

# Use of Procalcitonin and a Respiratory Polymerase Chain Reaction Panel to Reduce Antibiotic Use via an Electronic Medical Record Alert

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**Background.** Respiratory tract infections are often viral and but are frequently treated with antibiotics, providing a significant opportunity for antibiotic de-escalation in patients. We sought to determine whether an automated electronic medical record best practice alert (BPA) based on procalcitonin and respiratory polymerase chain reaction (PCR) results could help reduce inappropriate antibiotic use in patients with likely viral respiratory illness.

**Methods.** This multisite, pre–post, quasi-experimental study included patients 18 years and older with a procalcitonin level <0.25 ng/mL and a virus identified on respiratory PCR within 48 hours of each other, and 1 or more systemic antibiotics ordered. In the study group, a BPA alerted providers of the diagnostic results suggesting viral infection and prompted them to reassess the need for antibiotics. The primary outcome measured was total antibiotic-days of therapy.

**Results.** The BPA reduced inpatient antibiotic-days of therapy by a mean of 2.2 days compared with patients who met criteria but did not have the alert fire (8.0 vs 5.8 days, respectively,  $P < .001$ ). The BPA also reduced the percentage of patients prescribed antibiotics on discharge (20% vs 47.8%,  $P < .001$ ), whereas there was no difference in need for antibiotic escalation after initial discontinuation (7.6% vs 4.3%,  $P = .198$ ).

**Conclusions.** The automated antimicrobial stewardship BPA effectively reduced antibiotic use and discharge prescribing rates when diagnostics suggested viral respiratory tract infection, without a higher rate for reinitiation of antibiotics after discontinuation.

**Keywords.** procalcitonin; PCR; rapid diagnostics, EMR.

Lower respiratory tract infections (LRTIs) are a leading cause of hospitalizations in the United States [1, 2]. Acute differentiation of viral and bacterial causes of these infections presents a challenge, though viral pneumonia may be more common than bacterial pneumonia [3]. Difficulty with differentiation of viral vs bacterial presentations often leads to use of empiric antibiotics, thereby risking unnecessary antibiotic exposure. Often no pathogen is isolated and the cause of the infection remains unknown [3]. These factors can lead to prolonged continuation of antibiotics to cover potential bacterial pathogens that may not be the source. Reducing inappropriate antibiotic use in this setting could decrease drug-resistant organisms, adverse drug events, and healthcare costs.

Rapid diagnostic tests and biomarkers are available to assist in diagnosis of LRTIs. Procalcitonin (PCT) is a biomarker that

can assist in differentiating bacterial vs nonbacterial causes of LRTIs, with elevated levels in acute bacterial infections. Despite its association with reduction in days of antibiotic therapy, PCT use is not ubiquitous in the United States [4]. However, it is a safe and effective predictor of bacterial infections, particularly respiratory tract infections [4–10]. Despite PCT sensitivity ranging up to 88%, its use must be clinically correlated with other findings, such as physical examination, history, laboratory tests, and diagnostic imaging. Use of multiplex respiratory polymerase chain reaction (PCR) assays has also been increasing. These tests allow laboratories to quickly detect a wide array of respiratory viruses and select bacteria [11]. While individual test use, particularly PCT, has been well studied, impact on antibiotic therapy varies significantly [12–18]. In a study with stewardship intervention for patients on broad-spectrum antibiotics with a respiratory PCR positive for viruses, time to antibiotic de-escalation was not significantly affected [19]. Only a small number of studies have examined PCT and PCR in tandem. Branche and colleagues examined PCT use vs usual care in a randomized trial and found no difference in rates of antibiotic use at 48 hours or less, but subgroup analysis noted a trend toward improvement when PCT and PCR were suggestive of viral illness. There was also a reduction in patients prescribed

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antibiotics on discharge (20% vs 45%,  $P = .002$ ) [20]. The results showed promise regarding influencing prescribing and suggested need for further study. A recent report found that PCT plus respiratory PCR results can influence antibiotic duration in viral LRTIs, especially with active antimicrobial stewardship input [21]. Conclusively, the available literature suggests that leveraging PCT and respiratory PCR test results, when suggestive of viral illness, appears to be a viable option to minimize antibiotic exposure.

