JPPT | Multicenter Retrospective Study

Impact of a Procalcitonin Guided Antibiotic Management Strategy in Pediatric Sickle Cell Patients With Fever

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OBJECTIVE This study assessed the relationship between antibiotic durations and the use of procalcitonin (PCT) in febrile pediatric patients with sickle cell disease (SCD), including those diagnosed with acute chest syndrome (ACS) and/or vaso-occlusive crisis (VOC).

METHODS This multicenter, retrospective cohort study compared antibiotic durations in febrile pediatric SCD patients between 2 cohorts, 1 utilizing PCT (PCT cohort) and 1 not utilizing PCT (no-PCT cohort). Secondary endpoints compared the impact of PCT on antibiotic durations in those also diagnosed with ACS and/or VOC.

RESULTS A total of 258 patient encounters were included. The overall mean antibiotic duration in the PCT cohort was 4.2 days (SD 2.6) vs 4.7 days (SD 3.6) (p = 0.991). For those diagnosed with ACS (n = 17), the mean antibiotic duration was 6 days (SD 2.2) in the PCT cohort vs 9.7 days (SD 3.5) (p = 0.037; n = 7). Those diagnosed with both VOC and ACS (n = 40) averaged 5.6 days (SD 1.9) in the PCT cohort vs 9.3 days (SD 3.2) (p = 0.002; n = 9). Regression analyses revealed an increased odds of longer antibiotic duration in the no-PCT cohort for those with ACS (OR 1.51, 95% CI 1.07–2.13, p = 0.019), and for those with both VOC and ACS (OR 1.72, 95% CI 1.22–2.42, p = 0.002).

CONCLUSIONS There was not a significant difference in overall antibiotic durations between cohorts. However, in the PCT cohort there was a significant reduction of antibiotic durations seen in patients diagnosed with ACS or VOC and ACS, averaging 3.7 fewer days of antibiotics.

ABBREVIATIONS ACS, acute chest syndrome; AKI, acute kidney injury; ALT, alanine aminotransferase; CRP, C-reactive protein; LCL, lower control limit; PCT, procalcitonin; SCD, sickle cell disease; UCL, upper control limit; VOC, vaso-occlusive crisis; WBC, white blood cell

KEYWORDS acute chest syndrome; antibiotics; infection; pediatrics; procalcitonin; sickle cell disease; vaso-occlusive crisis

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Introduction

Patients with sickle cell disease (SCD) are at increased risk of infection due to functional asplenia and consequently, bacterial infections remain the leading cause of death in children with SCD worldwide.[1] Therefore, the presentation with fever is considered a potential medical emergency in SCD patients which frequently leads to the initiation of empiric antibiotics. However, fever often occurs in vaso-occlusive crisis (VOC) and acute chest syndrome (ACS) with non-bacterial etiologies such as viruses, fat emboli from bone marrow infarction, or vaso-occlusion in the vasculature of the lungs.[2] The potential for fevers to occur in this population from non-infectious etiologies poses a diagnostic challenge, which may lead to the use of unwarranted antibiotics and increased antimicrobial resistance. Therefore, there is a need for guidance on when to continue or discontinue empiric antibiotics within this population. While C-reactive protein (CRP) and the white blood cell (WBC) count are non-specific inflammatory markers, procalcitonin (PCT) is a more specific infectious biomarker validated in the general population.[3] Also, WBC counts and CRP levels can be affected by acute inflammation which can occur due to a VOC; whereas PCT concentrations appear to not be affected.[4] There is limited data with utilizing PCT in pediatric patients with SCD with fever in general. Therefore, this study intends to assess the relationship between antibiotic durations and the use of PCT in febrile pediatric patients with SCD, including those diagnosed with secondary complications such as ACS and/or VOC.

