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Research Article

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Effectiveness of implementing a pharmacy coordinated procalcitonin level monitoring protocol to direct antimicrobial therapy duration

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Abstract

Background: This is the first study that incorporated pharmacy into procalcitonin (PCT) level monitoring. **Objective:** The primary objective was to explore if implementing a pharmacist coordinated PCT level monitoring protocol can assist in safely reducing antibiotic use duration. The secondary objective was to investigate the accuracy and acceptance rate of implementing a pharmacist coordinated PCT protocol at the studied hospital. **Methods:** This was a case-control study at a single facility. Patient cases were selected based on the inclusion and exclusion criteria. The analysis compared the first 50 pneumonia and/or sepsis cases from the previous year without PCT guidance (control) to the cases with the PCT protocol (case). The primary outcome was duration of antibiotic therapy. Secondary outcomes evaluated length of hospital stay, rates of rehospitalization due to same diagnosis within one month, accuracy of successful PCT protocol implementation, and rate of acceptance of pharmacist's recommendations by hospitalists. Analysis comparing pharmacy coordinated PCT protocol to past data with no PCT protocol guidance was conducted. **Results:** There were 50 patients in the control group and 38 patients in the case group. The duration of antibiotic therapy was shorter for the PCT-guided group (4.45 vs 5.62 days, p=0.052). The findings for secondary results favored implementing pharmacy coordinated PCT monitoring protocol. **Conclusions:** Our study suggests that the pharmacy coordinated PCT monitoring protocol can be safely implemented to guide antibiotic therapy for sepsis and pneumonia patients.

Keywords antibiotics, bacterial infections, clinical pharmacy, pneumonia, procalcitonin, sepsis

Background

Procalcitonin (PCT) is the precursor hormone of calcitonin. PCT levels increase in response to severe systemic inflammation in part due to bacterium infection. PCT is generated through the activation of monocytic cells, which often occurs during sepsis and other conditions such as tissue trauma or pancreatitis. After the onset of infection, the PCT level rises within 6-12 hours and peaks between 24 to 48 hours. After reaching the peak level, it decreases by 50% within 1 to 1.5 days. PCT is eliminated through the kidneys; therefore any damage to the kidney can prolong the length of time PCT remains in the patient's body [1-2]. PCT as a biomarker has a sensitivity of 85% and specificity of 91% when differentiating systemic inflammatory response syndrome (SIRS) from sepsis in patients [3]. Furthermore, PCT has a sensitivity range from 67% to 80% and a specificity of 70% to 91% in the setting of critically ill patients when compared with other biomarkers such as IL-2, IL-8, CRP, and TNF-alpha [1,3]. There are some conditions and medications that can potentially cause false elevation of PCT levels, examples are provided under Supplements section (Figure 1). In a healthy individual the PCT level is <0.05 ng/mL, and the level can

increase to ≥ 0.5 ng/mL during a severe bacterial infection. In addition, high levels of PCT are indicative of increased mortality risk and poor prognosis [1-2]. In 2005, the U.S. Food and Drug Administration (FDA) approved PCT to be used in conjunction with other lab and clinical findings to assist in risk assessment for progression to severe infection (sepsis) in critically ill patients [4].

Literature support of PCT role in antibiotic use

Current literature supports the use of PCT levels to determine the patient's response to antimicrobial therapy [1, 5-7]. PCT can be used to determine when to initiate or discontinue antibiotics. Even though there are publications of PCT used as a biomarker in a broad array of diseases and infections, more studies have supported using PCT for early discontinuation of antibiotics in sepsis and/or pneumonia [5]. The multicenter, randomized PRORATA trial resulted in significantly more days without antibiotics in the PCT group when compared with the control group ($p<0.0001$) and was non-inferior in mortality. In the study, patients in the PCT group had their antibiotics discontinued based on pre-defined PCT levels, whereas the control group received antibiotics based on the hospital guidelines and the discontinuation of antibiotics were at the physician's discretion [8]. Bishop et al suggested that introducing PCT levels to physicians using an algorithm for guidance can significantly ($p= 0.02$) reduce duration of initial antibacterial therapy in patients with sepsis and/or pneumonia. Moreover, the reduction in duration of therapy was not associated with adverse treatment outcomes [5].A systematic review and meta-analysis by Soni et al on procalcitonin-guided antibiotic therapy suggested antibiotic usage was safely reduced when utilizing PCT levels to guide discontinuation in adult patients with respiratory tract infections in the ICU setting [6]. Their review revealed when utilizing PCT level with clinical criteria, compared to using clinical criteria alone, the duration of antibiotic use was reduced by 2.35 days (95% CI: -4.38 to -0.33), antibiotic prescription rate decreased by 22% (95% CI:-41% to -4%), and decreased total antibiotic exposure did not affect morbidity or mortality [7]. Reasons for limiting antibiotic exposure include: reduction in medication adverse events, decreased toxicity risk, minimized microbial resistance, and lower hospital cost.