The aim of our study was to determine if antibiotic use could be reduced by deploying an automated antimicrobial stewardship provider alert that prompted antibiotic de-escalation if 3 criteria were met: PCT <0.25 ng/mL, virus detected on respiratory PCR, and active use of systemic antibiotics. While the electronic medical record (EMR) has been used in various manners for antibiotic stewardship [22, 23], we are unaware of its use to automate stewardship recommendations for viral respiratory infections.

## METHODS

This was a quasi-experimental multisite study at 5 hospitals (4 community, 1 academic) within Saint Luke's Health System, Kansas City, Missouri. The study received investigational review board waiver approval. Patients were included if they had both a positive virus on PCR and a PCT value <0.25 ng/mL within 48 hours of each other, and at least 1 active systemic antibiotic. An automated, EMR best practice alert (BPA) for these patients was implemented in December 2017 (Figure 1) in Epic (Verona, Wisconsin; [www.epic.com](http://www.epic.com)). The alert fired upon any

provider opening an EMR when criteria were met. It contained the message "antimicrobial stewardship alert: your patient has a positive viral PCR + negative procalcitonin + one or more antibiotics ordered. These results suggest viral infection—please reassess necessity of antibiotics as indicated." It contained the PCR and PCT results and listed active antibiotics. Three options to proceed were available: "acknowledge"; "does not meet criteria"; and "not making antimicrobial decisions." The first 2 suppressed the alert permanently, and the last allowed it to continue firing each time the EMR was opened, until 1 of the other 2 options were selected. Electronic time stamps allowed assessment of provider responses and alert firing time(s). The prospective BPA group included all patients on which the alert fired from 15 December 2017 to 28 February 2018. The retrospective comparator group included patients who met the alert firing criteria from 1 December 2015 to 30 March 2016. Patients were excluded if they were <18 years old or if antibiotics were also being used for concomitant, nonrespiratory indications. These were identified based on indications included with antibiotic orders (which are required for all antimicrobial orders at our institution), as well as manual records review.

The primary endpoint was inpatient antibiotic-days of therapy, defined as each individual antibiotic given on any day. This was calculated by adding together the total number of days the patient received each individual antibiotic. Secondary endpoints were discontinuation of antibiotics within 24 hours of initiation, days of antibiotics after alert firing, reinitiation of antibiotics after discontinuation, *Clostridioides difficile* infection, discharge prescription rate, and days of antibiotics

**Antimicrobial Stewardship Alert: Your patient has a positive viral PCR + negative procalcitonin + one or more antibiotics ordered. These results suggest viral infection—please reassess necessity of antibiotics as indicated.**

Antibacterial Medications			
Start		Ordered	Stop
05/01/18 0830	vancomycin (VANCOGIN) 1,000 mg in sodium chloride 0.9 % (NS) 250 mL IVPB 1,000 mg, Intravenous, 260 mL/hr, Every 8 hours	05/01/18 0809	--

Results		
	05/01/18 0810	05/01/18
Adenovirus		
Coronavirus		
Human Metapneumovirus (HMPV)		
Human RhinoVirus Enterovirus		
Influenza A		Detected
Influenza B		
Parainfluenza Virus		
Respiratory Syncytial Virus		
Procalcitonin	0.22	

**Acknowledge Reason** \_\_\_\_\_

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**Figure 1.** Screenshot of a best practice alert for antimicrobial stewardship. Abbreviations: HMPV, human metapneumovirus; IVPB, intravenous piggy-back; NS, normal saline; PCR, polymerase chain reaction.

prescribed on discharge. The alert firing endpoint for the retrospective group was defined as the time point when all the information (PCT, PCR, and antibiotic ordered) was available to providers. Reinitiation of antibiotics after discontinuation was defined as any new antibiotic order for a respiratory indication after all antibiotics had been stopped for any significant period (eg, 1 day or more).

Serum PCT levels were measured by VIDAS BRAHMS (bioMérieux, Durham, North Carolina). The clinical detection range is 0.05–200 ng/mL. Our internal guidance for PCT in LRTIs strongly discourages antibiotic use if the PCT value is <0.1 ng/mL and discourages use if it is ≤0.25 ng/mL, consistent with US Food and Drug Administration labeling for PCT testing in LRTIs [24]. Respiratory PCR samples were tested using the FilmArray Respiratory Panel (BioFire Diagnostics, Salt Lake City, Utah), which detects 17 common respiratory viruses and 3 atypical bacteria.

