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Impact of a Pediatric Emergency Medicine Pharmacist, Institutional Guideline, and Electronic Order Set on Empiric Antimicrobial Use for Febrile Neutropenia

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Objectives: This study evaluated the difference in appropriateness of antimicrobial selection in pediatric patients with febrile neutropenia (FN) after implementation of an institutional guideline, a dedicated pediatric emergency medicine (EM) pharmacist, and an electronic order set.

Methods: This was a retrospective cohort study that included febrile patients aged younger than 18 years who were at risk of neutropenia, as defined by our institutional algorithm. Charts were evaluated for inclusion by searching for patients who presented to the emergency department (ED) between February 2018 and January 2022 who had *International Classification of Diseases, Tenth Revision* (ICD-10) codes for patients at risk of FN. Three independent groups were compared before, during, and after interventions. A historical control group (group 1), postdedicated EM pharmacist and institutional guideline cohort (group 2), and postdedicated EM pharmacist, institutional guideline, and electronic order set cohort (group 3) were compared. Secondary outcomes included time from registration in the ED to administration of the first dose of empiric antimicrobials, days to defervescence, pediatric intensive care unit length of stay, and hospital length of stay.

Results: Seventy-eight charts were reviewed for inclusion. Among those included (n = 38), there was an increase in appropriate use of antimicrobials from 71% to 92% to 100% ($P = 0.1534$) between group 1, group 2, and group 3, respectively. In addition, the interventions in this study lead to an overall decrease in the median time from registration to first dose of antibiotics from 142 minutes to 72 minutes ($P = 0.1370$).

Conclusions: This study demonstrated the positive impact a pediatric EM pharmacist along with an institutional guideline and an electronic order set have on appropriate antimicrobial selection in pediatric FN patients. Institutions should consider multipronged approaches to improve the selection and time to administration of appropriate empiric antimicrobials in the ED.

Key Words: febrile neutropenia, pharmacist, oncology

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BACKGROUND

Febrile neutropenia (FN) can be life-threatening, requiring urgent medical evaluation and management in the emergency department (ED). Pediatric oncology patients undergoing chemotherapy are at an increased risk of morbidity and mortality from infectious causes secondary to reduced immunity.[1,2] The risk of infection in patients with non–chemotherapy-induced neutropenia can vary but is high in diseases such as severe congenital neutropenia and aplastic anemia.[3] In many cases, fever can be the only indicator of a severe infection. Patients presenting with anticipated profound and prolonged neutropenia (absolute neutrophil count [ANC] ≤ 100 cell/mm^3, >7 d, respectively) after cytotoxic chemotherapy along with comorbid conditions or secondary high-risk infections should be admitted to the hospital and administered empiric antimicrobial therapy.

The Infectious Disease Society of America recommends that high-risk patients are started on monotherapy with an antipseudomonal β-lactam agent.[2] Studies have shown that a pharmacist-driven antimicrobial stewardship program, implementation of FN guidelines, and the use of an electronic order set have individually increased appropriate selection of antimicrobials for hospitalized patients.[4–6] A retrospective study assessing the impact of an antimicrobial stewardship program (ASP) and a clinical practice guideline demonstrated a 51% increase in the appropriate use of empiric antibiotics for children hospitalized with community-acquired pneumonia.[4] To reduce delays in the diagnosis and appropriate treatment of FN, EDs have implemented computerized protocols. A prospective study comparing the appropriate use of target antibiotics before and after the implementation of a standardized hospital order set for the management of septic shock in the ED showed a 15% increase in the administration of appropriate antibiotic treatment.[5] Furthermore, a prospective study looked at the incorporation of a pharmacist into an ASP and assessed the impact on appropriate use of target antibiotic for patients with FN. The correct choice of appropriate antibiotic was 37.8% higher in the pharmacist-driven ASP group versus the control group. These studies demonstrate the positive impact pharmacists, institutional guidelines, and standardized physician order sets have on improving antibiotic appropriateness for various indications.[6]

Our institutional FN guideline (Fig. 1) is used for patients with a documented fever either by history or at time of presentation to the ED, and who were presumed or known to be neutropenic, on chemotherapy, or off chemotherapy for less than 1 month. The guideline includes initial broad-spectrum antibiotic recommendations, which consist of administering cefepime to all patients with FN unless another choice is clearly indicated. The addition of vancomycin is indicated for high-risk patients such as those presenting with hemodynamic instability or sign and symptoms of sepsis. The primary objective of this study was to assess the impact a dedicated pediatric emergency medicine (EM) pharmacist, implementation of an FN guideline, and an electronic order set have on appropriate empirical antimicrobial selection in

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patients presenting to the ED with concern of FN. We hypothesized that these interventions would lead to a significant increase in the use of appropriate antimicrobials.