Pharmacy as a good candidate to provide close PCT monitoring

Clinicians are beginning to order PCT levels and use the levels to guide antimicrobial therapy. In addition, we had noticed that physicians were more likely to order medications and lab monitoring and were less inclined to discontinue medications and lab orders. Another possible candidate for PCT monitoring would be lab technicians, but due to limited access to patients' health records, lab technicians cannot determine when to advise physicians to discontinue PCT monitoring. Pharmacists have access to patients' health records and can assist physicians in screening for medications and labs that may be considered for discontinuation. However, few hospitals have incorporated pharmacists into the process of monitoring PCT levels and making recommendations for changes in antibacterial regimen based on the trend. Successful utilization of PCT levels to direct antimicrobial treatment duration requires frequent monitoring and knowledge of antibiotics and other important clinical factors [7, 9-10]. In addition, patient's PCT levels could be falsely elevated with concurrent use of immunomodulator medications. Therefore, identifying patients' medications that could potentially impede the PCT level's usefulness is crucial. Pharmacists are good candidates for PCT monitoring due to their understanding of medications and having existing systems in place to closely monitor lab values. The specific aim of this study was to promote the utilization of a PCT level protocol and incorporate pharmacists into the monitoring of PCT levels to help hospitalists in the decision making process regarding the appropriate time to discontinue antibiotics. By testing a pharmacy coordinated PCT level monitoring protocol and providing education to the providers, the results of this study can be used to decrease antibiotic exposure. Moreover, discontinuing antibiotics at the appropriate time is beneficial to patients, the hospital, and supports the antibiotic stewardship process.

Materials and Methods

Study aim

The objective of this trial was to determine if the pharmacy coordinated PCT protocol was beneficial and implementable at the studied hospital. The null hypothesis for this trial was pharmacy coordinated PCT protocol provided no difference in antibiotic treatment duration for pneumonia and sepsis patients.

Study design

This was an observational case-control study at a single facility. The study provided hospitalists and pharmacists with a Pharmacy and Therapeutics (P&T) committee approved PCT level protocol and algorithm (Figure 1) that guided their decisions on continuing or discontinuing antimicrobial treatment for their patients. The P&T committee consists of physicians, administrative representatives, pharmacists, and nurses. Diagnosis of sepsis and/or pneumonia was in accordance with national guidelines. The studied hospital had existing pneumonia and sepsis antibiotic treatment order sets in place for hospitalists to use in ordering. All physician orders were sent to pharmacists for verification. After the antibiotic was verified, pharmacists screened the patient for study eligibility, ordered PCT levels, and documented monitoring as directed by the protocol. The results collected from eligible participants were compared historically with data from the previous year in which no formalized PCT protocol was utilized. Data analysis included looking at case versus control in duration of antibiotic therapy (primary outcome), length of hospital stay, rates of rehospitalization due to same diagnosis within one month, accuracy of successful PCT protocol implementation, and rates of acceptance of the pharmacist's recommendations by hospitalists (secondary outcomes). For results on antibiotic therapy duration, length of hospital stay, and rates of rehospitalization due to same diagnosis within one month we set $p<0.05$ to determine if the results showed a statistically significant difference between the two groups. For accuracy of PCT implementation the goal was set at 80% with the consideration of first time implementing PCT protocol at the studied hospital. Patient's baseline statistics (age, sex, diagnosis, and comorbidity) were documented to screen for possible correlations.