Continuous variables are shown as mean ± standard deviation and were analyzed using Student *t* test, and categorical or nominal variables are shown as number (%) and were compared using  $\chi^2$  or Fisher exact test, as appropriate. A multivariable linear regression model was developed to assess the independent association between our prospective (BPA) group and days of therapy. We adjusted for the following variables based on clinical judgement: age; ventilator-days; Charlson comorbidity index; respiratory viral illness; community-acquired pneumonia; healthcare-associated pneumonia, hospital-acquired pneumonia, or ventilator-associated pneumonia; chronic obstructive pulmonary disease; upper respiratory infection; rhinovirus; adenovirus; human metapneumovirus; influenza A; influenza B; respiratory syncytial virus (RSV); and intensive care unit (ICU) length of stay. Two-tailed statistical tests were utilized, with a significance level set at  $P < .05$ . Statistical analysis was completed using SAS 9.4 software (SAS Institute, Cary, North Carolina).

## RESULTS

Two hundred twenty-six patients were included in the prospective (BPA) group and 161 in the retrospective group. There were no significant differences in age, sex, or race among the groups (Table 1). The BPA group had a significantly higher mean Charlson comorbidity index score (4.8 vs 4.0,  $P < .001$ ) and a lower mean ICU length of stay (5.0 vs 6.9 days,  $P = .043$ ).

Viral detection rates on PCR varied between the groups (Table 1). Influenza A and B were more common in the BPA group (27.4% vs 11.8%,  $P < .001$  and 8.8% vs 1.9%,  $P = .004$ , respectively). RSV was also more common in the BPA group (26.1% vs 15.5%,  $P = .012$ ), whereas fewer BPA group patients had rhinovirus (5.3% vs 22.4%,  $P < .001$ ).

The primary endpoint of antibiotic-days of therapy was significantly reduced in the BPA group by a mean of 2.2 days (5.8

**Table 1. Patient Characteristics**

Characteristic	BPA (n = 226)	Retrospective (n = 161)	P Value
<b>Demographics</b>			
Age, y, mean ± SD	71.6 ± 15.0	68.3 ± 18.5	.053
Male sex	104 (46)	74 (46)	.991
<b>Race/ethnicity</b>			
White	191 (84.5)	135 (83.9)	.860
Black	24 (10.6)	20 (12.4)	.581
Hispanic	2 (0.9)	1 (0.6)	.770
Other	4 (1.8)	4 (2.5)	.626
<b>Hospital admission</b>			
LOS, d, mean ± SD	6.2 ± 3.2	6.1 ± 4.1	.663
ICU admission	44 (19.6)	35 (21.7)	.600
ICU LOS, d, mean ± SD	5.0 ± 4.1	6.9 ± 5.2	.043
Ventilator-days, mean ± SD	0.2 ± 1.2	0.6 ± 2.4	.076
Charlson comorbidity index, mean ± SD	4.8 ± 2.1	4.0 ± 2.5	<.001
<b>Viruses isolated</b>			
Parainfluenza virus	2 (0.9)	4 (2.5)	.209
Rhinovirus	12 (5.3)	36 (22.4)	<.001
Coronavirus	32 (14.2)	26 (16.1)	.588
Adenovirus	2 (0.9)	8 (5.0)	.012
Metapneumovirus	44 (19.5)	42 (26.1)	.122
Influenza A virus	62 (27.4)	19 (11.8)	<.001
Influenza B virus	20 (8.8)	3 (1.9)	.004
Respiratory syncytial virus	59 (26.1)	25 (15.5)	.012

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: BPA, best practice alert; ICU, intensive care unit; LOS, length of stay; SD, standard deviation.

vs 8.0 days,  $P < .001$ ). Several secondary endpoints were also improved in the BPA group including mean days of therapy after BPA firing (4.5 vs 6.3,  $P < .001$ ), more patients having antibiotics discontinued within 24 hours of initiation (37.8% vs 18.6%,  $P < .001$ ), and fewer patients discharged on antibiotics (20.0% vs 47.8%,  $P < .001$ ). There was no difference in rates of antibiotic reinitiation after discontinuation (7.6% vs 4.3%,  $P = .198$ ) or *C. difficile* infection (0.4% vs 1.9%,  $P = .174$ ). Results can be found in Table 2. After adjusting for possible confounding variables, we showed that BPA is associated with 1.48 fewer days of therapy ( $P = .0002$ ).