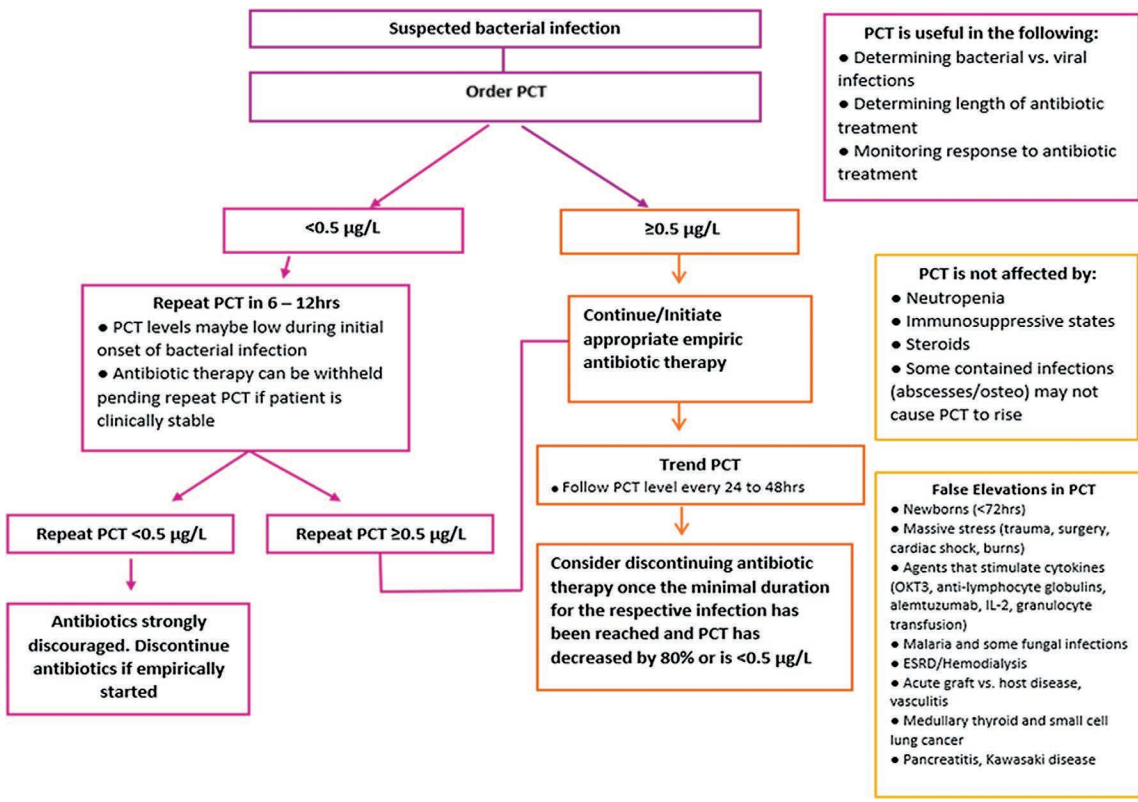
Materials and Methods

This was a multicenter, retrospective, observational cohort study conducted at Prisma Health Children's

Hospital–Midlands (Midlands) and Prisma Health Children's Hospital–Upstate (Upstate) from March 1, 2021–October 31, 2022. The study population included all pediatric sickle cell patients with a fever (≥ 100.4°F or 38°C who required hospitalization and were initiated on empiric antibiotics. Patients requiring prolonged durations of antibiotic therapy are typically diagnosed with complicated infections in which blood PCT concentrations may have no clear role or are not supported by current guidelines (i.e., osteomyelitis, endocarditis, mycobacterial infections, or infections requiring multiple surgical interventions for source control). Therefore, patients receiving >15 days of antibiotic therapy were excluded. Cohorts were divided based on patients with PCT concentrations (PCT cohort) and those without (no-PCT cohort). Our institution developed a PCT protocol which utilized PCT concentrations of ≥ 0.5 µ/L to suggest that a bacterial infection is probable in which antibiotics should be continued. While 2 PCT concentrations of <0.5 µ/L likely suggested a non-bacterial etiology in which antibiotics could be discontinued (see Figure).

