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BRIEF REPORT

Impact of Low Procalcitonin Results on Antibiotic Administration in Hospitalized Patients at a Tertiary Care Center

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ABSTRACT

Procalcitonin is a sensitive and specific marker of bacterial infection; low results allow clinicians to safely de-escalate antibiotics. This retrospective cohort study aimed to determine the effect of low procalcitonin results on withholding, discontinuing, or de-escalating antibiotics in hospitalized patients at a tertiary care center. Antibiotics were initiated or continued without de-escalation in 55% of patients with low procalcitonin results. Among patients with low procalcitonin results, the primary service, but not measures of patient complexity, disease severity, or underlying disease process (lower respiratory tract infection evaluation versus systemic inflammatory response syndrome/possible sepsis) was associated with initiation or continued broad-spectrum antibiotic use. Provider-level factors may be an important variable in the initiation or continued use of broad-spectrum antibiotics for patients with low procalcitonin levels.

Keywords: Antibiotic stewardship; Behavioral sciences; Discordance; Procalcitonin

INTRODUCTION

Procalcitonin is highly sensitive and specific for bacterial infections [1–3]. Low procalcitonin results support clinician decisions to withhold, discontinue or de-escalate antibiotics safely, especially in the evaluation of lower respiratory tract infection or patients with systemic inflammatory response syndrome (SIRS)/possible sepsis [4–6]. International studies, largely centered in Europe, demonstrate high overall concordance between procalcitonin algorithms and

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antibiotic use [5, 6]. However, antibiotic use stratified by low versus high procalcitonin result is lacking, especially among hospitalized patients in the USA. This study aimed to determine the association between low procalcitonin results and withholding, discontinuation, or de-escalation of antibiotics in patients hospitalized at a US tertiary care center with an existing procalcitonin guideline. Additionally, as procalcitonin-based algorithms are not intended to override clinical decision making by the provider, we aimed to understand better which factors may impact the decision of a provider to continue antibiotic therapy despite a low procalcitonin test result.

METHODS

Study Design and Population

This was a retrospective cohort study of all adult patients admitted to a US tertiary care center (University of Wisconsin Hospital and Clinics) between November 1 and December 31, 2014 who had procalcitonin ordered as part of their hospitalization. The hospital's procalcitonin guideline was in effect for 9 months prior to the study start date. The guideline was developed by the Antimicrobial Use Sub-Committee (AMUS) of the Pharmacy and Therapeutics Committee at the University of Wisconsin Hospital and Clinics. The guideline was distributed to all inpatient providers and the AMUS members held educational didactics with each inpatient physician group during the initial 6 months of the roll-out period. It is important to note during the study period a lab order for procalcitonin was not pre-selected (e.g. part of an order set) for any patient and therefore the provider must have specifically chosen to order the test. The guideline suggests ordering a baseline procalcitonin for patients with suspected lower respiratory tract infection and/or evidence of SIRS/possible sepsis [7]. For patients with values <0.25 ng/ml, the guideline suggests continuing to withhold antibiotic therapy or to consider de-escalation or discontinuation if antibiotics have already been initiated. As is consistent with other procalcitonin guidelines, our guideline also includes the caveat that procalcitonin result should not trump clinician decision making. The University of Wisconsin Institutional Review Board deemed this study exempt from review and waived the need for written informed consent. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Data Collection

Data were abstracted retrospectively from provider notes, laboratory results, and the medication administration record, all of which were available in the hospital's electronic medical record system. The dependent variable was antibiotic discordance, determined based on active antibiotic prescriptions ≥48 h after the procalcitonin result became available. Discordance was defined as (1) initiation or continued use of antibiotics without de-escalation or discontinuation in the setting of a low procalcitonin result or (2) discontinuation of antibiotics in the setting of a high procalcitonin result. The independent variable of interest was whether the patient had a low procalcitonin result, defined as <0.25 ng/mL. Other variables obtained from the medical record included age, gender, whether the patient had been hospitalized in the past 30 days, primary service caring for the patient, and the underlying clinical reason (i.e., lower respiratory tract infection, SIRS/possible sepsis,

or other) for ordering the test. The 3 M™ All Patient Refined DRG Classification system (APR-DRG) (3 M™ Health Information Systems, Salt Lake City, UT, USA) was used to measure disease severity, while the Charlson Comorbidity Index was used to capture patient complexity [8]. Both were calculated using billing codes (International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, Switzerland).

Statistics

Descriptive statistics were used to report the proportion and means of patient- and provider-level variables. Pearson's Chi-squared test and univariate odds ratio were used to examine whether the proportion of patients receiving discordant antibiotics varied based on low versus high procalcitonin results. Among the low procalcitonin subgroup, univariate odds ratios were calculated to assess patient- and provider-level factors that may be associated with discordant antibiotic use. Multivariate modeling was attempted, but the sample size precluded an adequate mathematical fit. All statistics were calculated using STATA (ver. 12; StataCorp LP, College Station, TX, USA).