Inclusion Criteria: Non-pregnant patients 18 years and older with diagnosis of sepsis and/or pneumonia were included in this study. Patients can either have sepsis, sepsis with pneumonia, or pneumonia. There was more literature to support the utilization of PCT in this population and therefore added reliability of using PCT as a biomarker [5].

Exclusion Criteria: The study excluded patients younger than 18 years old and pregnant patients. In addition, patients receiving medications such as: monoclonal antibodies- Muromonab-CD3 (OKT3 antibodies), polyclonal antibodies, tumor necrosis factors (TNF), immunosuppressant or interleukin therapies, or patients with conditions such as surgery, severe trauma, burn, pancreatitis, auto immune disorders, severe renal or liver dysfunction, end stage tumor disease, acute rhabdomyolysis, transplantation, and immunosuppression within three months prior to the study were excluded. Previous studies have suggested that these patient populations are highly likely to produce false elevations of PCT and hence could potentially skew interpretation of the recommendations made by pharmacists [9].

Study institution

The studied institution is a not-for profit community hospital with 204 beds. The hospital pharmacy offers 24-hour pharmacy coverage and daily patient rounding with medical teams. Additionally, it provides clinical services that include but are not limited to antibiotic, insulin, and warfarin dosing.

Protocol decision

The PCT protocol used in the study was constructed based on successful protocols from other institutions and was approved by the P&T committee of our studied hospital (Figure 1). The ranges of PCT levels were carefully reviewed with consideration for patient safety. Other protocols set a higher level of PCT (<0.25 ng/mL) for stopping antibiotics in patients with sepsis and a lower level of PCT (<0.1 ng/mL) for patients with pneumonia. Taking into consideration that some patients may be diagnosed with both pneumonia and sepsis, and the negative consequences of discontinuing antibiotics too soon, the committee decided to use lower levels of PCT (<0.1 ng/mL) as cut-off in lieu of higher levels (<0.25 ng/mL).

Many studies on PCT had limited patients in the critical care setting. For our study, we incorporated patients from both critical care and general medical units because we wanted to screen for all the pneumonia and/or sepsis patients that were managed by our institute's hospitalists in the two month study period.

Data Collection

The pharmacy coordinated PCT protocol was implemented at the studied institution on 1/5/2015. Data collection started on the same day as the PCT protocol implementation and continued for two months or for a total of 50

patients, whichever came first. Prior to the protocol implementation, there were mandatory educational meetings held for both the hospitalists and the pharmacists. Collected data included: patient's baseline characteristics, PCT level, duration of antibiotic therapy (primary outcome), length of hospital stay, rates of rehospitalization due to same diagnosis within one month, accuracy of successful PCT protocol implementation, and rates of acceptance of the pharmacist's recommendations by hospitalists (secondary outcomes).

Procalcitonin assays

VIDAS B·R·A·H·M·S PCT test from BioMérieux was used for determining PCT levels in patient's plasma. The PCT assay combined "a one-step immunoassay sandwich method with a final fluorescent detection (ELFA)" [11]. All procedures followed the BioMérieux PCT instructions for use. The PCT machine needed to be calibrated each time a new lot of reagents was used or every 28 days [11].

Sample size and statistical analysis

A Welch two sample t-test was used for data analysis. Analysis was completed with the R program (R version 3.2.3) [12]. Based on results reported from Bishop et al [4] with a two sided test, a sample size of 100 patients (50 from each control and PCT group) was needed to observe a three day difference in antibiotic therapy duration with an expected standard deviation of 5 days which provided a confidence interval of 95%, and 85% power [13].