The primary endpoint compared antibiotic durations between both cohorts. Secondary endpoints included proportional differences between cohorts. Specifically, antibiotic durations for patients who were also diagnosed with VOC, ACS, or VOC and ACS. Other comparisons between cohorts included confirmed bacterial infections, re-initiation of antibiotics for a suspected infection within 30 days of discontinuation, antibiotic associated complications (i.e., rash, neutropenia, thrombocytopenia, *C difficile* infection, acute kidney injury [AKI], or hepatotoxicity), hospital length of stay; protocol adherence, and 30-day mortality. A diagnosis of VOC or ACS was determined by clinician interpretation and empiric antibiotic selections were determined by the primary clinician as well. Confirmed bacterial infection was defined as any positive culture results (including blood, sputum, wound, urine, and cerebrospinal fluid cultures). AKI was defined as an increase in serum creatinine > 0.3 mg/dL or > 1.5-fold from baseline, or urine output < 0.5 mL/kg/hr for more than 6 hours.[5] Hepatotoxicity was defined as > 2-fold increase in ALT. Protocol adherence was defined as 100% compliance with the institution specific protocol (see Figure).

Figure. Procalcitonin (PCT) protocol.



Blood PCT concentrations were obtained on the first day of admission if being admitted for fevers and concerns for a bacterial infection. If already admitted, blood PCT concentrations were obtained on the first day of fevers. Repeat PCT were recommended to be obtained every 24 to 48 hr per protocol.

Table 1. Patient, Clinical, and Outcome Characteristics by Patient Cohort, PCT vs no-PCT

Characteristic	PCT Cohort (n = 190)	No-PCT Cohort (n = 68)	Total (N = 258)	p value
Age (yr), mean ± SD	10.3 ± 6.4	10.2 ± 6.2	10.2 ± 6.4	0.910
Weight (kg), mean ± SD	38.2 ± 24.2	39.9 ± 28.6	38.6 ± 25.4	0.985
Sex, n (%)				
Female	82 (43.2)	32 (47.1)	114 (44.2)	0.578
Male	108 (56.8)	36 (52.9)	144 (55.8)	
SCD genotype, n (%)				
HgbSC	30 (15.8)	6 (8.8)	36 (14.0)	0.314
HgbSS	129 (67.9)	48 (70.6)	177 (68.6)	
Other	31 (16.3)	14 (20.6)	45 (17.4)	
Immunizations current (yes), n (%)	178 (93.7)	66 (97.1)	244 (94.6)	0.367
100% adherent to PCT protocol,* n (%)	67 (35.3)	n/a	n/a	n/a
Prisma Health Children's Hospital, n (%)				
Midlands	170 (89.5)	18 (26.5)	188 (72.8)	<0.001
Upstate	20 (10.5)	50 (73.5)	70 (27.2)	
Admitted to ICU or Floor, n (%)				
Floor	172 (90.5)	64 (94.1)	236 (91.4)	0.363
ICU	18 (9.5)	4 (5.9)	22 (8.6)	
Patient on hydroxyurea (yes), n (%)	98 (51.6)	46 (67.7)	144 (55.8)	0.022
Secondary SCD complication, n (%)				
VOC	68 (35.8)	33 (48.5)	101 (39.2)	0.222
ACS	17 (9.0)	7 (10.3)	24 (9.3)	
VOC & ACS	40 (21.1)	9 (13.2)	49 (18.9)	
Neither	65 (34.2)	19 (27.9)	84 (32.6)	
Viral panel results (yes), n (%)				
RSV +	4 (2.1)	0 (0)	4 (1.6)	0.576
Covid +	17 (9.0)	7 (10.3)	24 (9.3)	0.743
Influenza +	4 (2.1)	1 (1.5)	5 (2.0)	1.000
Rhino/enterovirus +	11 (5.8)	13 (19.1)	24 (9.3)	0.001
Adenovirus +	4 (2.1)	0 (0)	4 (1.6)	0.576
Viral panel negative	140 (73.7)	40 (58.8)	180 (69.8)	0.022
Other	15 (7.9)	7 (10.3)	22 (8.5)	0.543
Chest X-ray interpretation, n (%)				
Chest involvement	70 (36.8)	21 (30.9)	91 (35.3)	0.670
No chest X-ray obtained	32 (16.8)	12 (17.7)	44 (17.0)	
No chest involvement	88 (46.3)	35 (51.5)	123 (47.7)	
Antibiotic used, n (%)				
Ceftriaxone	169 (89.0)	60 (88.2)	229 (88.8)	0.873
Ampicillin/sulbactam	9 (4.7)	2 (2.9)	11 (4.3)	0.733
Amoxicillin/clavulanate	19 (10.0)	3 (4.4)	22 (8.6)	0.157
Azithromycin	67 (35.3)	20 (29.4)	87 (33.7)	0.381
Levofloxacin	13 (6.8)	2 (2.9)	15 (5.8)	0.367
Other	50 (26.3)	21 (30.9)	71 (27.5)	0.469
Appropriate ABX dosing per institutional protocol (yes), n (%)	166 (87.4)	49 (72.1)	215 (83.3)	0.004
ABX for bacterial infection reinitiated w/in 30 days (yes), n (%)	18 (9.5)	6 (8.8)	24 (9.3)	0.874