RESULTS

All 181 hospitalized patients who underwent procalcitonin testing during the 2-month study period were included in the analysis, and cohort characteristics are presented in Table 1. Half of them ($n = 91$) had low procalcitonin levels. The average patient age was 60 years, and 69/181 (38%) were female. Thirty-two patients (18%) had been hospitalized in the past 30 days. The mean APR-DRG weighted value was 2.77 (0.28–17.75). This compares to a median weight of all patients admitted to the University of Wisconsin Hospital and Clinics for 2014 at 1.14 and 75th percentile at 2.02. The mean Charlson Comorbidity score was 2.54 (0–8). Patients were cared for by the following services: medicine 47%, critical care 33%, immunocompromised 8%, other 12%. The test was ordered as part of a pneumonia workup in 124 instances (69%). Twenty-eight patients (15%) had a procalcitonin ordered for SIRS/possible sepsis, while 29 (16%) had it ordered for other reasons (e.g., leukocytosis, fever, diarrhea, bleeding, trauma).

Overall antibiotic discordance with the procalcitonin result was 32% ($n = 58$). Not surprisingly, antibiotic discordance was heavily skewed by initiation or continued use without de-escalation in patients with low procalcitonin results. Indeed, 55% of patients with low procalcitonin results had antibiotics initiated or continued without de-escalation or discontinuation. In contrast, antibiotic discordance was observed in only 9% of patients with high procalcitonin levels (Pearson's Chi-squared $p < 0.001$, Fig. 1). Among the 50 patients with low procalcitonin results and discordant antibiotic use, 5 (10%) had positive microbiologic cultures that may have affected interpretation of the procalcitonin test. However, three patients had non-specific pathogens or amount of growth from sputum or urine cultures and only two patients had significant pathogens consistent with infection (*Staphylococcus aureus* and *Aspergillus fumigatus* from sputum cultures). In the total study population, the unadjusted odds ratio of discordant antibiotic use for low versus high procalcitonin results was 12.5 (95% CI 5.4, 28.8, $p < 0.001$).

Among patients with low procalcitonin results, provider- but not patient-level factors were statistically significant in the univariate

Table 1 Cohort characteristics stratified by concordant and discordant antibiotic use and unadjusted odds of discordant antibiotic use, restricted to patients with low procalcitonin results

Cohort characteristics				
Variable	**Full study cohort**		**Low procalcitonin subgroup**	
	Concordant ($n = 123$)	**Discordant ($n = 58$)**	**Concordant ($n = 41$)**	**Discordant ($n = 50$)**
Average age (years)	60	58	60	60
Female (%)	37.4	39.7	39.8	40.0
Hospitalized in the past 30 days (%)	15.4	22.4	14.6	24.0
Average APR-DRG weighted score	2.9	2.3	2.4	2.3
Average Charlson Comorbidity Index	2.7	2.6	1.7	2.4
Primary service				
Medicine (%)	50.4	41.4	75.6	42.0
Critical care (%)	34.2	29.3	12.2	30.0
Transplant (%)	5.7	12.1	0	12.0
Other (%)	9.7	17.2	12.2	16.0
Reason for ordering PCT				
Possible pneumonia (%)	65.0	75.9	63.4	76.0
SIRS/possible sepsis (%)	17.1	12.1	7.3	14.0
Other (%)	17.9	12.0	29.3	10.0

Unadjusted odds of discordant antibiotic use, restricted to patients with low procalcitonin results			
Variable	**Odds ratio**	**95% confidence interval**	***p* value**
Additional year of patient age	0.99	0.98, 1.02	0.943
Female (vs. male)	1.05	0.45, 2.42	0.925
Hospitalized in the past 30 days (vs. not)	1.84	0.62, 5.44	0.269
Additional unit increase in APR-DRG weighted score	0.99	0.86, 1.15	0.918
Additional unit increase in Charlson comorbidity index	1.23	0.97, 1.56	0.087
Service (reference = medicine)			
Critical care	4.43	1.40, 14.04	0.011
Transplant	Unable to calculate[a]		
Other	2.36	0.68, 8.22	0.177
Reason for ordering procalcitonin (reference = possible pneumonia)			
SIRS/possible sepsis	1.60	0.38, 6.75	0.525
Other	0.29	0.09, 0.91	0.033

APR-DRG All Patient Refined Diagnosis Related Group, *PCT* procalcitonin, *SIRS* systemic inflammatory response syndrome

[a] An odds ratio was unable to be calculated because all patients with low procalcitonin results cared for on an immunocompromised service continued to receive broad-spectrum antibiotics, making this variable a mathematically perfect predictor of discordance

analysis. In this subgroup, critical care services were more likely than medicine teams to use antibiotics discordantly (OR 4.43, $p = 0.011$, Table 1). Immunocompromised services were also more likely than medicine services to use antibiotics discordantly in patients with low