METHODS

This retrospective cohort study included febrile pediatric patients aged younger than 18 years who were at risk for neutropenia and presented to the Children's Hospital of Georgia ED. Patients were deemed at risk for neutropenia if they were currently on chemotherapy, off chemotherapy for less than 1 month, or had a history of congenital or acquired neutropenia. Fever was defined as temperature higher than 38.3°C or a temperature higher than 38°C sustained over a 1-hour period. Patients were included if they presented to the ED between February 2018 and January 2022 with a condition that would make them susceptible for neutropenia, as identified by *International Classification of Diseases, Tenth Revision* (ICD-10) codes. Three independent groups of individuals were compared before, during, and after the interventions (Fig. 2). A historical control cohort (group 1) was analyzed between February 2018 and December 2018. A postdedicated pediatric EM pharmacist and institutional guideline cohort (group 2) was evaluated between August 2019 and March 2021, and a postdedicated pediatric EM pharmacist and institutional guideline plus an electronic order set cohort (group 3) was evaluated between April 2021 and January 2022.

The primary outcome assessed was the percentage of appropriate empiric antimicrobials administered. Secondary outcomes included: time from registration in the ED to administration of the first dose of empiric antimicrobials, days to defervescence, pediatric intensive care unit (PICU) length of stay (LOS), and hospital LOS. For all study patients, the following patient characteristics were recorded: age, sex, body weight (kg), primary diagnosis contributing to neutropenia, disposition from the ED, ANC within the previous 48 hours, initial ANC and white blood cell count, blood pressure, temperature, heart rate, and respiratory rate on presentation to the ED.

Group 1, group 2, and group 3 define 3 independent groups of individuals. Thus, all statistical methods did not use repeated measures methods. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, N.C.) and statistical significance was assessed using an alpha level of 0.05. Descriptive statistics include frequencies and percentages for categorical variables, means and SDs for continuous variable, and medians and interquartile ranges for ordinal variables. The χ^2 test was used to examine differences in appropriate empiric antimicrobial administration between the 3 groups. To examine whether time of administration of the first dose of empiric antimicrobials and days to defervescence are