(*Table cont. on page 467*)

Table 1. Patient, Clinical, and Outcome Characteristics by Patient Cohort, PCT vs no-PCT *(cont.)*

Characteristic	PCT Cohort (n = 190)	No-PCT Cohort (n = 68)	Total (N = 258)	p value
Antibiotic Duration by infection type, mean ± SD				
VOC	3.4 ± 2.2	2.9 ± 1.6	3.2 ± 2.0	<0.001†
ACS	6.0 ± 2.2	9.7 ± 3.5	7.1 ± 3.1	
VOC & ACS	5.6 ± 1.9	9.3 ± 3.2	6.3 ± 2.6	
Neither	3.7 ± 2.9	3.9 ± 2.7	3.7 ± 2.9	
Suspected ABX complications, n (%)				
Rash	0 (0)	0 (0)	0 (0)	—
Neutropenia	1 (0.5)	0 (0)	1 (0.4)	1.000
Thrombocytopenia	0 (0)	0 (0)	0 (0)	—
C difficile infection	0 (0)	0 (0)	0 (0)	—
Acute kidney injury	2 (1.1)	0 (0)	2 (0.8)	1.000
Hepatotoxicity	1 (0.5)	2 (2.9)	3 (1.1)	0.171
No complications suspected	187 (98.4)	66 (97.1)	253 (98.1)	0.610
Bacterial infection confirmed by culture, n (%)	8 (4.2)	1 (1.5)	9 (3.5)	0.291
Blood culture, n (%)				
Staphylococcus epidermidis	2 (1.1)	0 (0)	2 (0.8)	1.000
Staphylococcus hominis	1 (0.5)	0 (0)	1 (0.4)	
Streptococcus pneumoniae	2 (1.1)	0 (0)	2 (0.8)	
Negative	180 (97.3)	65 (100)	245 (95)	
Not obtained = 8				
Urine culture, n (%)				
Escherichia coli	2 (5.9)	1 (8.3)	3 (1.2)	1.000
Escherichia coli ESBL positive	1 (2.9)	0 (0)	1 (0.4)	
Proteus mirabilis	1 (2.9)	0 (0)	1 (0.4)	
Negative	30 (88.2)	11 (91.7)	41 (15.8)	
Not obtained = 213				
Respiratory culture (negative), n (%)	3 (100)	1 (100)	4 (1.6)	—
Not obtained = 254				
30-day mortality (# deceased), n (%)	4 (2.1)	0 (0)	4 (0.01)	0.576

ABX, antibiotic(s); ACS, acute chest syndrome; ICU, intensive care unit; PCT, procalcitonin; RSV, respiratory syncytial virus; SCD, sickle cell disease; VOC, vaso-occlusive crisis

*The "Upstate" Children's hospital utilizes PCT without a standardized protocol.
†P value represents differences in ABX duration by infection type for all patients ("Total" column).
—Statistic could not be calculated.