Results

For the control group, we selected the first 50 pneumonia/sepsis patient cases from 2014 when no PCT level protocol was implemented. For the case group, there was a total of 135 pneumonia/sepsis patient cases accumulated within the two months of the 2015 study period. Of the 135 cases, 46 of the cases received PCT monitoring; whereas the remainder (89) did not have a PCT ordered. Of the 46 PCT monitored cases, 38 were eligible for the study. Of note, there were 22 patient cases in the 89 that did not receive PCT monitoring that could have participated in the study if a PCT level had been ordered. (Figure 2)

When we compared the patient's baseline characteristics between the control group and the case group, the average age, gender, and number of comorbidities (such as: anemia, asthma, chronic obstructive pulmonary disease (COPD), diabetes, smoker) on average of the patients were similar. In comparison, the control group had a higher percentage of patients that were diagnosed with sepsis, whereas the case group had higher percentage of patients who had the diagnosis of pneumonia. Both groups yielded high percentage of COPD diagnosis when compared to other comorbidities. (Figure 2)

For the primary result which looks at duration of antibiotic therapy (Chart 1), the PCT-guided group received a shorter duration of antibiotic therapy when compared to the non-PCT guided group (4.45 vs 5.62 days, p=0.052). When looking at secondary results, the length of the hospital stay was shorter for the PCT guided group (3.95 vs 5.26 days, p=0.069), and the readmission in one month due to the same diagnosis was similar between the two groups (8% vs 12%, p=0.524) (Table 1-A). For secondary results, we also wanted to evaluate if we could successfully implement the PCT protocol in the studied hospital. PCT had been ordered by hospitalists prior to this study for use as a reference, yet this was the first year we implemented the PCT algorithm and protocol in the studied hospital and some pharmacists were not familiar with PCT prior to this study. So with all these considerations in mind, we set the accuracy goal to be 80%. By the end of the second month study period, the pharmacy had an accuracy of 77.8%. There was a learning curve, at the end of the first month. The pharmacy had an accuracy of 76% and by the end of the second month, the pharmacy's accuracy rate increased slightly to 81%, which was at goal (Table 1-B). The result also showed that pharmacist were successful in excluding non-eligible patients (89.3%) but were unsuccessful in including eligible patients (63.3%) (Table 1-B). Additional secondary results also included the acceptance rate of recommendation, the hospitalist accepted 82% (19 out of 23) of the recommendations made and rejected 9% (2 out of 23) of the recommendations. There were 2 out of the total 23 recommendations (9%) that were pending at the time of discharge. Further extrapolation of the data showed that of the total accepted recommendations, 47% of the recommendations were to deescalate antibiotics, 16% to discontinue, 5% to escalate, and 32% to continue antibiotics based on compared PCT level trends (Chart 2). Of all

38 PCT-guided cases, 23 (60.5%) had recommendations made and documented, 4 cases (10.5%) had no recommendation documented, and 11 cases (29%) had no 2nd PCT levels due to early discharge.

Discussion

The study findings suggested that pharmacy coordinated PCT protocol was well accepted by institution's hospitalists and can be successfully implemented. There are many benefits to allocate PCT monitoring to pharmacists; physicians can allocate saved time in patient care, medications that cause false elevation of PCT could be screened early on during medication reconciliation phase, PCT non-eligible patients can be ruled out early on…and much more. Hospital pharmacists have been doing medication reconciliation, counseling on new medications, and sometime helping with antibiotic dosing for inpatient patients, therefore it is much more time efficient and efficacious to have pharmacists monitoring patient's PCT trends. The studied institution's pharmacy has been providing warfarin, insulin, vancomycin, and aminoglycoside dosing per hospitalists' consultation, hence the process for pharmacists to adapt the addition of PCT monitoring to daily workload was more resilient. This can be explained by the learning curve effect we observed between the first month and second month, in which accuracy increased from 77.8% to 81%. In addition, hospitalists were very receptive of the recommendations made by pharmacists with an acceptance rate of 82% (19 out of 23) with two recommendations pending prior to discharge and two rejected (9%) due to additional clinical findings that prompt reconsideration on antibiotic therapy.