## DISCUSSION

Antibiotic resistance continues to be a major threat to our healthcare community. Despite the advent of more expansive rapid diagnostic tests and biomarkers, our efforts are still insufficient to outpace resistance development. This has been supported by national and global efforts to raise awareness to the significance of this issue. To our knowledge, this is the first study to implement an automated clinician antimicrobial stewardship intervention by leveraging EMR-driven data for likely viral LRTIs, defined by negative PCT and positive viral respiratory PCR results.

**Table 2. Study Results**

Endpoint	BPA (n = 226)	Retrospective (n = 161)	P Value
Days of therapy, mean ± SD	5.8 ± 3.9	8.0 ± 5.3	<.001
Antibiotics discontinued within 24 h	85 (37.8)	30 (18.6)	<.001
Discharged on antibiotics	45 (20.0)	77 (47.8)	<.001
Days of antibiotics on discharge, mean ± SD	0.9 ± 2.1	2.4 ± 3.3	<.001
Days of antibiotics after BPA, mean ± SD	4.5 ± 3.9	6.3 ± 5.0	<.001
Reinitiation of antibiotics after discontinuation	17 (7.6)	7 (4.3)	.198
<i>Clostridioides difficile</i> infection	1 (0.4)	3 (1.9)	.174

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: BPA, best practice alert; SD, standard deviation.

Our intervention was highly effective in reducing antibiotic prescribing, with the BPA decreasing antibiotic-days of therapy by 2.2 days. Even after adjusting for select variables of interest, the BPA was still associated with a significant reduction in days of therapy. There is some provider concern that early (inappropriate) cessation of antibiotics may pose a risk of failure, but there was no increased need for reinitiation of antibiotics in the BPA group after they were initially stopped. The alert led to a 19.2% higher rate of antibiotic discontinuation within 24 hours of the alert firing.

The primary aim of the intervention is to quickly identify patients who no longer need antibiotics for LRTIs. However, some providers still feel compelled to continue therapy. Without active oversight of the patient discharge process, antibiotics can often be prescribed without regard for appropriateness or duration. The BPA group had a 27.8% reduction in rate of discharge prescriptions and notably decreased postdischarge antibiotics duration by 1.5 days, showing an impact beyond just initial de-escalation of therapy. Of note, this decrease in postdischarge duration of therapy is not accounted for in the primary outcome of inpatient-days of therapy, possibly extending the benefit of the alert beyond the inpatient stay.

Previous studies have shown inpatient viral respiratory infection management to have vast potential for targeted intervention, as providers often continue antibiotic therapy even when there is a low likelihood of bacterial involvement. A study by Timbrook and colleagues found low rates of antibiotic discontinuation in patients with positive viral respiratory PCR, negative PCT, or both, which were suggestive of viral etiology. Because this study did not include a direct intervention, the authors concluded that clinician intervention was likely needed to affect antibiotic prescribing in this subset of patients [17]. Branche and colleagues implemented a 1:1 randomized feasibility study in similar patients using respiratory PCR and PCT testing. In contrast to the previous study, they employed an intervention to inform providers of likely viral infections, though no difference was found in antibiotic use. However, they did

detect a reduction in antibiotic discharge prescriptions by 25%, which is in line with our findings of nearly 28% [20]. They note that they may have encountered a spillover effect, in which their intervention with the study group indirectly influenced the practices of providers in the control group. Our study was able to avoid this as it was carried out in 2 distinct time periods with no overlap. Importantly, the Branche study emphasized the need for provider intervention to leverage diagnostic testing output [20]. A study by File and colleagues evaluated respiratory PCR results coupled with PCR and/or active antimicrobial stewardship intervention. Stewardship input, as compared to availability of PCR plus PCT alone, yielded the most significant reduction in antibiotic use, though this required contact with providers [21]. Our findings suggest that similar efforts can be achieved without direct stewardship input, which allows shifting of efforts to other high-risk patients.

Benefits of respiratory PCR testing include its rapid turnaround time and inclusion of the most common respiratory viral pathogens. However, concerns for bacterial coinfection limit provider willingness to quickly de-escalate antibiotics based solely on PCR results. This concern is not unfounded, as coinfection rates may be as high as 40% [16]. By coupling temporally related PCT values (within 48 hours) to viral PCR results, we were able to suggest to providers a subset of patients who were unlikely to have bacterial coinfection. The targeted stewardship alert enhanced the use of rapid diagnostic tests in determining infectious source.

