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MAJOR ARTICLE

Impact of Procalcitonin Levels Combined With Active Intervention on Antimicrobial Stewardship in a Community Hospital

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Background. Procalcitonin (PCT) guidance alone or in conjunction with antibiotic stewardship programs (ASPs) has been shown to reduce antibiotic utilization and duration of therapy without adversely affecting patient outcomes.

Methods. In a community hospital, we investigated the impact of PCT with ASP recommendations on length of stay (LOS), length of antimicrobial therapy (LOT) after ASP recommendation, and total LOT over a 1-year period. Adult patients with at least 1 PCT value and concomitant ASP recommendations were included. Patients were grouped by provider ASP compliance and further stratified by normal versus elevated PCT values. No specific PCT algorithm was utilized.

Results. A total of 857 patients were retrospectively analyzed. Physicians complied with 73.7% of ASP recommendations. There were no significant differences in LOS based on ASP compliance. Mean LOT after ASP recommendations and mean total LOT were significantly shorter (2.5 vs 3.9 days, $P < .0001$ and 5.1 vs 6.6 days, $P < .0001$, respectively) in the ASP complier group. When stratified by initial PCT levels, ASP compliers for patients with normal PCT levels had the shortest duration of therapy for all groups; among patients with elevated PCT levels, the duration of therapy was significantly shorter in the ASP compliant group (5.79 vs 7.12 days, $P < .0111$). When controlling for baseline differences in initial PCT levels, LOS was found to be marginally shorter in the ASP compliant group ($P = .076$).

Conclusions. Procalcitonin-guided ASP physician recommendations, when accepted by providers, led to reduction in LOT in a community hospital. This benefit was extended across patient groups irrespective of initial PCT levels.

Keywords. ASP; community hospital ASP; length of antimicrobial therapy; prescriber compliance; procalcitonin.

Procalcitonin (PCT) is a peptide precursor of calcitonin that increases within 3–6 hours after onset of a bacterial infection. It has been useful in differentiating bacterial and nonbacterial etiologies for infections, and, when incorporated into an algorithm, it has been associated with reduction of antibiotic use [1]. These findings have been demonstrated in a variety of settings including critical care, where Agarwal and Schwartz [2] concluded that PCT guidance has an impact on treatment duration and may decrease length of stay (LOS) in the intensive care unit. ProHOSP, a large randomized controlled trial of PCT-based guidelines versus standard guidelines for antibiotic use in emergency department patients with lower respiratory tract infections (LRTIs), demonstrated both that mean duration of antibiotic use was shorter and antibiotic-associated adverse events were less frequent in the PCT arm [3].

Procalcitonin has been widely used in Europe and there is increasing adoption in the United States. A recent US study (ProACT) did not find a reduction in mean antibiotic days in patients with LRTIs in the PCT arm versus the control arm; however, compliance with the PCT guidelines was not optimal, and study physicians had very limited previous experience with PCT [4]. In addition, this study did not involve real-time prospective audit and feedback; implementation in the absence of an ASP review may have led to a failure to provide clinical benefit. Some postulated reasons for poor compliance with PCT guidelines include (1) difficulty in discontinuing antibiotics when PCT levels normalize as well as (2) extra costs and long turnaround time to obtain PCT results if tests are performed off site [5]. Another potential barrier to PCT use is provider reluctance to modify treatment based on PCT results. Providers may trust their own clinical judgment over a laboratory value and may not want to risk withholding antibiotics, especially in the absence of an infectious disease (ID) physician consult [6].

In recent years, antimicrobial stewardship programs (ASPs) have used PCT in protocols to assist with decisions on antibiotic initiation and discontinuation. The goals of an ASP are to

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improve the use of antimicrobial agents to reduce antibiotic resistance, enhance patient outcomes, and decrease unnecessary costs. Procalcitonin has the potential to improve provider decision making and support antimicrobial stewardship through reduction of both unnecessary antibiotic initiation and treatment duration. Published studies have shown the utility of PCT-guided ASP protocols in reducing antibiotic use without compromising patient safety [7–9].