The findings from our study should be interpreted in the context of several limitations. First of all, our study was a retrospective data analysis; therefore, any information that was not documented could not be analyzed. Secondly, due to the small sample size limited by time constraint of 2 months, this study only obtained nominal statistical significance ($p=0.052$) so it was difficult to extrapolate the true difference between comparison groups (power was reduced to 74%). We suspected that given enough sample size of 50 patients the result can show statistical significance ($p<0.05$). Thirdly, there were some cases that PCT levels were not analyzed due to early discharge with pending 2nd PCT levels. Early discharge can cause concerns with PCT monitoring because recommendations were based on comparing the trend of two levels that were drawn 48 hours apart. Lastly, even though we have considered excluding factors that have been shown by other literature to cause false elevation of PCT, there could be other unidentified medication or medical conditions that could potentially affect PCT as well and were not excluded from this study. With the above considerations, we will be updating our P&T approved PCT protocol and algorithm annually based on new findings from literature.

From the data analysis we also identified that during the verifying phase pharmacists have the most room for improvement. Pharmacists were successful in excluding non-eligible patients (89.3%) but were not successful in including eligible patients (63.3%). Verifying pharmacists at the studied institution verifies medication orders from all floors of the hospital, in addition they also verifies orders for tele-pharmacies around the area. To improve successfulness of including PCT eligible patients, we will assign the clinical pharmacists responsible for each units to screen their new pneumonia and/or sepsis patients that day for missed PCT eligible patients. The new implementation will add work load on clinical pharmacists, yet we suspect the burden is minimal because the PCT screening process could be incorporated into the medication reconciliation procedure which are mandated for new inpatients.

Future Aim

For future study directions, we recommend conducting further evaluation and analysis on antibiotic coverage, number of uses, and cost difference between the PCT guided group and the non-PCT guided group. Also, future studies can do research on finding other identified confounding factor such as disease state, comorbidity, or medications that could potentially affect PCT levels. Additional information collecting pharmacist's time spend on PCT monitoring, documenting, and making suggestions can be recorded for future cost and benefit analysis. In the end, it will be beneficial to do a parallel study comparing physician lead PCT guided groups to pharmacy lead PCT guided groups with non PCT guided groups as control and compare the pros and cons of each group. However, such study will require a larger scale of institutions with bigger patient sample cases.

Conclusions

Procalcitonin should be seen as another piece of evidence for clinical decisions of early discontinuation of antibiotics, and that other positive clinical findings should be included into the decision making as well. Clinical judgement is always the key when deciding the duration of antibiotics. Health care providers are encouraged to look at other labs, cultures, and patient's disease progressions as well. PCT has been proven by many studies to be an effective biomarker for early discontinuation of antibiotics in sepsis and/ or pneumonia patients. The successfully utilization of PCT levels to direct antimicrobial treatment duration requires frequent monitoring and knowledge of medications [7, 9-10]. Pharmacists are good candidates for PCT monitoring due to their understanding about medications and having existing systems in place to closely monitor lab values. By incorporating pharmacy into PCT monitoring, physicians can allocate more time in patient care, and patients who are not eligible for PCT monitoring due to drug induced false elevation of PCT can be detected early on. Furthermore, our data supports the implementation of pharmacy coordinated PCT monitoring at the studied hospital.

Regulatory

This study was submitted to Allen College Institutional Review Board (AC IRB) and was approved on 12/16/2014 to 12/16/2015 upon full committee review. The study's ACIRB ID was 14-0157.

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Authors' Note

The study results were presented at the Midwest Pharmacy Residents Conference (MPRC); May 8, 2015; Omaha, NE

