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BRIEF REPORT

Time Course of C-Reactive Protein and Procalcitonin Levels During the Treatment of Acute Bacterial Skin Infections

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In a pilot study of 22 patients with an acute bacterial skin infection, serum levels of C-reactive protein and procalcitonin tended to be elevated at presentation and declined within 3–5 days of treatment. Further study of a biomarker-guided treatment strategy to reduce antibiotic overuse in skin infections is warranted.

Keywords. acute bacterial skin and skin structure infection; antibiotic stewardship; biomarker; C-reactive protein; procalcitonin; skin and soft tissue infection.

Antibiotic overuse in the treatment of skin infections—both in ambulatory and inpatient settings—is problematic. Nearly half of patients receive antibiotic regimens with an unnecessarily broad spectrum of activity [1], and 70%–80% are prescribed a treatment duration that is longer than recommended [1, 2]. Measurement of serum biomarkers as an adjunct to the clinical evaluation may reduce such antibiotic overuse by helping clinicians determine whether a patient is responding appropriately to therapy and to determine when an infection has been adequately treated. Despite these potential clinical utilities, there have been few studies of biomarkers in patients with acute bacterial skin infections.

In other types of infections, C-reactive protein (CRP) and procalcitonin (PCT) have demonstrated promise as biomarkers to optimize antibiotic use. For example, in patients with sepsis, persistently elevated levels can identify patients not responding to therapy [3]. In critically ill patients with acute respiratory infection or sepsis, PCT-guided prescribing algorithms have been shown to safely reduce antibiotic therapy and may improve clinical outcomes [4, 5].

The objectives of this pilot study were to (1) describe the time course of CRP and PCT during the treatment of acute bacterial skin infections and (2) evaluate appropriate time points to obtain biomarker specimens in future studies of biomarker-guided treatment strategies. We hypothesized that CRP and PCT levels would be elevated at presentation and would decline by day 3 of treatment.

METHODS

Study Design

This was a prospective observational pilot study of patients treated at Denver Health for an acute bacterial skin infection between February 28, 2014, and March 9, 2017.

Study Setting and Population

Patients ≥18 years of age with cellulitis, cutaneous abscess, wound infection, or an infected ulcer were eligible. Key exclusion criteria were initiation of antibiotic therapy >2 hours prior to enrollment, suspected or confirmed deep tissue infection, presence of a co-existing infection requiring antibacterial therapy, neutropenia, malignancy, and use of immunosuppressing medications. The study was approved by the Colorado Multiple Institutional Review Board, and all patients provided written informed consent.

Study Visits and Biomarker Measurements

Clinical assessments were performed at enrollment and 24 (±8) hours, 3 (±1) days, 5 (-1/+3) days, and 28 (±4) days later. Infection type was classified according to Food and Drug Administration (FDA) definitions [6]. Blood specimens for CRP, PCT, and white blood cell (WBC) measurement were obtained prior to or within 2 hours of the start of antibiotics, 4–6 hours later (optional), and at the 24-hour, day 3, and day 5 visits. Biomarker measurements were performed only after completion of all study visits. CRP, PCT, and WBC values were classified as elevated when >10.0 mg/L, ≥0.05 ng/mL, or >10.0 K/μL, respectively. The PCT cutoff of ≥0.05 ng/mL was used because values from 0.05–0.5 ng/mL may be observed with localized bacterial infections [7].

Clinical Outcomes

On day 3, treatment success was defined according to FDA guidance as a 20% reduction in lesion size at 48–72 hours compared with baseline and absence of need for rescue antibiotic therapy [6]. On day 5, as no standardized definition of treatment success exists for this time point, we defined success as a

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50% reduction in lesion size compared with baseline, absence of need for rescue therapy, absence of purulent drainage, and no new sites of skin infection.

Statistical Analysis

Results were presented for the overall cohort and stratified by abscess vs nonabscess infections. For the overall cohort, the change in mean CRP, PCT, and WBC level from baseline (enrollment) to day 3 and from baseline to day 5 was evaluated by paired *t* test. As this was a pilot study, no formal sample size calculation was performed. R (Version 3.3.1) was used for data analysis.

RESULTS

Twenty-two patients were included: 15 with a cutaneous abscess, 5 with cellulitis, 1 with a wound infection, and 1 with an infected ulcer. The most common reasons for exclusion were inability to complete the serial visits or phlebotomy (n = 143), initiation of antibiotic therapy >2 hours prior to enrollment (n = 133), perirectal or perineal infection (n = 77), and suspected or confirmed deep tissue infection (n = 68).

Characteristics of the cohort are shown in Supplementary Table 1. Half of the patients were hospitalized for treatment. The mean age was 46 years; 20 (91%) were male. All patients received systemic antibiotic therapy, and all with an abscess underwent incision and drainage. At the day 3 and day 5 visits, 17 of 20 (85%) and 15 of 20 (75%) patients evaluated, respectively, were classified as treatment success.

At enrollment, CRP, PCT, and WBC levels were elevated in 20 (91%), 15 (68%), and 16 (73%) patients, respectively. Mean enrollment CRP, PCT, and WBC levels (SD) were 97.7 (86.7) mg/L, 0.98 (2.62) ng/mL, and 13.9 (6.6) K/μL, respectively (Table 1). By day 3 and day 5, the mean CRP levels (SD) had decreased to 63.0 (74.5) mg/L (P = .028) and 22.7 (31.8) mg/L (P < .001), respectively, and the mean WBC level (SD) had decreased to 9.3 (3.9) K/μL (P < .001) and 8.5 (3.1) K/μL (P < .001), respectively. The mean PCT level (SD) had decreased to 0.34 (0.99) ng/mL (P = .21) and 0.14 (0.4) ng/mL (P = .095), respectively; however, these declines were not statistically significant. Individual-patient CRP, PCT, and WBC levels after the start of antibiotic therapy are displayed in Supplementary Figure 1.

