RESEARCH ARTICLE

Study of Delayed Antibiotic in Pediatric Febrile Immunocompromised Patients and Adverse Events

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ABSTRACT

OBJECTIVES: Bone marrow transplant (BMT) patients or patients receiving chemotherapy for oncologic diagnoses are at risk for sepsis. The association of time to antibiotics (TTA) with outcomes when adjusting for severity of illness has not been evaluated in the pediatric febrile immunocompromised (FI) population. We evaluated the association of TTA with adverse events in a cohort of FI patients presenting to our pediatric emergency department.

METHODS: We performed a retrospective review of consecutive FI patients presenting over a 6.5-year period. Adverse events were defined as intensive care admission within 72 hours of emergency department arrival, laboratory signs of acute kidney injury, inotropic support subsequent to antibiotics, and all-cause mortality within 30 days. Vital signs and interventions were used to define severity of illness. Adjusting for severity of illness at presentation, age, and timing of an institutional intervention designed to reduce TTA in FI patients, we analyzed the association of TTA with individual adverse events as well as with adverse events in aggregate.

RESULTS: We analyzed 1489 patient encounters. In oncology patients, TTA was not associated with the aggregate measure of whether any adverse event subsequently occurred nor with other individual adverse events. For the BMT subpopulation, TTA >60 minutes did show increased odds of intensive care admission within 72 hours as well as for aggregate adverse events.

CONCLUSIONS: Although TTA >60 minutes did show increased odds of aggregate adverse events in the small subgroup of BMT patients, overall TTA was not associated with adverse events in oncology patients as a whole.

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Bloodstream infections in pediatric oncology and bone marrow transplant (BMT) patients are associated with significant morbidity and mortality.[1–5] Often, fever is the first sign of bacterial infection, and decreased time to antibiotics (TTA) has demonstrated improved outcomes in febrile adult patients with sepsis,[6] community-acquired pneumonia,[7] meningitis,[8] and solid organ transplant.[9] Consequently, attention has been focused on reducing TTA in febrile immunocompromised (FI) patients, such as oncology and BMT patients.

Studies reveal that a delay in TTA in FI patients is associated with increased morbidity and mortality in adult populations.[10,11] Consensus guidelines support TTA within 60 minutes of arrival for all adult patients with sepsis[12] and, by extension, FI patients.[13] Published recommendations exist regarding antibiotic choice in FI patients with cancer.[14–16] The national standard for pediatric FI patients presenting to the emergency department (ED) is to deliver antibiotics within 60 minutes of arrival.[17,18]

In pediatric FI patients, longer TTA has been shown to be associated with intensive care (PICU) admission as well as composite measures of discrete adverse events.[19,20] Studies in FI adult patients have revealed a decreased correlation between TTA and adverse events when considering confounders such as severity of illness at presentation.[21–23] Pediatric studies have not controlled for severity of illness at presentation. In our quality improvement (QI) work reducing TTA in FI patients,[24] we noted that many of the delays in TTA were in patients who presented with signs of septic shock. In our analysis of the TTA process, fluid resuscitation, inotropic support, and artificial ventilation were often done before antibiotic administration, delaying TTA. Given that these interventions frequently necessitate procedures such as complex vascular access and external ventilation, which may take longer in sicker patients, we performed a large-scale analysis of the pediatric FI population, controlling for severity of illness at presentation, to study the association of TTA with adverse events. We hypothesized that when severity of illness is taken into account, TTA will not be associated with adverse outcomes in the pediatric FI population.

METHODS

Setting

This study was conducted at the academic campus of a tertiary-care, urban (population 2 million people) children's hospital with an annual ED volume of 60 000 patients. This 600-inpatient, level 1 trauma, pediatric institution is responsible for 85% to 90% of pediatric admissions and houses the only inpatient pediatric critical-care units for this catchment area, exclusive of neonatology. The local institutional review board approved the research protocol.