Supplements

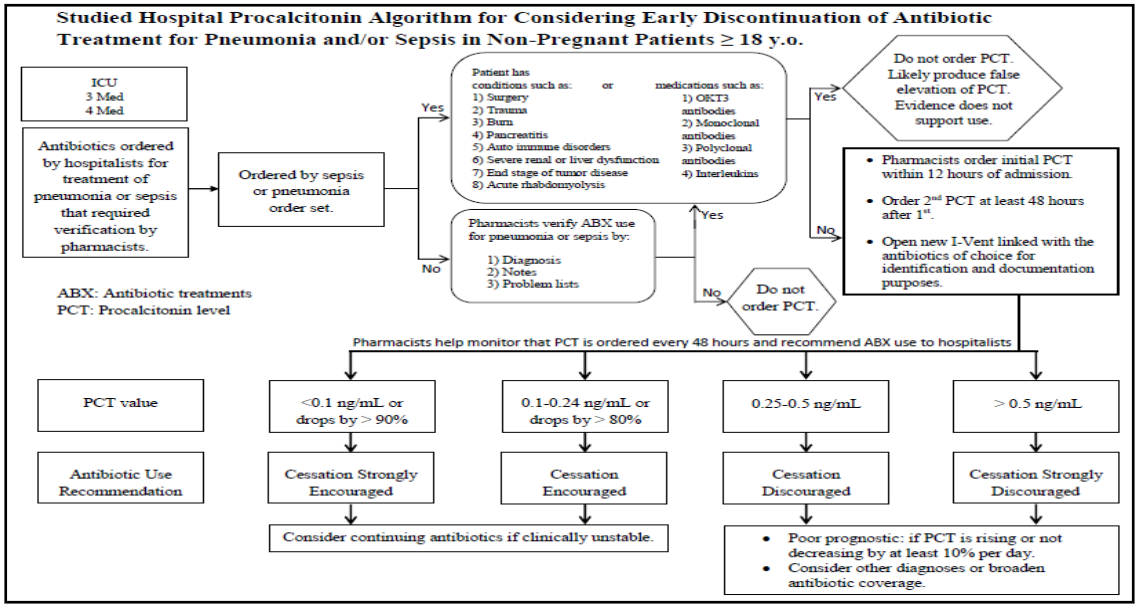
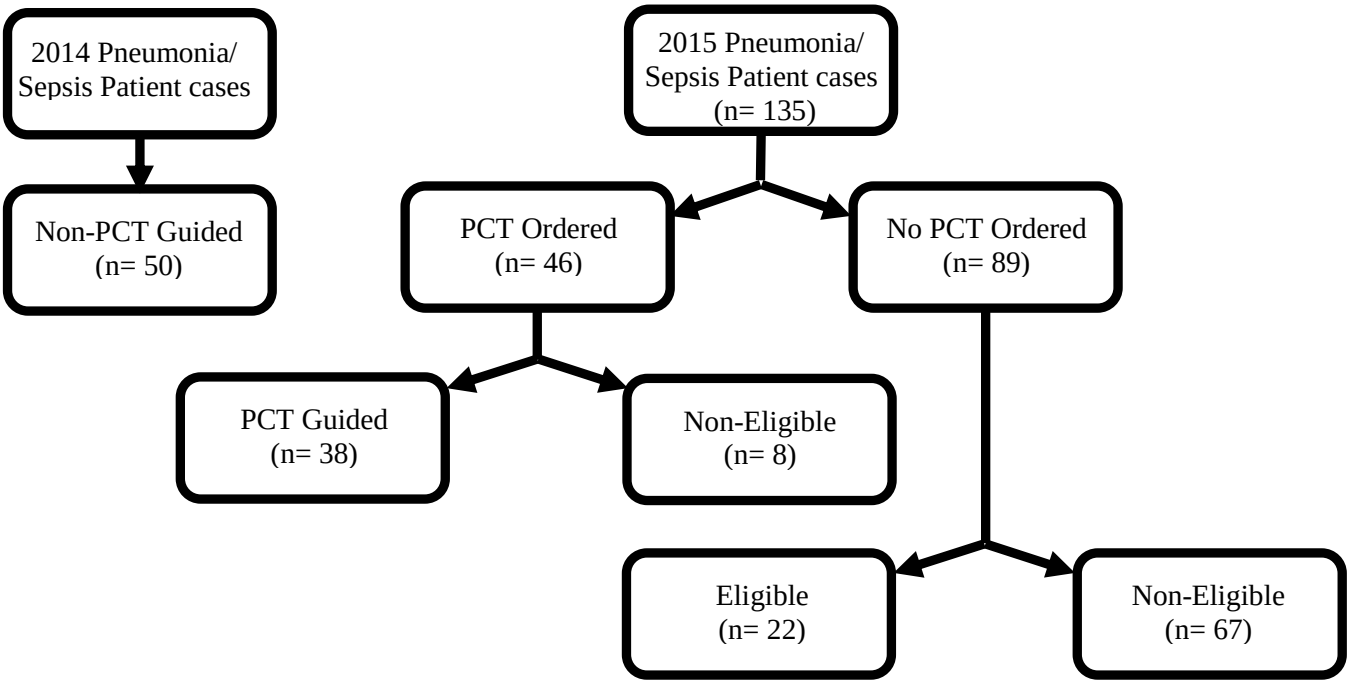