Despite multiple studies demonstrating the benefits of PCT in LRTIs, more broadly, and sepsis patients in academic medical centers, there are limited published data on PCT use in community ASPs. In a retrospective, quasi-experimental cohort study, researchers evaluated the impact of PCT on antibiotic duration in pneumonia in an acute-care community hospital [10]. The authors found that implementation of a PCT program did not affect antibiotic initiation decisions but was associated with a trend in earlier discontinuation of antibiotics. However, the sample size was small and included severely ill patients who required an ID consult or intensive care unit stay. These study results were replicated in a pharmacist-driven study by Brock et al [11] in which use of PCT-guided algorithms was associated with reduced antibiotic days of therapy in a community hospital. Two subsequent studies evaluated PCT guidance in "real-world" settings and found that antibiotic duration and inpatient LOS were significantly shorter when a PCT-guided algorithm combined with education was implemented [12, 13].

The objectives of the current study were to evaluate the impact of PCT use, combined with active recommendations from the ASP, on inpatient LOS, the length of antimicrobial therapy (LOT) after ASP recommendations, and total LOT. We hypothesized that patients whose providers complied with ASP recommendations and those with normal PCT levels would have shorter LOS and shorter LOT. For purposes of this study, a normal PCT value was an absolute level <0.25 ng/mL or a 90% reduction from the peak PCT level.

MATERIALS AND METHODS

Study Design, Setting, and Selection of Participants

This investigation was a retrospective analysis of patients admitted to Washington Regional Medical Center (a 366-bed, community hospital located in Fayetteville, AR), whose providers were given antimicrobial therapy guidance by the ASP. The ASP is led by a board-certified ID physician (1.0 FTE) since its inception in January 2012. However, no pharmacists provided ASP review during this study. Procalcitonin testing availability began in October 2012 with no restrictions on use. Procalcitonin testing was available "in-house" 24 hours a day, 7 days a week, with result turnaround time of less than 1 hour. Before the implementation of PCT testing, there was extensive didactic education (including continuing medical education) with electronic medical record (EMR) education alerts and electronic bulletin board postings. A PCT-guidance algorithm was not formally implemented. The current analysis represents findings based on interventions made through the ASP over a 1-year period (May 2013 to April 2014).

Adult inpatients who had at least 1 PCT level and whose provider received ASP recommendations based on that value were included. Because an algorithm was not utilized, PCT levels were ordered at the discretion of the treating physician. These PCT values included both single values measurements and serial values based on what the physician felt was clinically indicated. Pediatric patients (<16 years old) and patients under the care of an ID physician were excluded. At the time of the study, all broad-spectrum (carbapenems, beta-lactam/beta-lactamase inhibitor combination antibiotics, advanced generation cephalosporins, and fluoroquinolones) and restricted antibiotics (aztreonam, tigecycline, daptomycin, linezolid, ceftaroline, amphotericin, voriconazole, and ganciclovir), redundancies in anaerobic and Gram-negative coverage, culture orders, and culture results were reviewed daily by the ID physician for clinical appropriateness. Antimicrobial stewardship program recommendations were offered utilizing evidence-based clinical guidelines, clinical experience, and PCT results. Formal ASP recommendations were made electronically via the inbox function of the EMR unless the recommendation was urgent and either a face-to-face meeting or telephone call was made. De-escalation or discontinuation of antibiotic therapy was recommended for patients with PCT levels of <0.25 ng/mL or >90% reduction from the peak PCT level. The ASP physician used PCT values in concert with the clinical chart review to make ASP interventions as part of prospective audit and review. Antimicrobial stewardship program recommendations were "not" based on PCT values only.

Patient data including PCT levels, diagnoses, LOS, LOT, and prescriber acceptance of ASP recommendations were collected. Patients were stratified into 2 groups based upon acceptance or rejection of the ASP recommendations by the provider (compliance and noncompliance). Patients were further stratified based upon normal or elevated initial PCT levels.

Study Outcomes

The primary outcomes were LOS, LOT after ASP recommendation, and total LOT. Length of antimicrobial therapy was defined as the duration of antibiotic use from the date and time of the first antibiotic dose through the date and time of the completion of the last antibiotic dose administered. Length of antimicrobial therapy after ASP recommendation was defined as the duration of antibiotic use from the date and time of the formal ASP modification recommendation through the date and time of the completion of the last antibiotic dose administered.

Statistical Analysis

To assess the effect of compliance with ASP recommendations on patient outcomes while also accounting for the effect of

initial PCT level on patient outcomes, univariate and bivariate descriptive statistics were calculated including means, standard deviations, and linear correlation coefficients. Linear correlation coefficients (r values) were used to assess the strength of the linear association between initial PCT levels and each patient outcome measure, with associated *P* values provided to assess statistical significance.