Study Sample

This was a retrospective cohort study of consecutive FI patients (oncology, BMT, and immunodeficiency) who presented to the ED over 6.5 years (January 1, 2010, to June 30, 2016). Patient encounters were identified from a registry maintained by the Cancer and Blood Diseases Institute at our institution. Inclusion criteria were (1) presentation to the ED, (2) known oncology or immunodeficiency diagnosis or being under the care of the BMT service, and (3) reported or recorded fever at home or on initial vital signs in the ED. Fever was defined as any temperature ≥38.0°C (100.4°F). We did not include patients who received antibiotics before ED arrival (eg, at an outside facility) in the analysis. The unit of analysis was each discrete encounter over the 6.5 years (individual patients could present more than once). Patients who presented to the oncology clinic with a fever (~10% of the total patients who were directly admitted after receiving antibiotics) were not included in the study population.

Demographic and clinical data were collected on all patients. For each encounter, we recorded sex, age, race, and previous BMT status. Additionally, we included the first set of vital signs (temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation), volume of intravenous fluids administered, TTA, absolute neutrophil count (ANC), creatinine level, and inotrope use in the ED (type and time of administration). Outcome measures included hospital length of stay for each encounter, need for PICU admission within 72 hours of ED arrival, highest creatinine level within 7 days of ED arrival, and mortality within 30 days of ED arrival. Inotrope administration necessitates PICU admission.

TTA was defined as minutes from ED arrival to the recorded first dose of parenteral antibiotics given. Patients were dichotomized on the basis of whether they received antibiotics within 60 minutes of arrival to the ED. We accounted for severity of illness in FI patients presenting to the ED by retrospectively applying the International Pediatric Sepsis Consensus Conference Guidelines to all encounters. The International Pediatric Sepsis Consensus Conference Guidelines[25] were used to establish vital sign and intervention parameters to define severity of illness at presentation (sepsis, systemic inflammatory response syndrome [SIRS], and non-SIRS). Initial ED vital signs were used.

The severity of illness was assigned 1 of 3 categories: SIRS, non-SIRS, and sepsis. SIRS was defined as an initial ED temperature ≥38.5°C (101.3°F) or ≤36°C (96.8°F) while also having 1 of the following: age-based tachycardia or age-based tachypnea. Sepsis was defined as SIRS in the presence of 1 of the following: receiving more than the equivalent of 2 20 mL/kg fluid boluses, hypotension (age-based low systolic blood pressure as defined in the International Pediatric Sepsis Consensus Conference Guidelines), oxygen saturation <92%, receiving a vasoactive drug in the ED before antibiotic administration, or intubation in the ED before antibiotic administration. Although white blood cell count was used in the definition of SIRS for most patients in the International Pediatric Sepsis Consensus Conference Guidelines, an exception was made in the definition for patients with chemotherapy-induced leukopenia.[25] This exception encompassed our population and so was not used to define SIRS for our data set. Non-SIRS was defined as any patient meeting neither the definition for SIRS nor sepsis.

Adverse events were defined as PICU admission within 72 hours of ED arrival,

acute kidney injury (50% increase in creatinine within 7 days of ED arrival), inotropic support after first antibiotic administration, and all-cause mortality within 30 days of ED arrival. An aggregate binary variable was created as a measure of whether any of these adverse events occurred for a given encounter. Given that mortality was a rare event, the association of mortality with TTA was not modeled for any population, although mortality was included in the measure of aggregate adverse events.

Statistical Analysis

Descriptive statistics and frequency distributions were generated for baseline and demographic characteristics. Demographic and transplant-related characteristics were compared between patients who received antibiotics within 60 minutes and those who did not by using χ^2 or Fisher's exact test for categorical variables and Student's *t* tests for age. We used logistic regression to measure the association of TTA within 60 minutes with adverse events. We developed models for each type of adverse event as well as for the aggregate adverse event variable, which denotes whether a patient experienced any adverse event included in this study. The dependent variable was an indicator variable for whether a patient experienced the adverse event. The independent variable of interest was an indicator variable for whether a patient received antibiotics within 60 minutes. Adjusted and nonadjusted odds ratios along with 95% confidence intervals (CIs) were developed. We included additional terms in the models to adjust for severity of illness, patient age, and whether a given encounter occurred before or after institutional QI methodologies designed to reduce TTA in FI patients were initiated. We performed this analysis for the population as a whole as well as for the BMT and oncology (non-BMT) subpopulations. Because of the relatively small number of BMT patients with adverse events, we only analyzed PICU admissions in addition to the aggregate adverse event variable for this subpopulation. Similarly, models were not developed for mortality for the population as a whole or subpopulations.

