

Impact of a Pharmacist-Managed Procalcitonin Program on COVID-19 Respiratory Tract Infection Outcomes and Health Care Resource Utilization

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Patients hospitalized with coronavirus disease 2019 (COVID-19) often receive empiric antibiotic coverage. Procalcitonin (PCT) is a biomarker with Food and Drug Administration–approved guidance cutoffs for antibiotic use in lower respiratory tract infections. Herein we describe the implementation and impact of a pharmacist-managed PCT monitoring program in hospitalized patients with COVID-19. In this quasi-experimental, single-center, retrospective study of a prospective antimicrobial stewardship pharmacist-managed program, inpatients who were severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction positive were reviewed during weekday working hours and evaluated for appropriateness of antibiotic treatment by utilizing the PCT biomarker. As needed, the infectious diseases pharmacist offered feedback around antibiotic discontinuation in patients with PCT values ≤ 0.25 ng/mL. Adherence to PCT cutoffs, clinical outcomes, and utilization of health care resources were quantified and compared with a time frame immediately preceding the program's implementation. A total of 772 patients hospitalized with COVID-19 were analyzed. The pre-intervention cohort was comprised of 519 patients, and 253 patients were included after program implementation. Antibiotics were prescribed within 72 hours of admission to 232 (44.7%) and 108 (42.7%) patients during the control and intervention phases, respectively. There was no difference in the primary outcome of percentage of patients who received >1 day of antibiotic therapy (23.5% vs 21.7%; $P = .849$) or in any secondary outcome including hospital length of stay, 30-day readmission rates, or discharge disposition. In a hospital where

the majority of COVID-19 patients did not receive empiric antibiotics, the implementation of a pharmacist-managed PCT monitoring program did not significantly decrease antibiotic use or health care resource utilization.

Keywords. antimicrobial stewardship; biomarker; coronavirus; pneumonia.

The appropriate treatment of acute respiratory tract infections is complicated by the difficulty of distinguishing the causative pathogen and whether it is viral, bacterial, or both [1]. The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has brought this concern to the forefront. This diagnostic uncertainty can lead to the unnecessary administration of antibiotics to patients with strictly viral infections on a large scale [2, 3]. Indeed, multiple studies have reported that the majority (57%–75%) of patients with suspected or diagnosed COVID-19 received empiric antibiotic coverage, while bacterial coinfection is typically uncommon on initial presentation (1.2%–3.5%) [4–6]. The harms of overprescribing antibiotics are well documented [7, 8]. Therefore, interventions designed to limit inappropriate antibiotic therapy without harming patients are encouraged.

Investment in diagnostic tools to improve differentiation of bacterial vs viral infections such as the procalcitonin (PCT) biomarker may improve antibiotic utilization and potentially lead to better use of health care resources. PCT cutoff values have been approved by the Food and Drug Administration for lower respiratory tract infections [9], although these approved ranges precede the COVID-19 pandemic. However, recent studies have found utility in similarly applying them to COVID-19 [10]. Pharmacist intervention in response to diagnostic tests has also been shown to improve antibiotic stewardship metrics, including time to appropriate therapy and antibiotic duration, across a spectrum of infectious diseases [11–13]. Herein, we describe the implementation and impact of an antimicrobial stewardship program (ASP) pharmacist-managed PCT intervention program on antibiotic utilization and outcomes for patients with COVID-19 respiratory tract infection.

METHODS

Study Design and Population

This was a quasi-experimental, single-center, retrospective study of a pharmacist-managed prospective ASP at an 890-bed tertiary care teaching hospital. Patients were included in these analyses if they were ≥ 18 years of age with laboratory-diagnosed COVID-19 within 72 hours of admission between November 1, 2020, and February 26, 2021, which was in the

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midst of the second COVID-19 wave in New England states. Patients were ineligible if they met any of the following criteria: (1) discharged directly from the emergency department or observation unit, (2) admitted directly to a critical care or step-down unit, or (3) were already receiving antibiotics for a nonrespiratory infection within 7 days before presentation.