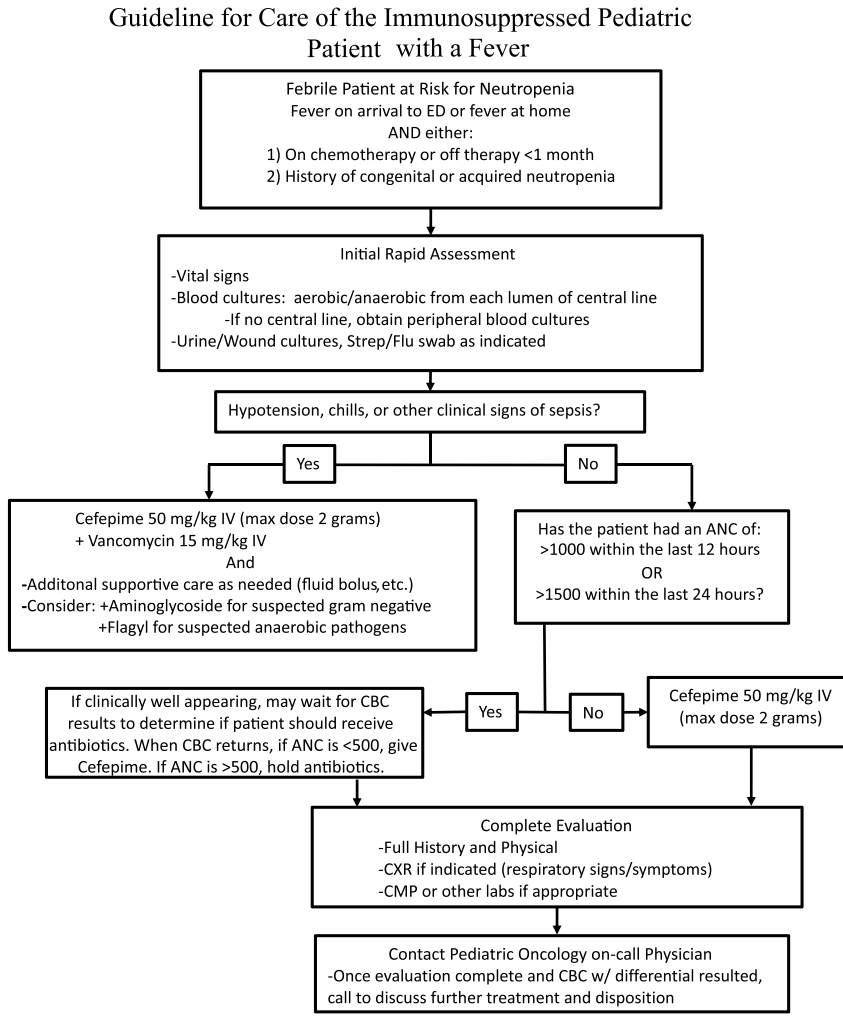

FIGURE 1. Institutional guideline.

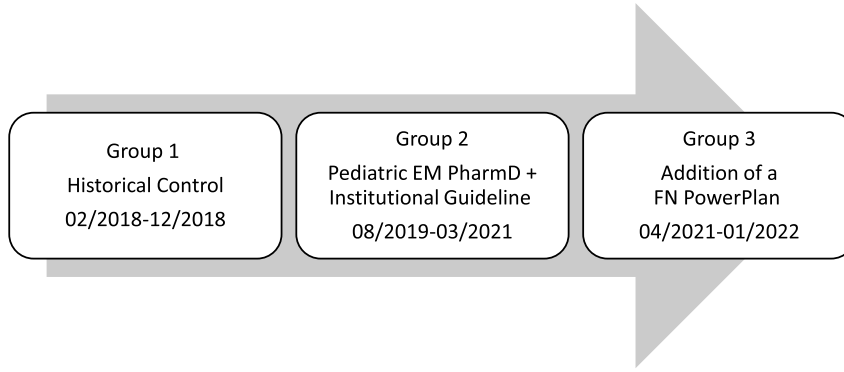

FIGURE 2. Intervention timeline. FN indicates febrile neutropenia.

different from group 1, group 2, and group 3, Kaplan-Meier survival curves with a log-rank test for differences between the groups was performed. Adjustment for the multiple post hoc pairwise comparisons was performed using a Tukey-Kramer multiple comparison test. To examine whether PICU LOS and hospital LOS are different between the 3 groups, a Kruskal-Wallis test was used with a Dwass-Steel-Critchlow-Fligner multiple comparison method. For other continuous variables, a 1-way analysis of variance was used with a Tukey-Kramer multiple comparison test. If assumptions to the 1-way analysis of variance were not met, a Kruskal-Wallis nonparametric test was performed with a Dwass-Steel-Critchlow-Fligner multiple comparison method.

RESULTS

Overall, 78 charts were reviewed. Forty patients (51.3%) were excluded for 1 or more of the following reasons: off chemotherapy for more than 1 month (n = 19), no history of acquired or congenital neutropenia (n = 15), afebrile (n = 25), and aged older