Figure 1: PCT protocol diagram

The institution's hospitalists ordered antibiotic to treat patient's pneumonia and/or sepsis infection(s). The order was sent to pharmacist for verification. Pharmacist screened for exclusion criteria and only order PCT if patient was eligible for study. If patient was eligible, pharmacist ordered initial PCT within 12 hours of admission and a 2nd PCT at least 48 hours after 1st level. For identification purposes, pharmacists opened I-Vents with associated antibiotics in

Epic. After the 2nd PCT level was gathered, pharmacists made recommendations to hospitalists based on the algorithms suggestion and ordered another 48 hour PCT level as guided by the protocol.



Baseline Characteristics		**PCT Guided (n=38)**	**Non-PCT Guided (n=50)**
Age, average years ± SD (95% CI)		73 ± 16 [68,78]	71 ± 14 [67,75]
Male gender, n (%)		17 (45%)	25 (50%)
Diagnosis	**Pneumonia, n (%)**	19 (50%)	16 (32%)
	Sepsis, n (%)	7 (18%)	23 (46%)
	Both, n (%)	12 (32%)	11 (22%)
Number of comorbidities on average (Anemia, asthma, COPD, T2DM, smoker)		1	1
Comorbidities	**Anemia, n (%)**	7 (18%)	1 (2%)
	Asthma, n (%)	3 (8%)	3 (6%)
	COPD, n (%)	19 (50%)	17 (34%)
	T2DM, n (%)	7 (18%)	15 (30%)
	Smoker, n (%)	6 (16%)	0 (0%)

Figure 2. PCT-Guided and Non-PCT-Guided group case distribution and baseline characteristics comparison.

The flow chart accounted for the distribution of the pneumonia/sepsis patient cases. The table listed baseline characteristics comparison between the control and case groups.

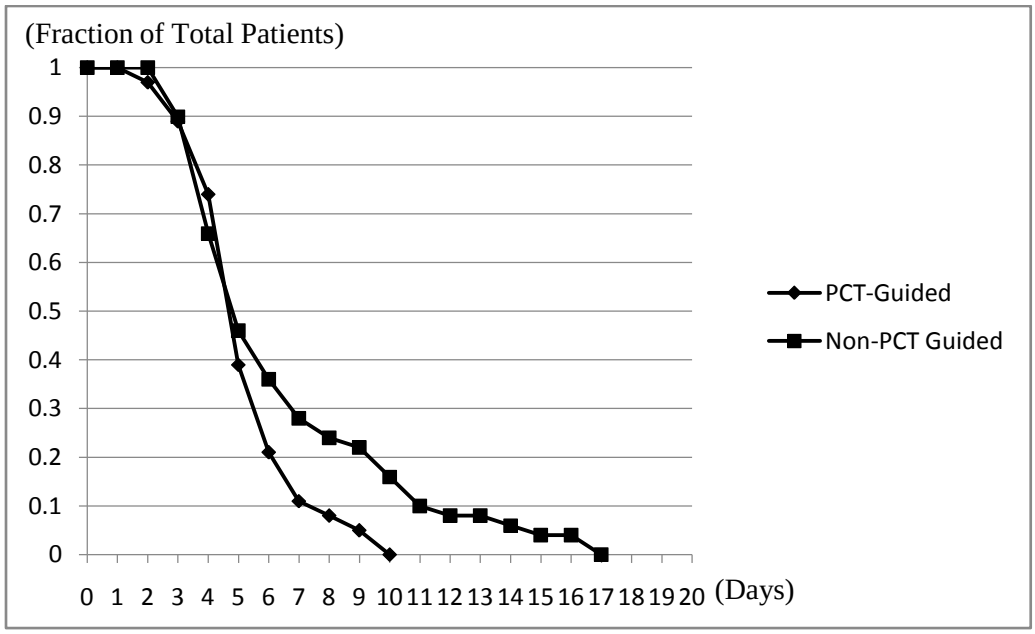


Chart 1: Plot diagram of duration of antibiotic therapy for PCT guided and non-PCT guided groups.