Stewardship Intervention

Starting on January 4, 2021, a list was generated by an ASP pharmacist that identified all inpatients who were SARS-CoV-2 polymerase chain reaction (PCR) positive. Through February 26, 2021, this list was reviewed daily during weekday working hours as part of standard of care, and each patient was evaluated (as detailed in the [Supplementary Data](#)) for appropriateness of antibiotic treatment by utilizing the PCT biomarker. Eligible patients admitted between November 1, 2020, and December 31, 2020, were included as the control group. No education was provided to prescribers before implementation of the pharmacist-managed intervention so as to not influence their antibiotic prescribing behaviors.

Outcomes and Data Analysis

The primary outcome was the frequency of patients in each cohort (control vs intervention period) who received antibiotics within 72 hours of admission for >1 day. A list of the secondary outcomes and details regarding the data analyses employed in this study is presented in the [Supplementary Data](#). Adherence to PCT was defined as follows: for PCT values ≤ 0.25 , antibiotics were discontinued within 24 hours of the test results (or not empirically initiated), and conversely for PCT values > 0.25 , the patient had to remain or be initiated on antibiotics within 24 hours after the test result.

RESULTS

A total of 1092 unique SARS-CoV-2 PCR-positive patients were admitted to Hartford Hospital between November 2020 and February 2021. Ultimately, 320 patients were excluded ([Supplementary Data](#)). The demographics, baseline characteristics, and symptomatology of each cohort are provided in [Table 1](#). Notably, differences in multiple patient baseline characteristics were observed between the control and intervention cohort periods ([Table 1](#)).

Use of PCT by prescribers was ubiquitous in the study population—only 1 patient of 772 did not have a recorded value at any time during admission. The biomarker was utilized early with 714 (92.5%), 734 (95.1%), and 748 (96.9%) patients having a level drawn within 24, 48, and 72 hours of hospital admission, respectively. During the intervention phase, only a single SARS-CoV-2-positive patient started on antibiotics required contacting the provider to order a PCT. The minority of patients had PCT concentrations > 0.25 ng/mL, and this was not different for patients

before vs during intervention (26.2% vs 30.8%; $P = .207$; respectively). This was consistent with limited objective evidence of bacterial coinfection ([Table 2](#)).

Antibiotics were prescribed within 72 hours of admission to 232 (44.7%) and 108 (42.7%) patients ($P = .651$) during the control and intervention phases, respectively ([Supplementary Table 1](#)). There was no difference in the primary outcome of percentage of all patients who received >1 day of antibiotic therapy (23.5% vs 21.7%; $P = .849$) or for any of the secondary end points ([Table 2](#)). There were also no differences in end points for the subset of patients who received any antibiotic upon admission to the hospital ([Supplementary Table 2](#)). When controlling for baseline differences in the full study population between cohorts using multiple logistic regression, only higher CCI score (odds ratio [OR], 1.22; 95% CI, 1.13–1.31) and younger age (OR, 0.984; 95% CI, 0.970–0.998) were significantly associated with >1 day of antibiotic therapy, while the pharmacy intervention remained insignificant (OR, 0.90; 95% CI, 0.64–1.29). Controlling for baseline differences among the subset of patients with a PCT ≤ 0.25 ng/mL who received empiric antibiotics yielded similar findings (data not shown).

During the intervention cohort, there were 52 patients who received antibiotics within 72 hours of a weekday admission who had a PCT ≤ 0.25 ng/mL, thus making them eligible for pharmacist intervention. Of these, antibiotics were discontinued by the prescriber within 24 hours in the majority ($n = 31$, 60%), thus requiring no intervention. Of the remaining 21, a pharmacist intervened in 13 patients whose antibiotics had not been discontinued by the care team despite a negative PCT value, with a 69% acceptance rate ($n = 9$ patients). Ultimately, 8 eligible patients were missed who were admitted on a weekday and received >24 hours of antibiotic therapy despite a PCT ≤ 0.25 ng/mL. Of note, in all 8 of these instances, antibiotics were discontinued without pharmacist intervention before receiving 48 hours of antibiotics.