Analysis of variance procedures were used to assess the effect of compliance with ASP recommendations upon nonnormally distributed patient outcomes, with the robustness of these results confirmed using equivalent nonparametric procedures such as the Kruskal-Wallis test. In addition, analysis of covariance (ANCOVA) procedures were used to assess the effect of compliance with ASP recommendations, while controlling for initial PCT levels.

All statistical analyses were performed using SAS version 9.4 (Cary, NC) with statistical significance defined as $P < .05$. This study was approved by the Washington Regional Medical Center Institutional Review Board.

RESULTS

Of 16 394 patient charts screened, 4685 (28.6%) patients were eligible for ASP review between May 2013 and April 2014. Antibiotic use was deemed appropriate in 3110 patients (66.4%) and thus ASP recommendations were not offered. Antimicrobial stewardship program recommendations were offered in 1575 patients (33.6%). Of these, 857 patients had at least 1 PCT measurement and a concomitant ASP recommendation documented during the study period (Figure 1). Over half (57.9%) of these patients had only 1 PCT level documented. Providers complied with ASP recommendations for 73.7% (n = 632) of included patients. The remaining providers, who rejected ASP recommendations, were considered ASP noncompliers (n = 225 patients). The most common diagnoses among patients were pneumonia (22.9% of compliers and 23.1% of noncompliers), cystitis (13.3% of compliers and 15.1% of noncompliers), and undifferentiated sepsis (11.7% of compliers and 9.8% of noncompliers). There were no statistically significant differences in 60-day mortality rates, sex/gender, diagnoses, age, or initial PCT levels between the compliant and noncompliant groups (see Table 1). Respiratory viral panel testing via multiplex polymerase chain reaction was not available during this study.

Descriptive statistics for the 3 patient outcome measures of interest were calculated and are provided in Table 2, stratified by compliance. Although mean LOS did not differ significantly between the 2 groups ($P = .649$), there was a significantly shorter mean LOT after ASP recommendations (2.5 vs 3.9 days, $P < .0001$) and a significantly shorter mean total LOT (5.1 vs 6.6 days, $P < .0001$) in the ASP complier group compared to the ASP noncomplier group. Therefore, ASP compliance was associated with (1) a reduction in mean LOT after ASP recommendations of 1.43 days (95% confidence interval [CI], 0.86–1.98) and (2) a reduction in mean total LOT of 1.45 days (95% CI, 0.82–2.07).

Additional descriptive statistics for the patient outcome measures of interest were calculated, stratified by compliance and by normal or elevated PCT levels (see Table 3). Patients with elevated PCT levels had longer LOS and longer antibiotic therapy durations than patients with normal PCT levels. Mean length of therapy after ASP recommendations was shortest

Figure 1. Algorithm for patient inclusion. ABX, antibiotics; ASP, antimicrobial stewardship program; ID, infectious disease; PCT, procalcitonin; Peds, pediatrics.

Table 1. Demographic and Sample Characteristics Among ASP Compliers and Noncompliers

Variable	Compliers (N = 632)*	Noncompliers (N = 225)*	*P* Value**
60-Day Mortality			.7980
No	542 (85.8)	197 (87.6)	
Yes (Hospice)	48 (7.6)	15 (6.7)	
Yes	42 (6.6)	13 (5.8)	
Sex/Gender			.2538
Female	360 (57.0)	138 (61.3)	
Male	272 (43.0)	87 (38.7)	
Diagnosis			.9420
Cellulitis	16 (2.5)	7 (3.1)	
Cystitis	84 (13.3)	34 (15.1)	
Peritonitis or colitis	16 (2.5)	5 (2.2)	
Pneumonia	145 (22.9)	52 (23.1)	
Sepsis	74 (11.7)	22 (9.8)	
Other	297 (47.0)	105 (46.7)	
Age (years)	68.28 (16.58)	68.62 (17.22)	.7934
PCT level (ng/mL)	4.89 (20.29)	3.65 (15.10)	.3365

Abbrevations: ASP, antimicrobial stewardship program; PCT, procalcitonin; SD, standard deviation.

*Values for categorical variables are count (%) and values for continuous variables are mean (SD).

