP) test.
Methods: We retrospectively reviewed the results of 21,422 synovial fluid samples sent to one common laboratory for the purpose of diagnostic testing for periprosthetic joint infection. Both a synovial fluid CRP result and a positive culture were present for 1789 submitted samples. The cultured organisms were grouped by species, virulence, and gram type; and the median CRP level was determined for each group.
Results: The median synovial fluid CRP level was significantly lower for less-virulent organisms, when compared to those organisms classified as virulent (15.10 mg/L vs 32.70 mg/L; $P < .0001$). Some less-virulent species such as yeast and *Staphylococcus epidermidis* were associated with a 4-10 times lower CRP response than those of virulent organisms such as *Streptococcus agalactiae* and *Staphylococcus aureus* ($P < .0001$). Bacterial gram type had no influence on the median CRP result. The rate of false-negative CRP values was 50.9% for yeast, 29.4% for *S. epidermidis*, 28.5% for all less-virulent organisms, and 11.6% for all virulent organisms.
Conclusion: The CRP response appears to be highly dependent on the infecting organism and is more likely to provide false-negative results in the setting of less-virulent organisms. Although the use of a CRP level is an important part of the workup for periprosthetic joint infection, surgeons must be aware that this protein may yield a false-negative result in the setting of less-virulent organisms.

The C-reactive protein (CRP) test is arguably the most commonly used test for periprosthetic joint infection (PJI) due to the simplicity of a blood draw and its wide availability as a standard medical test. Both the American Academy of Orthopaedic Surgeons [1] and the Musculoskeletal Infection Society (MSIS) [2] recommend the use of the serum CRP as part of an algorithm for diagnosing PJI.

However, there are some methodologic limitations and concerns arising from the historical studies demonstrating the utility of CRP in diagnosing PJI. First, most studies evaluating the performance of CRP were conducted before the MSIS definition of PJI, resulting in variation in the definition of PJI in those studies [3-7]. Second, most studies evaluating the performance of CRP include a small group patients with PJI, resulting in large confidence intervals or no confidence intervals associated with test sensitivity [3,4,6,7].

Recently, the search for biomarkers of PJI has generated a significant number of publications, with most focusing on synovial fluid biomarkers [8-12]. Measurement of the synovial fluid CRP has been suggested by some to be more accurate than the serum CRP [13-15] and by others to be equivalent to the serum CRP [16]. Nevertheless, study of the synovial fluid CRP could provide the field with an enhanced understanding of this protein, specifically in regard to its response to infection.

Recent studies which have used the MSIS definition of PJI demonstrate that the sensitivity of serum CRP in detecting PJI is closer to 80% [9,10], suggesting that the CRP test may fail to detect

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infection more often than previously thought. One specific study has suggested that the serum CRP test may fail to detect some cases of PJI caused by indolent organisms [17]. Understanding the limitations of the CRP test could improve our ability of using this test clinically. The aim of the present study was to evaluate the influence of organism type on the performance of synovial fluid CRP test.

Methods

This study was approved by the institutional review board.

This retrospective review used deidentified testing results from synovial fluids aspirated from joint arthroplasties and submitted to a common laboratory (Citrano Laboratories, subsidiary of CD Diagnostics, Towson, MD) for the specified purpose of diagnostic testing for PJI. From September 2013 to October 2015, a total of 21,421 synovial fluid samples were submitted for testing at this common laboratory. All tests performed in this study were performed and reported by the same laboratory, which received synovial fluid samples by overnight delivery for diagnostic testing.

When restricting the review to those samples from a joint replacement that had both a CRP test result and a positive culture from the same synovial fluid sample, we identified 1789 samples that were included in this study. In this sample population, every synovial fluid with a positive culture also had a simultaneous synovial fluid CRP level available for study. These samples were sent to the common laboratory by 792 physicians from 49 states in the United States. Overall, 73.8% of samples were from a knee replacement, 15.1% were from a hip replacement, 2.2% were from a shoulder replacement, and 8.8% did not have a specified arthroplasty location.

The laboratory assay for synovial fluid CRP used the Beckman Olympus AU480 (Beckman Coulter Inc., Brea, CA) laboratory chemistry analyzer. Previous studies evaluating the synovial fluid CRP test identified a range of optimal thresholds for PJI. For this study, the threshold of 6.6mg/L was used, as it was a midrange threshold in studies reviewed [13-16] and the result of one study's receiver operating characteristic analysis [16]. However, the false-negative rate of CRP for both virulent and less-virulent groups was also calculated at a threshold of 3.0 mg/L, which is a low threshold intended to maximize test sensitivity.