RESULTS

There were 651 unique patients representing 1489 FI encounters in this period, with a mean of 2.3 (range 1–17) ED visits per patient. For all encounters, TTA was skewed to the right with a mean of 62 minutes (SD = 46) and a median of 47 minutes. For 66% of encounters (n = 984), TTA was within 60 minutes of arrival to the ED (Fig 1).

Among all encounters, 81% (n = 1206) were oncology patients. Of those, the majority had acute lymphoblastic leukemia (n = 558) or sarcoma (n = 181). The other 19% of encounters (n = 283) were patients who had previously undergone BMT, mainly for malignancy (n = 129) or immunodeficiency (n = 80; Table 1).

Nearly 12% (n = 169) of all encounters experienced an adverse event. Of those who received antibiotics within 60 minutes, 10% (n = 102) experienced adverse events compared with 13% (n = 67) of those whose TTA was >60 minutes. All-cause mortality within 30 days occurred for 5 patients each for both TTA ≤60 minutes (0.5%) and TTA >60 minutes (1%; Table 2).

Overall, receiving antibiotics within 60 minutes was not significantly associated with having 1 or more adverse events. The results of the adjusted models for individual adverse events, however, showed that patients for whom TTA was >60 minutes

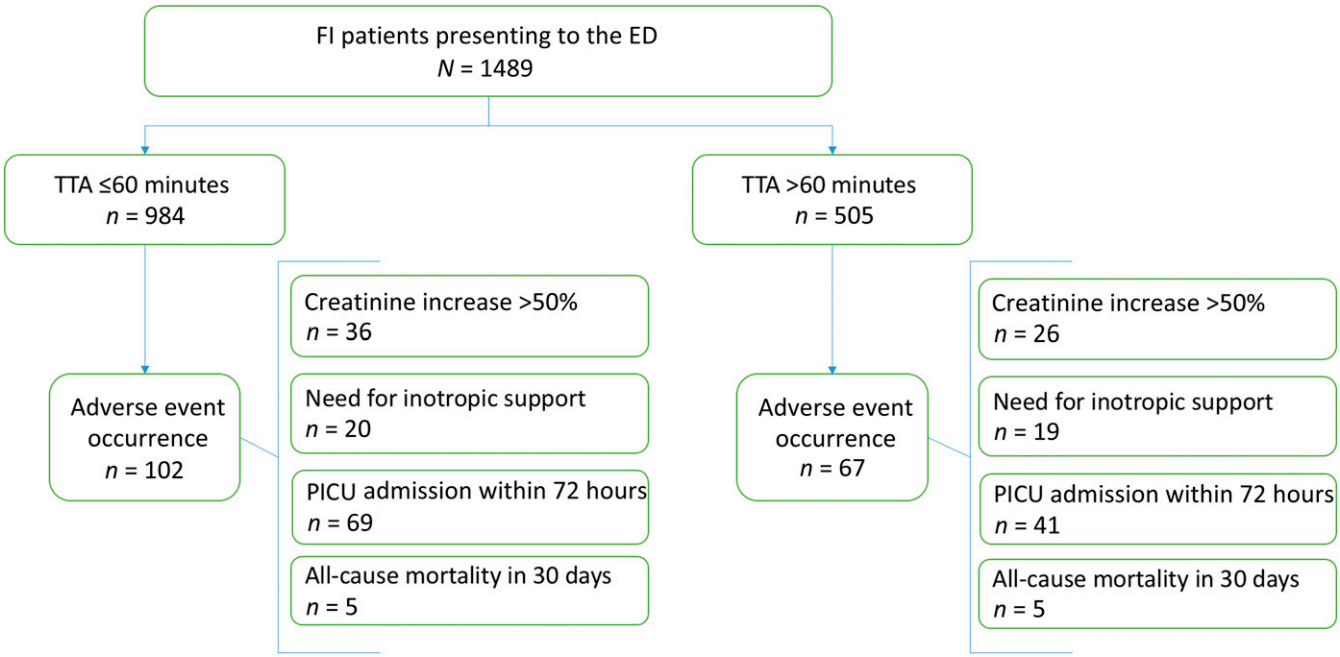

FIGURE 1 Outcomes in FI patients presenting to the ED from January 1, 2010 to June 30, 2016 (n = 1489). Adverse events were defined as intensive care admission within 72 hours of ED arrival, acute kidney injury (50% increase in creatinine within 7 days of ED arrival), inotropic support after the first antibiotic administration, and all-cause mortality within 30 days of ED arrival.

TABLE 1 Demographic and Clinical Characteristics of Population by TTA

	All Patients (N = 1489)	TTA ≤60 min (n = 984)	TTA >60 min (n = 505)	P
Sex, *n* (%)				.55
Girls	659 (44.3)	430 (43.7)	229 (45.3)	
Boys	830 (55.7)	554 (56.3)	276 (54.7)	