Descriptive statistics were used to summarize patient demographics, clinical data, and outcomes data. Mean (SD) or median (IQR) are reported for continuous variables, as appropriate, while counts and proportions are reported for categorical variables. For continuous data, differences by PCT and no-PCT protocols were evaluated using the Wilcoxon rank sum test. For other continuous data, either the Wilcoxon rank sum or the Kruskal-Wallis tests were used, depending on the number of levels for the classification variable. Normality was evaluated using the Shapiro-Wilk test and visual inspection of histogram plots with a normal curve overlay. A significant Wilcoxon rank sum test, which is based on ranks, indicates that either mean or median values tended to be larger (or smaller) for 1 group compared with the other. For categorical variables, the χ^2 test or Fisher exact test was used to evaluate differences between cohorts. Logistic regression was used to obtain ORs with 95% CIs for PCT status with other factors. All data were analyzed in SAS Enterprise Guide v8.3 with statistical significance based on resulting p-values ($p < 0.05$).

Results

A total of 648 encounters were screened for inclusion. After applying exclusion criteria, a total of 258 encounters were included in the final analysis, with 190 encounters in the PCT cohort and 68 encounters in the no-PCT cohort. Reasons for exclusion were patients being afebrile during hospitalization (n = 327), patients being admitted to an adult hospital within this health

Table 2. Association of PCT and ABX duration by Secondary Diagnosis

Characteristic	Antibiotic Duration			
	Mean ± SD			OR (95% CI)†
	PCT	no-PCT	p value*	(ref = PCT)
ABX Duration (all data)	4.2 ± 2.6	4.7 ± 3.6	0.991	1.12 (1.01–1.24)‡
VOC, ABX duration	3.4 ± 2.2	2.9 ± 1.6	0.307	0.88 (0.69–1.11)
ACS, ABX duration	6.0 ± 2.2	9.7 ± 3.5	0.037	1.51 (1.07–2.13)
VOC & ACS, ABX duration	5.6 ± 1.9	9.3 ± 3.2	0.002	1.72 (1.22–2.42)
Other, ABX duration	3.7 ± 2.9	3.9 ± 2.7	0.548	1.02 (0.86–1.22)

ABX, antibiotic(s); ACS, acute chest syndrome; PCT, procalcitonin; SCD, sickle cell disease; VOC, vaso-occlusive crisis

*P value for mean durations based on Wilcoxon rank sum test.
†Logistic regression: OR and 95% CI.
‡OR and 95% CI *after controlling for type of secondary diagnosis*.

system (n = 48), being febrile without the initiation of antibiotics (n = 7) or receiving antibiotics for >15 days (n = 8). The patients who received antibiotics for >15 days included 6 patients diagnosed with osteomyelitis and 2 patients diagnosed with necrotizing pneumonia which required repeated surgical interventions.