**Statistically significant differences between compliers and noncompliers assessed at $P < .05$ significance level utilizing χ^2 tests for categorical variables and *t* tests for continuous variables.

among patients with normal PCT levels whose providers complied with ASP recommendations. Among patients with normal PCT levels, mean LOT after ASP recommendations was significantly shorter in the ASP complier group compared to the noncomplier group (2.1 vs 3.6 days, $P < .0001$). Among patients with normal PCT levels, mean total LOT was also significantly shorter in the ASP complier group compared to the noncomplier group (4.7 vs 6.2 days, $P < .0001$). Furthermore, among patients with elevated PCT levels, mean LOT after recommendations (3.1 vs 4.4 days, $P = .004$) and mean total LOT (5.8 vs 7.1 days, $P = .011$) were significantly shorter in the ASP complier group compared to the noncomplier group.

The relationships between initial PCT levels and patient outcome measures, stratified by compliance, were summarized with linear correlation coefficients in Table 4. There were significant positive linear relationships between initial PCT levels and patient outcome measures overall and for complying providers, demonstrating that as initial PCT levels increased, LOS, LOT after ASP recommendation, and total LOT also increased. For complying providers, patients with lower initial PCT levels had shorter LOS and shorter antibiotic therapy durations, whereas patients with higher initial PCT levels had longer LOS and longer antibiotic therapy durations.

One-way ANCOVA procedures were conducted to determine the effect of ASP compliance on each patient outcome measure while adjusting for the initial PCT levels of each patient. There was a trend that did not meet statistical significance between the complier and noncomplier groups for LOS when controlling for baseline differences in initial PCT levels of patients ($P = .076$). There was a significant difference between the complier and noncomplier groups for LOT after recommendation ($P < .0001$) and total LOT ($P < .0001$) when controlling for baseline differences in initial PCT levels.

DISCUSSION

Our findings indicate that compliance with ASP recommendations is associated with shorter LOT after ASP recommendation and total LOT irrespective of initial PCT levels. Patients with elevated initial PCT levels whose providers did not

Table 2. Length of Stay, Duration of Antimicrobial Treatment After ASP Recommendations, and Total Duration of Antimicrobial Treatment Among ASP Compliers and ASP Noncompliers in Days

	Compliers (N = 632)		Noncompliers (N = 225)		
Variable	Mean	SD	Mean	SD	*P* Value
Length of stay (days)	8.46	6.66	8.21	7.61	.6493
Length of antimicrobial therapy* (after ASP recommendation) (days)	2.50	3.33	3.93	4.38	<.0001
Total length of antimicrobial therapy (days)*	5.10	3.74	6.55	4.96	<.0001

Abbrevations: ASP, antimicrobial stewardship program; SD, standard deviation.

*Statistically significant difference between compliers and noncompliers at $P < .05$ significance level utilizing analysis of variance and Kruskal-Wallis procedure.

Table 3. Comparison of Length of Stay, Duration of Antimicrobial Treatment After ASP Recommendations, and Total Duration of Antimicrobial Treatment Among Compliers and Noncompliers by Initial Procalcitonin Level

	Normal Procalcitonin Level			Elevated Procalcitonin Level		
	Compliers (N = 380)	Noncompliers (N = 144)		Compliers (N = 252)	Noncompliers (N = 81)	
Variable	Mean (SD)	Mean (SD)	*P* Value	Mean (SD)	Mean (SD)	*P* Value
Length of stay	7.98 (6.09)	7.77 (6.88)	.7464	9.17 (7.40)	9.01 (8.76)	.8537
Length of antimicrobial therapy (days)* (after ASP recommendation) (days)	2.11 (2.83)	3.64 (4.38)	<.0001	3.11 (3.89)	4.43 (4.37)	.0043
Total length of antimicrobial therapy (days)*	4.65 (3.39)	6.23 (4.75)	<.0001	5.79 (4.12)	7.12 (5.30)	.0111

Abbrevations: ASP, antimicrobial stewardship program; SD, standard deviation.

*Statistically significant difference between groups at $P < .05$ significance level utilizing analysis of variance and Kruskal-Wallis procedures with planned contrast comparisons.

comply with ASP recommendations had the longest duration of antimicrobial therapy, and patients with normal PCT levels whose providers complied with ASP recommendations had the shortest mean duration of antimicrobial therapy. Patients with high initial PCT levels whose providers complied with recommendations had shorter duration of antimicrobial therapy than patients with normal PCT levels whose providers did not comply with recommendations. However, adherence to ASP recommendations did not lead to significant reductions in LOS. These findings suggest that in the "real world," provider compliance with PCT-guided ASP recommendations can result in shorter antibiotic duration, even if a specific PCT algorithm is not utilized.