The synovial fluid culture results evaluated for the study were generated by BacT/ALERT FAN FA/FN culture bottles for recovery of both aerobic and anaerobic organisms (Biomerieux, Durham, NC). The organisms were identified and evaluated for susceptibilities using the VITEK 2 ID/AST system (Biomerieux), a fully automated system that provides rapid microbial identification and susceptibility testing. For sample submissions that specified a shoulder arthroplasty, cultures were incubated in a supplemented broth to allow for Propionibacterium acnes growth and held for 2 weeks.

The organisms identified by culture were classified by species, virulence, and gram type. Organisms classified subjectively as virulent included *Staphylococcus aureus, Staphylococcus lugdunensis, Streptococcus agalactiae,* the *Enterobacteriaceae*, and the nonfermenting gram-negative bacilli. All other organisms were classified as less virulent. A total of 671 synovial fluid samples in this study resulted in the growth of a virulent organism and 1073 resulted in growth of a less-virulent organism. Forty-five fluid samples yielded multiorganism growth and were not included in subgroup analysis. Among the 1744 samples yielding single organism growth, 1480 yielded a gram-positive organism, 207 yielded a gram-negative organism, and 57 yielded yeast. The organisms isolated from the overall study group of fluid samples was highly typical of PJI, when considering the type and proportion of species isolated (Table 1).

Table 1
Study Groups.

Organism Category	(N)
Gram type	
Gram positive	1480
Gram negative	207
Yeast	57
Multiorganism	45
Virulence	
Virulent	671
Less virulent	1073
Species with N > 20	
Staphylococcus epidermidis	523
Staphylococcus aureus	362
Staphylococcus lugdunensis	117
Enterococcus faecalis	59
Yeast species	57
Pseudomonas aeruginosa	54
Streptococcus mitis	46
Streptococcus agalactiae	43
Staphylococcus caprae	32
Escherichia coli	29
Staphylococcus capitis	26
Staphylococcus hominis	22
Corynebacterium striatum	21

Median CRP synovial fluid levels were calculated for various organism species, gram-type groups, as well as for virulent and less-virulent groups. The median CRP values from each organism grouping were compared for statistical significance using the 2-tailed Mann-Whitney test for nonparametric data when comparing 2 groups. When more than 2 groups were being compared for a statistically significant difference, a 1-way analysis of variance test for nonparametric data was used, adjusting for multiple comparisons with Dunn's test. These data are presented along with interquartile ranges. When analyzing species-specific results, only organisms that included sample N > 20 were compared. A power analysis could not be completed, as no studies have provided a basis by which to make educated assumptions about the results.

Results

The median synovial fluid CRP levels are highly dependent on the infecting organism. Both the species and virulence of the organism have a very significant influence on the associated median synovial fluid CRP levels.

When grouping organisms by species (Fig. 1), *S. epidermidis* and yeast demonstrated lower associated synovial fluid CRP levels when compared with other organisms. Synovial fluids yielding *S. epidermidis* had a median synovial fluid CRP (13.60 mg/L) that was statistically significantly lower than the median synovial fluid CRP levels associated with *S. agalactiae* (53.30 mg/L; $P < .0001$), *S. aureus* (40.15 mg/L; $P < .0001$), *Escherichia coli* (35.3 mg/L; $P = .012$), and *Streptococcus mitis* (30.2 mg/L; $P = .0021$). Synovial fluids yielding yeast growth had a median synovial fluid CRP (5.300 mg/L) that was statistically significantly lower than the median synovial fluid CRP levels associated with *S. agalactiae* (53.30 mg/L; $P < .0001$), *S. aureus* (40.15 mg/L; $P < .0001$), *E. coli* (35.3 mg/L; $P < .0001$), and *S. mitis* (30.2 mg/L; $P < .0001$), *S. lugdunensis* (21.60; $P < .0001$), *S. epidermidis* (13.60 mg/L; $P = .0054$), *Enterococcus faecalis* (18.8 mg/L; $P = .0017$), and *Pseudomonas aeruginosa* (21.20 mg/L; $P = .0011$).

Synovial fluid samples yielding less-virulent organism growth were associated with a lower mean synovial fluid CRP level than those yielding virulent organism growth (15.10 mg/L vs 32.70 mg/L; $P < .0001$) (Fig. 2).