Age, y, median (IQR)	6.2 (3.8–11.0)	5.9 (3.8–10.1)	6.7 (4.0–12.5)	.06
Race, *n* (%)				.46
White	1100 (73.9)	716 (72.8)	384 (76.0)	
African American	72 (4.8)	49 (5.0)	23 (4.5)	
Other	309 (20.8)	215 (21.9)	94 (18.6)	
Unknown	8 (0.5)	4 (0.4)	4 (0.8)	
Severity of illness, *n* (%)				.05
Non-SIRS	1108 (74.4)	746 (75.8)	362 (71.7)	
SIRS	287 (19.3)	186 (18.9)	101 (20.0)	
Sepsis	94 (6.3)	52 (5.3)	42 (8.3)	
Median LOS, d, median (IQR)	2.8 (0.7–6.1)	2.6 (0.2–5.7)	3.6 (1.8–6.8)	.10
ANC,[a] *n* (%)				
<500	382 (26.9)	244 (25.9)	138 (28.8)	.24
<1000	493 (34.7)	327 (34.7)	166 (34.7)	.98
BMT status, *n* (%)				.12
No previous BMT	1206 (81.0)	808 (82.1)	398 (78.8)	
Previous BMT	283 (19.0)	176 (17.9)	107 (21.1)	
Diagnosis: no previous BMT, *n* (%)				—
ALL	558 (46.3)	402 (49.8)	156 (39.2)	
AML	11 (0.9)	8 (0.9)	3 (0.8)	
Lymphoma	85 (7.1)	47 (5.8)	38 (9.5)	
Sarcoma	181 (15)	106 (13.1)	75 (18.8)	
Neuroblastoma	45 (3.7)	32 (3.9)	13 (3.3)	
CNS	105 (8.7)	72 (8.9)	33 (8.3)	
Other (oncology)	116 (9.7)	92 (11.3)	24 (6.1)	
Other (nononcology)	105 (8.7)	49 (6.1)	56 (14.1)	
Diagnosis: previous BMT, *n* (%)				—
Malignancy	129 (45.6)	84 (47.8)	45 (42.1)	
Immunology	80 (28.3)	44 (25)	36 (33.6)	
Marrow failure	44 (15.6)	28 (15.9)	16 (14.9)	
Benign hematology	13 (4.6)	10 (5.7)	3 (2.8)	
Genetic	17 (6.1)	10 (5.7)	7 (6.5)	

TTA is in minutes from ED arrival. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; IQR, interquartile range; LOS length of stay; —, not enlightening due to small cell sizes.

[a] Percentages reflect the percentage of patients for whom ANC was measured: total (N = 1421), TTA ≤60 min (n = 942), TTA >60 min (n = 479).

had significantly higher odds of receiving subsequent inotropic support. Similarly, BMT patients exhibited higher odds of having 1 or more adverse events and experiencing a PICU admission. The adjusted models for the subpopulation of oncology patients showed no significant association with adverse events (Table 3).