DISCUSSION

We hypothesized that a pharmacist-managed intervention using PCT would result in a reduction in patients with COVID-19 who received antibiotics beyond 1 day. However, we observed no such differences in antibiotic duration beyond 1 day, beyond 2 days, or even total antibiotic duration of therapy. Less than half (42.7%–44.7% by cohort) of these non-critically ill patients with COVID-19 received empiric antibiotics on admission. This is in stark contrast to many of the first reports of antibiotic usage in COVID-19, which were as high as 75% [6]. As evidenced by only 23.5% of patients in the control arm receiving >1 day of antibiotics, the margin of opportunity for this intervention was narrow. We hypothesize that combined continuous education on appropriate antibiotic use, quicker turnaround time of COVID-19 test results, and

Table 1. Demographics, Baseline Characteristics, and Symptomatology of COVID-19 Patients Admitted to the General Ward Before and During a Pharmacist-Managed Procalcitonin Monitoring Program

Baseline Characteristics	Pre-intervention (n = 519)	Intervention (n = 253)	P Value
Age, y	66 (55–78)	72 (56–82)	.010
Male sex, No. (%)	284 (54.7)	130 (51.3)	.426
Ethnicity—Hispanic, No. (%)	184 (35.5)	65 (25.7)	.008
Race, No. (%)	≤.001
White or Caucasian	236 (45.5)	144 (56.9)	...
Black or African American	86 (16.6)	33 (13.0)	...
Asian	11 (2.1)	5 (2.0)	...
Other	183 (35.3)	60 (23.7)	...
Unknown	3 (0.6)	11 (4.3)	...
Admitted from facility, No. (%)	88 (17.0)	44 (17.4)	.961
Charlson Comorbidity Index	4 (2–6)	5 (3–7)	.010
Received antibiotics for respiratory indication within 7 d of admission, No. (%)	12 (2.3)	14 (5.5)	.034
Time from admission to COVID (+), median (IQR), d	0.77 (0.52–1.03)	0.85 (0.62–1.19)	.009
Time from admission to first PCT result, median (IQR), h	2.5 (1.8–5.0)	2.6 (1.8–4.1)	.885
Symptoms, No. (%)
>3 d before admission	318 (61.3)	180 (71.1)	.009
Fever	256 (49.3)	115 (45.5)	.350
Fatigue	269 (51.8)	118 (46.6)	.202
Shortness of breath	352 (67.8)	164 (64.8)	.453
Headache	39 (7.5)	35 (13.8)	.008
Altered mental status	36 (7.0)	35 (13.8)	.003
Nausea/Vomiting/Diarrhea	178 (34.3)	70 (27.7)	.077
Sore throat	20 (3.9)	4 (1.6)	.137
Rhinorrhea	32 (6.2)	7 (2.8)	.064
Myalgia	134 (25.8)	63 (24.9)	.852
Cough	281 (54.1)	138 (54.5)	.977
Ageusia or anosmia	21 (4.0)	12 (4.7)	.795
Chest x-ray suggestive of pneumonia, No. (%)	398 (76.7)	202 (79.8)	.370
Culture taken during admission, No. (%)	371 (71.5)	170 (67.2)	.255
Congestive heart failure, No. (%)	111 (21.4)	78 (30.8)	.006
COPD, No. (%)	191 (36.8)	95 (37.5)	.902
Former or current smoker, No. (%)	220 (42.4)	129 (51.0)	.030
Received remdesivir, No. (%)	337 (64.9)	183 (72.3)	.048
First PCT >0.25 ng/mL, No. (%)	136 (26.2)	78 (30.8)	.207
PCT levels per patient, median (IQR)	1 (1–2)	1 (1–2)	.830

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; N/A, not applicable; PCT, procalcitonin.

an expanded “comfort” among prescribers to discontinue antibiotics once COVID-19 was confirmed resulted in lower empiric antibiotic use than previously anticipated for our institution, as well as shorter durations when empiric therapy was initiated.