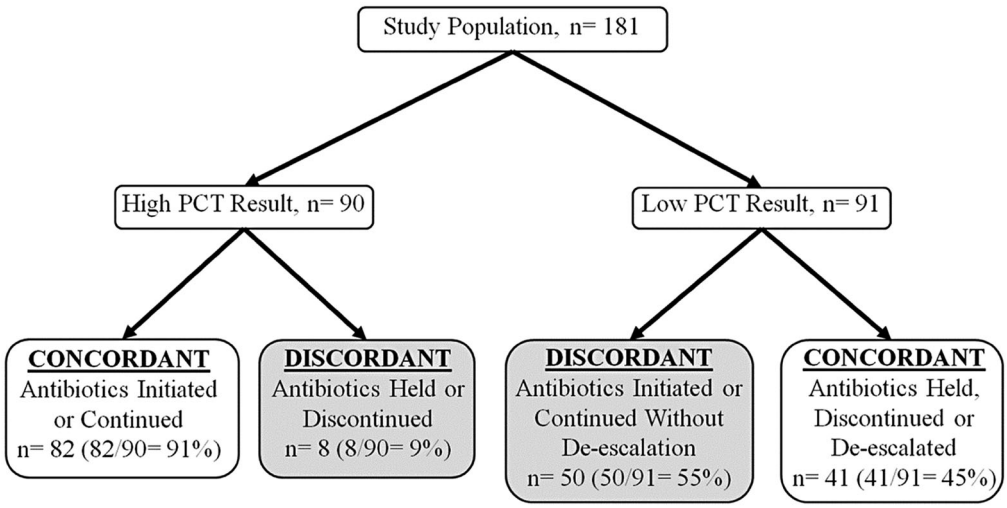

Fig. 1 Antibiotic use in the study population, grouped based on procalcitonin result. *PCT* procalcitonin

procalcitonin results, although an odds ratio could not be calculated because all patients cared for on these services continued to receive antibiotics without de-escalation. It is important to note that our guideline did not recommend testing or use of procalcitonin for immunocompromised patients, as there were insufficient data at the time of the study (including sensitivity, specificity, safety, and outcome) to recommend its use for those patients. Variables measuring disease severity (APR-DRG) and patient complexity (Charlson Comorbidity Index) were not associated with increased odds of antibiotic discordance in the low procalcitonin group (Table 1). Patients with low procalcitonin values who had the test ordered because of SIRS/possible sepsis did not have a statistically significant increase in the unadjusted odds of antibiotic discordance compared to patients who had the test ordered as part of a pneumonia workup. Patients who had the test ordered for reasons other than possible pneumonia or sepsis were more likely to have their antibiotics discontinued or de-escalated. However, the pre-test probability of infection in the "other" category was often very low.

A limitation in the current study was the inability to analyze serial procalcitonin measurements, which are commonly performed in septic patients, on concordance. In our data set, there were less than ten patients who had serial measurements and all had initial high procalcitonin levels.

DISCUSSION

The effectiveness of low procalcitonin results to encourage physicians to withhold, de-escalate, or discontinue antibiotics in this retrospective study at a US tertiary care center is lower than the efficacy reported in predominantly European clinical trials [5, 6]. Antibiotics were held, stopped, or de-escalated in less than half of the patients with low procalcitonin levels (<0.25 ng/mL), despite its excellent negative predictive value. Positive cultures could only account for a small proportion of this discrepancy. Although our overall concordance rate was on par with prior studies, this value is strongly skewed by very high concordance in patients with elevated

procalcitonin levels. Future studies examining the impact of procalcitonin algorithms on antimicrobial prescribing practices should consider stratifying their analysis based on procalcitonin results in addition to reporting an overall antibiotic concordance rate.

Additionally, we hypothesized that the severity of the disease or patient complexity might be a plausible explanation for antibiotic initiation or lack of de-escalation despite a low procalcitonin result. Medical care of hospitalized patients is increasingly complex in terms of severity of illness on presentation and comorbidities. However, classic health services measures of disease severity and patient complexity were not associated with increased odds of discordant antibiotic use among patients with low procalcitonin values in our study. Moreover, SIRS/possible sepsis was not significantly associated with discordance in comparison to lower respiratory tract infection evaluation. Despite these findings, we did note that the primary service (critical care and transplant services) was statistically associated with increased discordance in the low procalcitonin group. The combination of these results indicates that a more complicated paradigm may be playing a role in antibiotic prescribing decisions for inpatients. Provider-level factors, rather than disease severity or patient complexity, may be an important variable in the initiation or continued use of broad-spectrum antibiotics for patients with low procalcitonin levels.

CONCLUSION

Less than 50% of inpatients with a low procalcitonin result had their antibiotics held, de-escalated, or discontinued despite its excellent negative predictive value. Our study suggests an important area for continued research on antimicrobial prescribing practices, and improved antibiotic stewardship using procalcitonin should include the use of behavioral sciences approaches, for example social psychology and behavioral economic principles [9–11], in addition to traditional stewardship interventions such as direct oversight using prospective audit and feedback by an antibiotic stewardship team [12–14].

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Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

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