Figure 2 summarizes the percentage of adverse events by TTA. Overall, it shows a nonlinear relationship in that the percentage of adverse events peaks at 90 to 105 minutes and then declines until TTA reaches ≥150 minutes, at which point it increases again.

DISCUSSION

We performed a retrospective analysis of FI patients at a pediatric ED presenting over 6.5 years to evaluate the effect of TTA on adverse events. This is the first pediatric study examining the relationship between TTA and adverse events in FI patients while attempting to adjust for severity of illness at presentation. We discovered that by adjusting for potential confounders and covariates, the association between TTA and adverse events was strengthened for BMT patients. This may be partly due to a larger representation in encounters with longer TTA of patients with lower-risk assessment (eg, decreased severity of illness at

TABLE 2 Adverse Events by TTA

Patient Encounters	All Encounters, *n* (%)	TTA ≤60 min, *n* (%)	TTA >60 min, *n* (%)
All (*N* = 1489)			
Aggregate adverse events[a,b]	169 (11.7)	102 (10.4)	67 (13.3)
Subsequent need for inotropic support	39 (2.6)	20 (2.0)	19 (3.8)
Creatinine increase of >50%[b]	62 (4.3)	36 (3.8)	26 (5.4)
PICU admission within 72 h	110 (7.4)	69 (7.0)	41 (8.1)
Mortality <30 d	10 (0.7)	5 (0.5)	5 (1.0)
Oncology (*n* = 1206)			
Aggregate adverse events[a]	131 (11.3)	82 (10.5)	49 (12.9)
Subsequent need for inotropic support	31 (2.6)	16 (2.0)	15 (3.8)
Creatinine increase	56 (4.8)	34 (4.4)	22 (5.8)
PICU admission within 72 h	80 (6.6)	53 (6.6)	27 (6.8)
Mortality	6 (0.5)	3 (0.4)	3 (0.8)
BMT (*n* = 283)			
Aggregate adverse events[a]	38 (13.7)	20 (11.6)	18 (17.1)
Subsequent need for inotropic support	8 (2.8)	4 (2.3)	4 (3.7)
Creatinine increase	6 (2.2)	2 (1.2)	4 (3.8)
PICU admission within 72 h	30 (10.1)	16 (9.1)	14 (13.1)
Mortality	4 (1.4)	2 (1.1)	2 (1.9)

TTA, is in minutes from ED arrival.
[a] Aggregate adverse events represent encounters with subsequent need for inotropic support, creatinine increase of >50%, PICU admission within 72 h, or mortality within 30 d.
[b] Percentages reflect the percentage of patients for whom creatinine was measured: total (*N* = 1440), TTA ≤60 min (*n* = 955), TTA >60 min (*n* = 485).

presentation), which could have resulted in decreased urgency of treatment. Furthermore, we found a positive relationship between TTA and subsequent need for inotropes when looking at all FI patient encounters. For the BMT subpopulation, TTA was positively associated with the need for PICU admission within 72 hours as well as with aggregate adverse events. Although our data did not demonstrate an association between TTA and outcomes in the oncology-patient population, multiple studies have demonstrated a significant time-dependent association with antibiotics and outcomes.[19,20]

TABLE 3 Odds Ratios for Patients Experiencing an Adverse Event

Patient Encounters	Unadjusted Odds Ratio (95% CI)	*P*	Adjusted[a] Odds Ratio (95% CI)	*P*
All (*N* = 1489)				
Aggregate adverse events[b]	1.34 (0.96–1.86)	.08	1.25 (0.83–1.86)	.28
Subsequent need for inotropic support	1.88 (1.00–3.56)	.05	2.17 (1.05–4.52)	.04
Creatinine increase	1.45 (0.86–2.43)	.16	0.90 (0.47–1.74)	.76
PICU admission with 72 h	1.17 (0.78–1.75)	.44	1.33 (0.83–2.13)	.24
Oncology (*n* = 1206)				
Aggregate adverse events[b]	1.26 (0.87–1.84)	.22	1.01 (0.64–1.61)	.96
Subsequent need for inotropic support	1.97 (0.96–4.02)	.06	1.91 (0.82–4.45)	.14
Creatinine increase	1.35 (0.78–2.35)	.28	0.84 (0.42–1.69)	.62
PICU admission within 72 h	1.05 (0.65–1.70)	.84	1.01 (0.57–1.79)	.98
BMT (*n* = 283)[c]				
Aggregate adverse events[b]	1.58 (0.80–3.15)	.19	2.76 (1.17–6.50)	.02
PICU admission within 72 h	1.51 (0.70–3.22)	.29	3.34 (1.34–8.36)	.01