Recent studies have estimated that half of hospitalized patients are prescribed a course of antibiotics, and the likelihood of inappropriate antibiotic use is 30%–50% [14]. Therefore, ASPs play a critical role in reducing inappropriate antibiotic use. However, implementation of ASPs can be a major challenge for some institutions, especially in community hospitals where staffing shortages and resource limitations pose substantial barriers. In a survey conducted in 2011, only 15.4% of 568 community hospitals reported having ASP committees, of which only 5.2% reported physicians being the point of contact [15]. Hence, there is an urgent need for ID physician leadership and strategies to overcome barriers and improve efficiency of ASPs, including educating prescribing clinicians.

Rapid diagnostic testing should also be incorporated to assist in timely antimicrobial de-escalation as recommended in the Centers for Disease Control and Prevention's "The Core Elements of Hospital Antibiotic Stewardship Programs" [16]. In this study, we demonstrate that incorporation of PCT with ASP recommendations reduced LOT in a large community hospital, despite limited resources—a single ASP physician, in the absence of dedicated pharmacy support, made all ASP recommendations. This suggests a beneficial role of PCT in improving efficiency of ASPs that may be limited by staffing. Shorter LOT may also reduce the risk of adverse events and decrease the further development of antimicrobial resistance.

One of the challenges with implementation of PCT-guided ASP protocols include the turnaround time and costs involved with the testing; however, in the longer term, reduction in antimicrobial use due to shorter LOT can offset these minimal extra costs. Procalcitonin turnaround time at our hospital is <1 hour and total expense per test is <$30. A recent study from Mercy Medical Center in Iowa showed no significant difference in the total cost of treatment and laboratory expenditures when PCT was used; the benefits of PCT-guided ASP protocols in improving efficiency of ASPs outweigh the costs of laboratory PCT tests [11]. In addition to identifying physician and pharmacy champions for ASPs, educational campaigns on appropriate antimicrobial prescribing and proper PCT utilization can also boost efficacy of PCT-guided ASP protocols. In this study, an ID physician used PCT values and clinical experience to provide ASP advice, which may have contributed to our successful reduction in antibiotic duration in contrast to other studies using PCT guidance for antimicrobial stewardship [5, 6].

Table 4. Linear Correlation Between Initial Procalcitonin Level and Patient Outcomes

	Overall (N = 857)	Compliers (N = 632)	Noncompliers (N = 225)
Variable	R (*P* Value)	R (*P* Value)	R (*P* Value)
Length of stay, days	0.08 (.025)*	0.09 (.022)*	0.03 (.662)
Length of antimicrobial therapy (after ASP recommendation), days	0.15 (<.0001)*	0.19 (<.0001)*	0.10 (.140)
Total length of antimicrobial therapy, days	0.13 (.0002)*	0.17 (<.0001)*	0.06 (.344)

Abbrevations: ASP, antimicrobial stewardship program.

*Statistically significant linear correlation at $P < .05$ significance level.

Limitations of our study include our single-center, retrospective approach. The majority of patients had only 1 PCT level tested; therefore, we were unable to associate trends in PCT levels with intervention acceptance rates. Only 73.7% of ASP recommendations were accepted. The addition of a standard PCT clinical algorithm would have further supported ASP recommendations. In addition, all infections were included; therefore, we cannot evaluate the impact of PCT on LOS and LOT for specific infectious diagnoses, but this would be useful to collect and stratify in future studies. We were also unable to collect patient safety outcomes such as recurrence rates and readmission rates. Further study to compare outcomes in patients who received ASP advice without the benefit of PCT guidance and the ASP group who had PCT guidance is warranted.

CONCLUSIONS

In conclusion, active ASP intervention assisted by PCT, outside of a specific PCT algorithm, in a community hospital can help augment ASPs, and result in the reduction of LOT. Antimicrobial stewardship programs should consider providing guidance on how to use PCT levels in hospitalized patients as a core activity.

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Potential conflicts of interest. L. Z. is an employee of bioMérieux. 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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