Supplementary Figure 2 shows the change in CRP, PCT, and WBC levels between baseline and day 3 stratified by the classification of treatment success or failure. Biomarker levels declined by day 3 in most cases of successful treatment; however, CRP and PCT levels remained stable or increased slightly in several cases. In the 3 cases classified as treatment failure, CRP and PCT levels increased by day 3 in 1 patient, declined in 1, and were undetectable in 1.

Baseline CRP, PCT, and WBC levels were generally higher among patients with nonabscess infections as compared with abscesses (Supplementary Figure 3); however, levels tended to decline by day 3 and day 5 in both groups. In addition, baseline levels were higher, and the declines by day 3 and day 5 appeared to be more precipitous among hospitalized patients as compared with those treated as outpatients (Supplementary Figure 4).

DISCUSSION

In patients with an acute bacterial skin infection, initial CRP, PCT, and WBC levels were elevated in the majority of cases. Overall, mean CRP and WBC levels declined significantly by

Table 1. Mean Biomarker Levels at Presentation and During Treatment[a]

	All Subjects (n = 22)	Change From Baseline Level	P[b]	Cutaneous Abscess (n = 15)	Nonabscess (n = 7)
C-reactive protein, mg/L					
Baseline level[c]	97.7 ± 86.7			73.9 ± 62.8	148.8 ± 112.5
24 h	89.5 ± 90.7	–8.2 ± 42.2		74.0 ± 82.6	122.7 ± 105.0
Day 3	63.0 ± 74.5	–38.7 ± 70.7	.028	53.1 ± 80.3	80.0 ± 65.6
Day 5	22.7 ± 31.8	–74.4 ± 69.9	<.001	15.1 ± 21.1	37.9 ± 44.7
Procalcitonin, ng/mL					
Baseline level[c]	0.98 ± 2.62			0.47 ± 1.28	2.08 ± 4.26
24 h	0.65 ± 1.88	–0.33 ± 0.85		0.26 ± 0.6	1.47 ± 3.22
Day 3	0.34 ± 0.99	–0.51 ± 1.74	.21	0.14 ± 0.4	0.69 ± 1.55
Day 5	0.14 ± 0.4	–0.88 ± 2.3	.095	0.05 ± 0.1	0.32 ± 0.68
White blood cells, K/μL					
Baseline level[c]	13.9 ± 6.6			12.6 ± 5.4	16.6 ± 8.4
24 h	11.5 ± 6.1	–2.4 ± 3.8		10.8 ± 6.3	12.8 ± 6.1
Day 3	9.3 ± 3.9	–5.2 ± 4.5	<.001	8.5 ± 3.0	10.8 ± 5.1
Day 5	8.5 ± 3.1	–4.8 ± 5.0	<.001	7.7 ± 2.9	10.3 ± 2.8

[a]Data presented as mean ± standard deviation.

[b]Only prespecified statistical comparisons between baseline and day 3/day 5 levels for the overall cohort were performed to minimize risk of type 1 error.

[c]Obtained prior to or within 2 hours of starting antibiotic therapy.

day 3 and day 5 of treatment; although the mean PCT level also declined by days 3 and 5, the trend did not reach statistical significance.

There has been limited research regarding biomarkers in skin infections to date. In several prior studies, only single CRP or PCT levels were obtained at the time patients presented with a suspected skin infection; therefore, only the diagnostic or prognostic utility of these biomarkers could be evaluated [8–11]. To our knowledge, there has only been 1 study besides ours evaluating the potential utility of serial CRP and PCT levels in the management of skin infections. In this study, Eder and colleagues measured serial CRP and PCT levels in 50 inpatients with heterogeneous skin infections [12]. Similar to our study, they found initially elevated levels in most patients and observed declines over the first week of treatment.

Analogous to the use of serial PCT levels to guide antibiotic prescribing in patients with sepsis or acute respiratory infection [4, 5], our results and those of Eber and colleagues indicate a potential role for serial CRP or PCT levels to guide prescribing in patients with skin infections. Appropriately declining levels may reassure clinicians about the adequacy of initial therapy, thus preventing unnecessary escalation of antibiotic therapy or prolonged treatment durations. The time course of CRP and PCT levels we observed suggests that in a future study of a biomarker-guided prescribing strategy, it would be appropriate to obtain levels at presentation, day 3, and day 5. Our data also suggest that a biomarker-guided prescribing strategy is most likely to be effective among hospitalized patients where initial levels tend to be more highly elevated and decline more precipitously.

This study has important limitations. First, the small sample size and heterogeneous infections limit conclusions that can be drawn; however, this work was largely intended to be hypothesis-generating and to inform the development of future studies. Second, there are no gold standard criteria for the diagnosis of skin infections or for treatment outcomes, which may have led to misclassification in some cases. Third, due to the timing of biomarker levels obtained in our study, we may not have identified the peak level in any given case. Finally, in the absence of a control group, the specificity of the biomarkers for bacterial skin infection could not be evaluated.

In summary, this study adds to the sparse literature describing biomarkers in acute bacterial skin infections. Our data demonstrate that CRP and PCT are usually elevated at presentation and decline over 3 to 5 days of treatment. Thus, a biomarker-guided prescribing strategy as an adjunct to clinical decision-making could reduce unnecessarily broad-spectrum and prolonged antibiotic regimens and warrants further study.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. bioMérieux provided PCT test kits but was not involved in study design or conduct, data analysis, or manuscript preparation. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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