Referent is receiving antibiotics within 60 min.
[a] Adjusted for severity, age, and timing of an institutional intervention to reduce TTA in the ED.
[b] Aggregate adverse events represent encounters with subsequent need for inotropic support, creatinine increase of >50%, PICU admission within 72 h, or mortality within 30 d.
[c] PICU admissions and creatinine increase were not modeled because of the small number of events for this population.

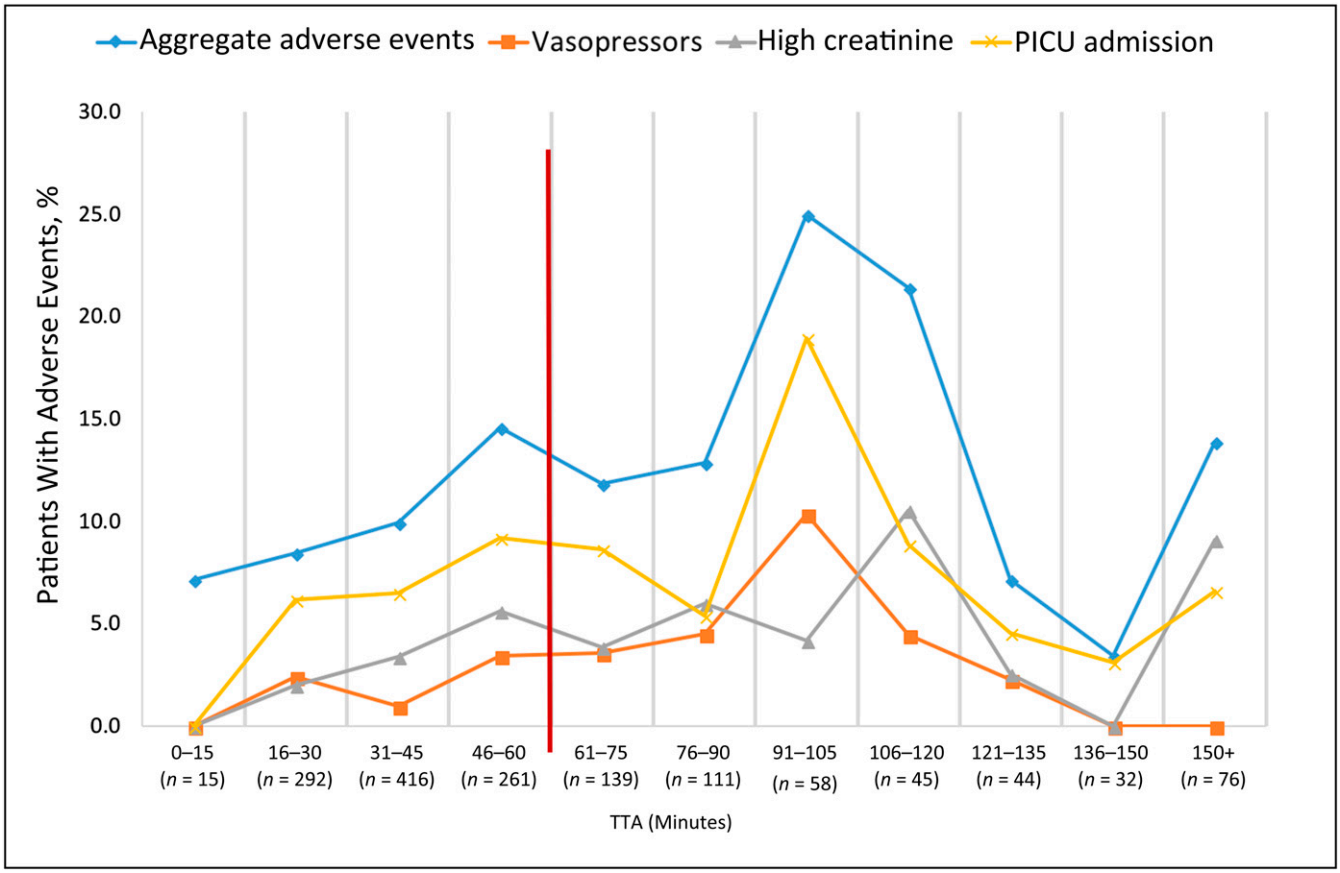

FIGURE 2 TTA 15-minute intervals and percentage of patients with an adverse event. Adverse events were defined as intensive care admission within 72 hours of ED arrival, acute kidney injury (50% increase in creatinine within 7 days of ED arrival), inotropic support after the first antibiotic administration, and all-cause mortality within 30 days of ED arrival.

Authors of multiple studies have aimed to decrease TTA in pediatric FI patients,[17,18,24,27–29] and hospitals dedicate considerable resources to the timely delivery of antibiotics. Validation of these efforts is important because the resources needed to adhere to the 1-hour TTA metric are considerable in terms of cost and manpower, having the potential to impact the timely care of other patients.[30] In 2016, we described our QI efforts in decreasing the TTA in patients presenting to the ED at our center.[24] Using the Model for Improvement,[26] we identified barriers to timely antibiotic delivery. We found that timely antibiotic success requires significant communication, resources, and leadership dedication to the process.[24] This study lends support to these efforts and suggests that 60 minutes as a TTA benchmark for subpopulations of pediatric FI patients is reasonable.