TABLE 1. Demographic and Clinical Features According to Group

Variable		Group 1 n = 17	Group 2 n = 13	Group 3 n = 8	*P*
Age*		10.3 (4.6)	8.1 (5.9)	12.8 (5.1)	0.0226
Sex†	Male	18 (64.3)	23 (71.9)	6 (42.9)	0.1695
	Female	10 (35.7)	9 (28.1)	8 (57.1)	
Race†	Black/African American	4 (14.8)	11 (34.4)	6 (42.9)	0.3936
	Hispanic	1 (3.7)	1 (3.1)	0 (0)	
	Other	1 (3.7)	1 (3.1)	0 (0)	
	White	21 (77.8)	19 (59.4)	8 (57.1)	
Unit transferred to†	3C – PICU	4 (14.8)	6 (19.4)	4 (33.3)	0.1988
	4C – General	0 (0)	4 (12.9)	0 (0)	
	4U – PIMCU	0 (0)	1 (3.2)	0 (0)	
	5C	23 (85.2)	20 (64.5)	8 (66.7)	
Weight (kg)‡		32.6 (20.1–56.1)	17.7 (13.8–41.3)	52 (19.7–57.7)	0.0359
Temperature (°C)*		37.6 (0.9)	37.9 (1.3)	37.9 (1)	0.6557
SBP*		108.1 (14)	106.1 (14.2)	105.6 (18.9)	0.8940
DBP*		65.9 (12.7)	65.7 (14.7)	73.1 (14.8)	0.4147
Initial HR*		125.3 (17.1)	147.9 (26.6)	139.8 (15.9)	0.0111
Initial RR*		23.4 (5.5)	27.9 (9)	21.3 (3.8)	0.0593
ANC per laboratory result last 48 h*		0.5 (0.8)	0.1 (0.2)	0 (0)	0.4526
ANC per laboratory result – chart*		2.4 (5.9)	0.5 (0.9)	2 (2.9)	0.4890
WBC*		3.3 (6.3)	1.2 (1.3)	2.7 (3.4)	0.4535
Type of empiric antimicrobial(s)†	Ceftriaxone	3 (10.7)	1 (3.1)	0 (0)	—
	Vancomycin	3 (10.7)	3 (9.4)	1 (7.1)	
	Cefepime	11 (39.3)	12 (37.5)	8 (57.1)	
	Other(s)	3 (10.7)	0 (0)	0 (0)	

ANC, absolute neutrophil count; DBP, diastolic blood pressure; HR, heart rate; PICU, pediatric intensive care unit; PIMCU, pediatric intermediate care unit; RR, respiratory rate; SBP, systolic blood pressure; WBC, white blood cells.

*Data are presented as mean (SD). The test statistic is the F-test from a 1-way analysis of variance.

†Data are presented as n (%). The test statistic is the χ^2 test. Indicates Fisher exact test was performed and the Fisher exact *P* value is presented.

‡Data are presented as median (IQR). The test statistic is the Kruskal-Wallis χ^2 test.

TABLE 2. Primary and Secondary Outcomes According to Group

Variable	Group 1 n = 17	Group 2 n = 13	Group 3 n = 8	*P*
Appropriate empiric antimicrobial(s)*	12 (70.6)	12 (92.3)	8 (100)	0.1534
Time to empiric antibiotic (min)†	142.2 (91.0–369.9)	81 (60.0–93.0)	72 (45.0–96.0)	0.1370
Days to defervescence†	1.1 (0.8–1.1)	2.1 (1.1–3.1)	2.5 (0.1–3.4)	0.0002
PICU LOS (d)‡	1.1 (0.6–6.5)	2.4 (0.7–5.6)	2.2 (0.6–9.1)	0.8984
Hospital LOS (d)‡	3.7 (2.1–8.1)	10 (6.9–15.1)	4.4 (3.2–8.4)	0.0027

*Data are presented as n (%). The test statistics is the χ^2 test. Indicates Fisher exact test was performed and the Fisher exact *P* value is presented.
†Data are presented as median (95% CI). The test statistic is the log-rank test statistic using a Kaplan-Meier survival curve analysis.
‡Data are presented as median (IQR). The test statistic is the Kruskal-Wallis χ^2 test.

than 18 years (n = 6). The baseline characteristics of all patients for each FN episode are shown in Table 1. Among those included (n = 38), there was an increase in the appropriate use of the antimicrobials from 71% to 92%, and then to 100% ($P = 0.1534$) between group 1, group 2, and group 3, respectively (Table 2). There was no statistically significant difference in the appropriate use of antimicrobials or time to antimicrobial administration between the 3 intervention periods. However, the mean time to antimicrobial administration numerically improved over time: 142 minutes for group 1, 82 minutes for group 2, and 72 minutes for group 3. There was a statistically significant difference in days to defervescence, with group 1 having significantly lower median days to defervescence than the group 2 (post hoc test $P = 0.0046$) and group 3 (post hoc test $P = 0.0019$) periods. There was no statistically significant difference in PICU LOS between the intervention periods (Table 2). A difference was found for hospital LOS, with group 1 having significantly lower median hospital LOS than group 2 (post hoc test $P = 0.0035$).