The ability of the BPA to affect provider decision making on antibiotic prescribing played a large part in our study as there was no directed follow-up to BPA results or responses. Providers were willing to stop antibiotics in many cases, with fewer antibiotic-days of therapy and a 37.8% rate of antibiotic discontinuation within 24 hours of the alert firing. While providers may not be willing to immediately discontinue antibiotics in some cases, they may still do so earlier than if they had not been prompted with the initial EMR alert. A question of what factors caused providers to continue antibiotics is raised. In their follow-up analysis of their randomized trial, Branche and colleagues found that while several factors were mentioned by providers as reasons for deviation from their PCT de-escalation protocol including illness severity, fever, abnormal complete blood count, and others, only diagnosis of pneumonia was significantly associated with nonadherence [25]. An important distinction in this case is that viruses are able to cause radiographic changes [26–28].

The EMR has untapped potential to enhance antimicrobial stewardship functions by extracting meaningful data points. Leveraging effective alerts allows stewardship principles to be active all times of the day, meaning patients admitted or evaluated during off-hours or at sites with less antimicrobial stewardship presence still receive the same interventions. While we do not suggest that alerts should replace staffing as many factors

contribute to appropriate evaluation of therapy optimization, alerts have been shown to increase appropriate antimicrobial selection [22]. Our study highlights the value of minimally invasive stewardship by allowing the EMR to assist in identifying patient subsets and affecting antibiotic use.

Our study did have limitations. First, our evaluation of data from a single health system may not be representative of prescribing of other institutions. Second, the retrospective design did not allow for the most minimally biased comparison between the groups. While our study did attempt to minimize confounding variables, there are always potential unidentified effects. One such effect may have been differences in influenza seasons. The 2017–2018 influenza season was more severe than the 2015–2016 season, as evidenced by Centers for Disease Control and Prevention influenza data [29]. Our regression analysis still supported a significant reduction in days of therapy with the BPA. We began collecting the prospective data immediately after the alert was launched in December 2017, not allowing for an adaptation period to lapse, which may have skewed the true effect of the BPA. Another limitation was nonconsistent timing of the BPA regarding days of therapy. It is possible that earlier firing of BPA led toward earlier discontinuation of antibiotics. However, a temporal relationship cannot be established based on our data alone. A future study might examine how the timing relates to the outcome to further determine BPA effect on antibiotic prescribing. Other limitations to the study included lack of stratification by provider and lack of follow-up on influence of bacterial culture result with therapy duration. It is possible certain providers were inherently more open or resistant to the alert intent, which may lend itself to more targeted feedback in the future when providers decline a suggestion. Other factors beyond PCR and PCT results may have influenced treatment decisions. For example, imaging changes can affect prescriber habits, though imaging alone cannot differentiate bacterial vs viral illness. Another consideration is that our alert does not fire when only respiratory PCR or PCT is suggestive of viral infection, nor does the alert include standalone PCR tests such as influenza or influenza/RSV combination tests. Finally, an issue with the BPA is that it fires for all providers. If one inadvertently selects “acknowledge” or “does not meet criteria,” the alert stops firing. We did not track unintentional alert suppression but realize that it could have affected success rate of the alert.

There are several future directions for research using similar approach. First, we did not include any nonneonatal pediatric inpatients as we do not currently provide care for this population in our health system. Second, we did not characterize the cost benefit to implementing a targeted BPA intervention on care received. Finally, there may be a relationship between timing of the BPA and antibiotic exposure, an area that may prove to be related but was not fully answered in this study.

In conclusion, our study showed a significant reduction in antibiotic exposure for patients with likely viral respiratory illness. It also proves that well-constructed EMR provider alerts that integrate PCR, PCT, and antibiotic data can target patients in whom antibiotic therapy can be rapidly narrowed, without need for direct antimicrobial stewardship oversight. This minimally invasive stewardship practice can easily be replicated by other institutions and represents a step forward in the fight against antibiotic misuse.

## Notes

**Potential conflicts of interest.** S. B. was given travel reimbursement and an honorarium from Kurin for 1 day of travel to the Centers for Disease Control and Prevention for vendor day to express her personal views on the importance of blood culture contamination on antimicrobial stewardship and clinical impacts. All other authors report no potential conflicts. 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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