One limitation of this study was that there were several competing QI initiatives taking place in our ED at the same time, some of which were focused on TTA for other diseases. Other limitations include those inherent in this being a single-center, retrospective study. In determining the severity of illness, our analysis was dependent on accurate recording of the first set of vital signs, amount of fluid resuscitation, and timing of inotropes in relation to antibiotic administration. Additionally, although acute kidney injury remains an important outcome measure, we did not separate out the contribution of specific antibiotics to nephrotoxicity independent of the disease processes involved. Statistically, although we report *P* values along with the odds ratios, we did not take into account multiple comparisons and used .05 as a cutoff for statistical significance. Finally, the implementation of sepsis bundle elements described by Evans et al,[26] including timely antibiotic delivery and rapid intravenous fluid administration, was started during the time period of this analysis, which is difficult to adjust for in the analysis. Furthermore, the sepsis pathway was constantly being changed during the acquisition of this data set.

Although a prospective randomized controlled trial would not be feasible, well-designed prospective studies in which data collection (eg, vital signs, laboratory testing) is standardized and validated would be helpful to study the extent of the association between TTA and adverse events and further aid in determining which FI subpopulations are most likely to be adversely affected by antibiotic delays.

CONCLUSIONS

This large retrospective cohort study reveals that although the timely administration of antibiotics in a medically vulnerable population (in this study, specifically, BMT patients) may be beneficial, the same decrease in adverse events was not seen in the larger oncology population. Given the resources and time required to accomplish the goal of administering antibiotics within 60 minutes, hospital administrators might want to consider which populations would benefit most.