This pharmacist-managed initiative was designed to be practical and minimally interruptive to existing daily stewardship workflows. This program required ~15–45 minutes of effort daily from our ASP pharmacists, who consisted of 1 FTE in addition to an infectious disease pharmacy resident or fellow. Competing tasks were comprised mainly of prospective audit and feedback of antipseudomonal agents, echinocandins, and antivirals, while the trainee also rounded with an inpatient consult service. SARS-CoV-2 positivity and PCT results were not received or reviewed on a continuous, rolling basis in real time. Instead, a report was run often twice daily—first thing in the morning and

again in the late afternoon, as competing tasks allowed—that provided a static list of all currently hospitalized patients with COVID-19. Therefore, we anticipated that there would be patients for whom intervention would not be possible before receiving 24 hours of antibiotic therapy. Indeed, as alluded to previously, there were 8 patients who were likely affected by the static nature of the monitoring program. With the above taken into consideration, the pharmacist-managed COVID PCT program was discontinued because the added value at our specific institution was minimal. However, pharmacist intervention using PCT among non-COVID patients remains in practice at our institution. While ID-trained pharmacists may be best suited for this intervention, we believe that institutions without full-time ASP pharmacist coverage could reasonably implement a similar program monitored by other staff pharmacists who demonstrate competency, but this should be studied prospectively.

Table 2. Study Outcomes in COVID-19 Patients Admitted to the General Ward Before and During a Pharmacist-Managed Procalcitonin Monitoring Program

Outcomes	Pre-intervention (n = 519)	Intervention (n = 253)	P Value
Received antibiotics, No. (%)
Started within 72 h of admission
Any	232 (44.7)	108 (42.7)	.849
>1 d	122 (23.5)	55 (21.7)	.951
>2 d	98 (18.9)	41 (16.2)	.761
Antibiotic duration of therapy, median (IQR), d	0 (0–1.13)	0 (0–1.04)	.942
Hospital length of stay, median (IQR), d	5.2 (3.7–8.2)	5.5 (3.9–9.7)	.195
Discharge disposition, No. (%)315
Facility	114 (22.0)	67 (26.5)	...
Home	368 (70.9)	166 (65.6)	...
Death	37 (7.1)	20 (7.9)	...
30-d readmission, No. (%)	44 (8.5)	19 (7.5)	.748
<i>Clostridioides difficile</i> infection, No. (%)	17 (3.3)	5 (2.0)	.431
Positive bacterial culture anytime during admission, No. (%)	48 (9.2)	21 (8.3)	.765
Blood culture, No. (%)	19 (3.7)	5 (1.6)	...
Respiratory culture, No. (%)	14 (2.7)	9 (3.6)	...
Other culture, No. (%)	15 (2.9)	7 (2.8)	...
PCT adherence, ^a No. (%)	387 (74.6)	180 (71.1)	.356
≤0.25 subgroup	332 (86.5)	152 (86.9)	.996
>0.25 subgroup	55 (40.4)	28 (35.9)	.609

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; PCT, procalcitonin.

^aPCT adherence defined as follows: for PCT values ≤0.25, antibiotics were discontinued within 24 hours of the test results (or never empirically initiated), and conversely for PCT values >0.25, the patient remained or started on antibiotics within 24 hours after the test result.

Our study has other limitations. First, each arm spanned different, nonoverlapping periods of time. The COVID-19 standards of care were rapidly transforming over the study period, and differences between groups as well as seasonal risk for bacterial coinfection may have unknowingly impacted study outcomes. Additionally, only antibiotics that were received inpatient were quantified, so the reported durations of therapy are likely conservative estimates. Finally, certain patient-specific characteristics make uniform PCT cutoff values problematic to implement, as numerous noninfectious causes can elevate PCT [14–18]. These factors can lead to difficulty with adherence definitions where the one-size-fits-all cutoffs may misinterpret nonadherence as an incorrect clinical decision being made, which in select cases may not be accurate.

In conclusion, in a hospital where the majority of COVID-19 patients did not receive empiric antibiotic therapy, the implementation of a pharmacist-driven PCT monitoring program did not significantly decrease antibiotic use or health care resource utilization. The program was minimally disruptive to existing practice but was not able to produce many interventions in our hospital and may be better suited for institutions with higher rates of empiric antibiotic therapy.

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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Patient consent. The study was reviewed and approved by the Institutional Review Board, and a waiver of informed consent was granted.

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