Demographic, clinical, and outcome characteristics are shown in Table 1. The distribution of patients by age, weight, and sex did not differ between cohorts. The mean age of the PCT cohort was 10.3 years (SD 6.4) and 10.2 years (SD 6.2) in the no-PCT cohort (p = 0.91). The PCT cohort was composed of 108 (56.8%) males and 82 (43.2%) females, while the no-PCT cohort had 36 (52.9%) males and 32 (47.1%) females (p = 0.578). Regarding sickle cell disease genotypes between the cohorts, the PCT cohort included 30 (15.8%) patients with HgbSC, 129 (67.9%) patients with HgbSS, and 31 (16.3%) patients with other genotypes, while the no-PCT cohort was composed of 6 (8.8%), 48 (70.6%), and 14 (20.6%), respectively (p = 0.314). In the PCT cohort, 17 (9%) of patients were diagnosed with ACS only, 40 (21.1%) with ACS and VOC, 68 (35.8%) with VOC only, and 65 (34.2%) diagnosed with neither. While the no-PCT cohort included 7 (10.3%) patients with ACS only, 9 (13.2%) with ACS and VOC, 33 (48.5%) with VOC only, and 33 (48.5%) diagnosed with neither (p = 0.222). There was a lower percentage of patients on baseline hydroxyurea in the PCT cohort (98/190, 51.6%) vs the no-PCT cohort (46/68, 67.7%), (p = 0.022). The percentage of negative respiratory pathogen panel results was higher in the PCT cohort (140/190, 73.7%) vs the no-PCT cohort (40/68, 58.8%), (p = 0.022). There were more patients in the PCT cohort at the "Midlands" facility (170/190, 89.5%) vs the "Upstate" facility (20/190, 10.5%), (p < 0.001). Appropriate antibiotic dosing per institutional protocol was higher in the PCT cohort (166/190, 87.4%) vs the no-PCT cohort (49/68, 72.1%) (p = 0.004). There were 8 patients (4.2%) in the PCT cohort with confirmed bacterial infections vs 1 patient (1.5%) in the no-PCT cohort (p = 0.291). Confirmed bacterial infections consisted of bacteremia (n = 5 PCT vs n = 0 no-PCT, p = 1.000) and urinary tract infections (n = 4 PCT vs n = 1 no-PCT p = 1.000). There were no differences with antibiotic associated complications between cohorts and documented complications were rarely seen. There were also no differences in re-initiation of antibiotics (p = 0.874) or 30-day mortality (p = 0.576) between both cohorts.

Comparisons of antibiotic duration use by patient cohort and by secondary diagnosis are shown in Table 2. The overall mean antibiotic duration in the PCT cohort was 4.2 days (SD 2.6) compared with 4.7 days (SD 3.6) in the no-PCT cohort (p = 0.991). Antibiotic duration in the PCT vs no-PCT cohort was similar amongst patients with VOC alone, 3.4 (SD 2.2) vs 2.9 (SD 1.6) days (p = 0.307). For patients with an ACS diagnosis alone, the mean antibiotic duration was 6 days (SD 2.2) in the PCT cohort compared with a higher antibiotic duration of 9.7 days (SD 3.5) in the no-PCT cohort (p = 0.037). Patients with both a VOC and ACS diagnosis averaged 5.6 days (SD 1.9) on antibiotics in the PCT cohort which was significantly lower than the 9.3 days (SD 3.2) in the no-PCT cohort (p = 0.002).

Outcomes were further evaluated with logistic regression models to assess risk for increased antibiotic duration by patient cohort ("PCT cohort" was the reference value). (Regression results are also shown in Table 2.) Antibiotic duration by PCT cohort was significant after controlling for secondary diagnosis (i.e., ACS and/or VOC). For every 1-day increase in antibiotic duration, patients had 12% greater odds of being in the no-PCT cohort (OR 1.12, 95% CI 1.01–1.24). Stratified results by secondary diagnosis showed no difference in antibiotic duration between cohorts for patients diagnosed with

VOC (OR 0.88, 95% CI 0.69–1.11), however significant differences were found for patients diagnosed with ACS only (OR 1.51, 95% CI 1.07–2.13) and for those diagnosed with both ACS and VOC (OR 1.72, 95% CI 1.22–2.42).

Discussion

The above findings demonstrate no significant difference in overall antibiotic exposures (crude association) when utilizing a procalcitonin guided antibiotic management strategy in pediatric sickle cell patients with fever. However, there were significant antibiotic exposure reductions that were observed in patients who were also diagnosed with ACS or VOC & ACS, averaging 3.7 fewer days of antibiotics in the PCT cohort.