The PCT guided group had a shorter duration of therapy days on average (p=0.052). In addition, at the 0.5 mark on the y-axis which means half of the patient in each group, non-PCT guided group showed longer therapy days. Non-PCT guided group also had a longer tail curve which indicated more percentage of patients received more days on antibiotic.

Table 1: <A> Table of primary and secondary results for PCT and Non-PCT guided groups. <B> Analysis table for accuracy rate of implementing pharmacy coordinated PCT monitoring protocol at the studied institution.

<A>

Outcomes	**PCT Guided (n=38)**	**Non-PCT Guided (n=50)**	**P-Value 95%CI**
Duration of antibiotic therapy (Days) 95%CI	4.45 [3.86,5.03]	5.62 [4.58,6.66]	0.052 [-0.011,2.356]
Length of hospital stay (Days) 95%CI	3.95 [3.12,4.77]	5.26 [4.09,6.43]	0.069 [-0.104,2.730]
Readmission in one month (n, %)	3 Patients 8%	6 Patients 12%	0.524 [-0.087,0.169]

<B>

		Condition		
	Total patient (n=135)	PCT ordered	Not ordered	
Test outcome	Eligible	38	22	Successful inclusion 38/(38+22) → 63.3%

	Non-Eligible		8	67	Successful exclusion 67/(8+67) → 89.3%
	1st Month	**2nd Month**	Ability to order Correctly (Sensitivity) 38/(38+8) → 82.6%	Ability to exclude Correctly (Specificity) 67/(22+67) → 75.3%	Accuracy (38+67)/135→ 77.8%
Accuracy	76%	81%			

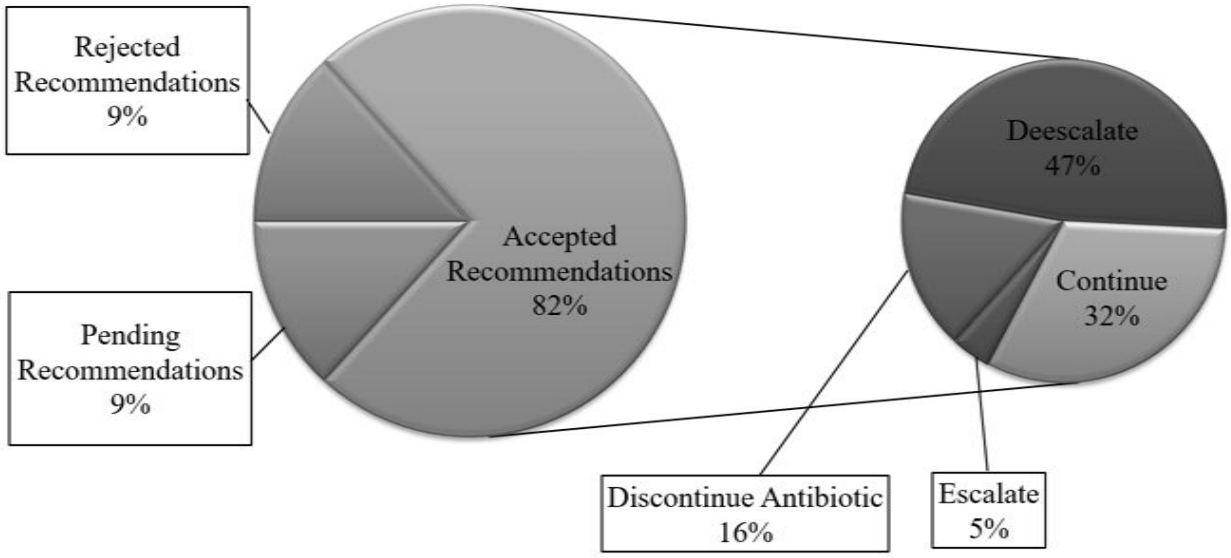


Chart 2: Recommendation acceptance rates.

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