DISCUSSION

Previous studies have shown comparable results to our study. Newman et al[4] showed a reduction in the use of the most common inappropriate antibiotics for community-acquired pneumonia by 51% through the addition of a clinical practice guideline. Furthermore, Bailey et al[7] demonstrated that patients seen in the ED while a pediatric EM pharmacist was working received appropriate first antibiotics 93.4% of the time. Our results confirm and further validate these findings.

In this study, we were able to successfully demonstrate the impact a dedicated pediatric EM pharmacist, an institutional guideline, and an electronic order set have on increasing appropriate antimicrobial selection and decreasing time to first dose of antimicrobials for pediatric patients with FN presenting to the pediatric ED. For the primary outcome, there was an absolute 21% increase from 71% to 92% in appropriate antimicrobial selection from group 1 to group 2. After the addition of an FN electronic order set, appropriate antimicrobial selection reached 100%. Although a statistically significant difference in our primary outcome was not achieved, a clinically significant difference was observed. The major goal of these 3 interventions was to facilitate the selection of guideline-directed therapy with an antipseudomonal β-lactam agent and to reduce the use of inappropriate antibiotics such as ceftriaxone as empiric therapy. Ceftriaxone use decreased from 10.7% to 3.1% and then to 0% in group 1, group 2, and group 3, respectively.

The median time to first dose of antimicrobials decreased by 61 minutes (43%) when comparing group 1 and group 2 and decreased by an additional 9 minutes when comparing group 2 and group 3. The interventions made in this study lead to a 51% overall decrease in the median time to first dose of antibiotics. This was a noteworthy improvement because longer time to antibiotic administration (TTA) is widely recognized as a mortality risk factor in sepsis and septic shock.[8,9] Pediatric patients with FN remain at a high risk for sepsis, with reports of mortality rates described as high as 17%.[10] A prospective cohort study of 307 adult patients with FN concluded that for every hour delay in TTA, the 28-day mortality risk increased by 18%.[9] Although our study did not assess mortality as an outcome, it can be extrapolated from previous literature that decreasing TTA could improve patient outcomes. There was a statistically significant difference in days to defervescence and hospital LOS, but these differences were likely due to outliers, with 1 patient in group 3 having a fever for more than 9 days and another patient in group 2 having a hospital LOS of 49 days.

This study has several limitations. This was a retrospective chart review performed within a single pediatric ED at an academic medical center. The variation in staff experience and knowledge of the guideline could have been limiting factors as well. The availability of our pediatric EM pharmacist is limited to 40 hours per week, which likely adds a barrier, when they are not present, for prompt interventions from a pharmacist and potentially increases the time from dispensing to administering antimicrobials. In our study, we did not distinguish between hours of specific pediatric EM pharmacist coverage versus those hours without dedicated coverage. Most, but not all, antibiotics included in the guideline were made available in the automated dispensing cabinets located in the ED. Antibiotics not located in the automated dispensing cabinets can contribute to a delay in time to first dose of antimicrobials because they are prepared in the pharmacy and then delivered to the ED. Because 2 distinct interventions—a pediatric EM pharmacist and an institutional guideline—were included in group 2, the percentage of observed benefit of either intervention cannot be determined. This study had a small sample size and did not meet power, which could have limited the ability to see a statistically significant difference in our primary outcome.

CONCLUSIONS

This study demonstrated the positive impact a pediatric EM pharmacist along with an institutional guideline and an electronic order set have on appropriate antimicrobial selection in pediatric patients with FN. These interventions not only increased appropriate empiric antimicrobials in pediatric patients with FN, but also decreased the time from patient registration to first dose of empiric antimicrobials. These improvements, in turn, improve patient care

by providing appropriate antimicrobial coverage in a timely manner. Given the improvement in appropriate medication selection and timely medication administration in patients with FN, these results suggest that multidisciplinary involvement in the standardization of care and enhancements to clinical decision support systems can be applied to other disease states to improve care. Institutions should consider the addition of a dedicated pediatric EM pharmacist who can facilitate a streamlined medication use process.

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