Adult studies have demonstrated the ability for blood PCT concentrations to predict rates of bacterial infections and reduce antibiotic durations of therapy, but there is a lack of data within the pediatric population.[6] Patel et al[7] evaluated the utility of PCT as an early biomarker of bacterial infections, within 6 hours of presentation, in adult patients with SCD with VOC and signs of sepsis. They concluded a blood PCT concentration <0.5 μ/L was associated with a low risk of bacterial infections and that those patients may be managed with just monitoring and supportive care.[7] Similarly another study identified significantly higher PCT concentrations (mean = 8.99 μ/L, range = 0.03–78.36 μ/L) in confirmed bacterial infections within adult patients presenting to the emergency department with SCD, VOC, and fever compared with viral infections or VOC only. They defined confirmed bacterial infections as a positive bacterial culture (blood, body fluid, urine, respiratory or cerebrospinal fluid) or *C difficile* toxin assay. The most common organisms detected in that study were *E coli, C difficile,* Staphylococcus species and Enterobacter species. They concluded that a PCT level >0.5 μ/L demonstrated an 81% sensitivity and 85% specificity for predicting confirmed bacterial infections within this population.[8] Therefore, our PCT protocol utilized the PCT value of >0.5 μ/L to guide our clinicians to either continue or initiate appropriate empiric antibiotics.

While PCT does have the ability to identify bacterial infections, it also can impact antibiotic exposures. Razazi et al[3] evaluated if a PCT based antibiotic prescribing regimen would reduce antibiotic exposure without increasing risk of adverse effects in adult patients with ACS. Results demonstrated more patients, diagnosed with ACS episodes (n = 103), received ≤ 3 days of antibiotics in the PCT-guided cohort (31% vs 9%; p < 0.01) with no infection relapse or pulmonary superinfection seen in the entire cohort.[3] The current study demonstrated that pediatric sickle cell patients with fever and diagnosed with ACS received 3.7 fewer days of antibiotics when a procalcitonin protocol was utilized (6 days vs 9.7 days; p = 0.037). This study also identified shorter antibiotic durations in the PCT cohort in patients diagnosed with both ACS and VOC (5.6 days vs 9.3 days; p = 0.002). There were also very few antibiotic associated complications across both cohorts. Most antibiotic re-initiations were due to the patient being readmitted for another fever or concern for a viral infection (empiric antibiotics were initiated upon admission prior to determining a viral etiology by utilizing a respiratory pathogen polymerase chain reaction assay). We did not identify that any antibiotic re-initiations were due to an actual confirmed bacterial infection (i.e., a positive blood culture). However, a multicenter retrospective cohort study including 35,548 encounters representing 11,181 individual patients with sickle cell disease from thirty-six children's hospitals who presented to the emergency department with fevers noted that bacteremia was uncommon (1.1%).[9]

Limitations of Study

There were limitations in this study, including that the institution specific PCT protocol was not fully implemented during the entire study period (35.3% had PCT protocol adherence). This may have contributed to the low adherence rates to the PCT protocol. Common reasons for PCT protocol non-adherence included only a single PCT being obtained without a repeat value, or antibiotics being continued with repeat PCT values <0.5 μ/L. This may have resulted in no significant difference in overall antibiotic durations between cohorts. However, even with the low adherence, statistical significance was still met in certain circumstances, showing lower antibiotic exposures when utilizing PCTs in patients diagnosed with ACS or VOC and ACS. Uneven cohorts did exist due to clinical practice differences observed among sites as well as with the differences in the size of SCD populations between hospital locations within the state.

Conclusions

In conclusion, this study provides evidence for implementing a PCT guided antibiotic management protocol in pediatric sickle cell patients with fever (see Figure). Although the overall impact on reduced antibiotic durations was not significant between procalcitonin cohorts, reduced antibiotic durations were seen for patients with certain comorbid conditions. Specifically, shorter antibiotic durations were seen in febrile pediatric patients with SCD and other complications, such as ACS or VOC and ACS. Therefore, the addition of utilizing a PCT algorithm may be beneficial in not only assisting with the inpatient infectious work-up but by reducing antibiotic durations in pediatric patients with SCD presenting with fever who are also diagnosed with ACS or VOC and ACS.

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