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REFERENCES

1. El-Bietar J, Nelson A, Wallace G, et al. RSV infection without ribavirin treatment in pediatric hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2016;51(10):1382–1384
2. Dandoy CE, Ardura MI, Papanicolaou GA, Auletta JJ. Bacterial bloodstream infections in the allogeneic hematopoietic cell transplant patient: new considerations for a persistent nemesis. *Bone Marrow Transplant*. 2017; 52(8):1091–1106
3. Brückmann C, Lindner W, Roos R, et al. Severe pulmonary vascular occlusive disease following bone marrow transplantation in Omenn syndrome. *Eur J Pediatr*. 1991;150(4):242–245
4. Cecinati V, Brescia L, Tagliaferri L, Giordano P, Esposito S. Catheter-related infections in pediatric patients with cancer. *Eur J Clin Microbiol Infect Dis*. 2012;31(11):2869–2877
5. Wilson MZ, Rafferty C, Deeter D, Comito MA, Hollenbeak CS. Attributable costs of central line-associated bloodstream infections in a pediatric hematology/ oncology population. *Am J Infect Control*. 2014;42(11):1157–1160
6. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589–1596
7. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. *Arch Intern Med*. 2002; 162(6):682–688
8. Køster-Rasmussen R, Korshin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. *J Infect*. 2008;57(6):449–454
9. Hamandi B, Holbrook AM, Humar A, et al. Delay of adequate empiric antibiotic therapy is associated with increased mortality among solid-organ transplant patients. *Am J Transplant*. 2009;9(7): 1657–1665
10. Lynn JJ, Chen KF, Weng YM, Chiu TF. Risk factors associated with complications in patients with chemotherapy-induced febrile neutropenia in emergency department. *Hematol Oncol*. 2013;31(4): 189–196
11. Rosa RG, Goldani LZ. Cohort study of the impact of time to antibiotic administration on mortality in patients with febrile neutropenia. *Antimicrob Agents Chemother*. 2014;58(7):3799–3803
12. Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1): 296–327
13. Rolston KV. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. *Clin Infect Dis*. 2005;40(suppl 4):S246–S252
14. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2013; 31(6):794–810
15. Freifeld AG, Bow EJ, Sepkowitz KA, et al; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52(4):e56–e93
16. Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. *J Clin Oncol*. 2017;35(18):2082–2094
17. Yoshida H, Leger KJ, Xu M, et al. Improving time to antibiotics for pediatric oncology patients with suspected infections: an emergency department-based quality improvement intervention. *Pediatr Emerg Care*. 2018; 34(1):47–52
18. Daniels P, Pate A, Flesch L, et al. Improving time to antibiotic administration for bone marrow transplant patients with first fever. *Pediatrics*. 2018;141(1):e20171549
19. Fletcher M, Hodgkiss H, Zhang S, et al. Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer. *Pediatr Blood Cancer*. 2013;60(8): 1299–1306
20. Salstrom JL, Coughlin RL, Pool K, et al. Pediatric patients who receive antibiotics for fever and neutropenia in less than 60 min have decreased

intensive care needs. *Pediatr Blood Cancer*. 2015;62(5):807–815

21. Perron T, Emara M, Ahmed S. Time to antibiotics and outcomes in cancer patients with febrile neutropenia. *BMC Health Serv Res*. 2014;14:162
22. Ko BS, Ahn S, Lee YS, Kim WY, Lim KS, Lee JL. Impact of time to antibiotics on outcomes of chemotherapy-induced febrile neutropenia. *Support Care Cancer*. 2015;23(9):2799–2804
23. Szwajcer D, Czaykowski P, Turner D. Assessment and management of febrile neutropenia in emergency departments within a regional health authority-a benchmark analysis. *Curr Oncol*. 2011;18(6):280–284
24. Dandoy CE, Hariharan S, Weiss B, et al. Sustained reductions in time to antibiotic delivery in febrile immunocompromised children: results of a quality improvement collaborative. *BMJ Qual Saf*. 2016;25(2):100–109
25. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2–8
26. Evans IVR, Phillips GS, Alpern ER, et al. Association between the New York sepsis care mandate and in-hospital mortality for pediatric sepsis. *JAMA*. 2018;320(4):358–367
27. Volpe D, Harrison S, Damian F, et al. Improving timeliness of antibiotic delivery for patients with fever and suspected neutropenia in a pediatric emergency department. *Pediatrics*. 2012;130(1):e201–210
28. Cohen C, King A, Lin CP, et al. Protocol for reducing time to antibiotics in pediatric patients presenting to an emergency department with fever and neutropenia: efficacy and barriers. *Pediatr Emerg Care*. 2016;32(11):739–745
29. McCavit TL, Winick N. Time-to-antibiotic administration as a quality of care measure in children with febrile neutropenia: a survey of pediatric oncology centers. *Pediatr Blood Cancer*. 2012;58(2):303–305
30. Michelson KA, Bachur RG, Levy JA. The impact of critically ill children on paediatric ED medication timeliness. *Emerg Med J*. 2017;34(1):8–12

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