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Prompt Administration of Antibiotics Is Associated With Improved Outcomes in Febrile Neutropenia in Children With Cancer

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Background. Time-to-antibiotic (TTA) administration is a widely used quality-of-care measure for children with cancer and febrile neutropenia (FN). We sought to determine whether TTA is associated with outcomes of FN. ***Procedure.*** A single-center, retrospective cohort study was conducted of 1,628 FN admissions from 653 patients from 2001 to 2009. Outcome variables included (1) an adverse event (AE) composite of in-hospital mortality, pediatric intensive care unit (PICU) admission within 24 hours of presentation, and/or fluid resuscitation ≥40 ml/kg within 24 hours of presentation and (2) length of stay (LOS). TTA was measured as a continuous variable and in 60-minute intervals. Mixed regression models were constructed to evaluate associations of TTA with the outcome variables after adjusting for relevant covariates including cancer diagnosis, degree of myelosuppression, and presence of bacteremia. ***Results.*** The composite AE outcome occurred in 11.1% of admissions including 0.7% in-hospital mortality, 4.7% PICU admission, and 10.1% fluid resuscitation. In univariate analysis, TTA was associated with the composite AE outcome (Odds Ratio [OR] 1.29, 95% CI 1.02–1.64) but not LOS. In multivariate analysis, after adjustment for relevant covariates, 60-minute TTA intervals were associated with the composite AE outcome (61–120 minutes vs. ≤60 minutes, OR 1.81, 95% CI 1.01–3.26). Unexpectedly, admission from the emergency department (ED) was also independently associated with the composite AE outcome (ED vs. clinic, OR 3.15, 95% CI 1.95–5.09). ***Conclusions.*** TTA and presentation to the ED are independently associated with poor outcomes of FN. Pediatr Blood Cancer 2013;60:1299–1306.

Key words: febrile neutropenia; prevalence; quality-of-care; time-to-antibiotics

INTRODUCTION

Febrile neutropenia (FN) is a major source of morbidity and mortality among pediatric patients with cancer. The prompt administration of empiric parenteral antibiotics is a mainstay in the initial treatment of FN [1]. Recent studies have investigated outpatient treatment with parenteral or oral antibiotics in certain low-risk populations [2], but inpatient management with broad spectrum parenteral antibiotics remains standard care for FN [3]. The Infectious Disease Society of America guidelines for the treatment of FN recommend prompt administration of antibiotics but do not specify a time within which antibiotics should be administered [4,5]. Justification for the prompt administration of antibiotics includes the potential for rapid progression of infection and the inability to distinguish those with and without serious infection at the time of initial evaluation.

The promptness of initial antibiotic administration, or time-to-antibiotics (TTA), has been proposed as a quality-of-care (QOC) measure for other infectious diseases. TTA explicitly measures a care process rather than an outcome; however, the appeal of TTA as a QOC measure is that prolonged TTA is independently associated with the outcomes of increased mortality and length of stay (LOS) in conditions like bacterial meningitis [6,7], septic shock [8–10], and fever in solid organ transplant patients [11]. Additionally, TTA has been endorsed as a QOC measure in adults with community acquired pneumonia (CAP), although this remains controversial [12–14].

No published reports have evaluated the potential association of TTA with poor outcomes in pediatric patients with FN. Nevertheless, at the 23rd Annual Meeting of the American Society of Pediatric Hematology-Oncology in April 2010, a symposium on QOC included a session detailing the use of TTA as a QOC measure for pediatric oncology patients with FN. Subsequently, a research survey of Children's Oncology Group centers in North America revealed that 45% actively utilize TTA as a QOC measure [15]. Additionally, beginning in 2010, the US News and World Report has collected TTA from pediatric cancer centers along with other data used to rank centers. Three previously published reports describe quality improvement initiatives designed to decrease TTA in pediatric patients with FN. Underlying these reports is the unstated assumption that decreased TTA is associated with improved outcomes of pediatric patients with FN [16–18]. Therefore, we sought to test this assumption and determine whether TTA is associated with outcomes of FN in the setting of pediatric cancer. We hypothesized that prolonged TTA would be associated with poor outcomes in FN.

METHODS

Study Design

We conducted a retrospective cohort study of FN admissions to Children's Medical Center Dallas (CMCD) between 2001 and 2009. TTA has been prospectively collected for all FN patients

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since 2001 by members of the Performance Improvement (PI) committee of the Center for Cancer and Blood Disorders at CMCD. For this study, we retrospectively collected clinical and outcome data. The Institutional Review Board of the University of Texas Southwestern Medical Center approved this retrospective study and waived the requirement for informed consent.

Subject Identification

A single nurse from the PI committee at CMCD has been responsible for prospectively identifying and collecting TTA for all FN admissions since 2001 using the case definition of (1) new fever by history or documented as $\geq$38.5 or 38.0–38.4°C on two occasions 1 hour apart; (2) absolute neutrophil count (ANC) $<500/mm^3$; and (3) diagnosis of cancer or other neutropenic conditions. Due to concerns that the PI committee nurse may have missed some FN admissions, a second identification technique was utilized. Administrative records from CMCD were queried using a previously published technique for identification of FN in administrative data (Supplemental Appendix 1) [19,20]. FN cases identified by query of the administrative records were subsequently collated with the PI committee records. To this final list of patients, the eligibility criteria were applied (Fig. 1) to create the final cohort. Inclusion criteria were (1) new episode of fever (as defined above); (2) severe neutropenia, defined as ANC $<500/mm^3$; and (3) current treatment for cancer at our institution. Exclusion criteria included (1) history of hematopoietic stem cell transplantation (HSCT), (2) initial presentation to a facility other than CMCD, (3) onset of fever or neutropenia after initial presentation, and (4) severe sepsis on initial presentation, defined as FN and systolic hypotension (<5th percentile for age) on first blood pressure measurement [21,22]. Patients with a history of HSCT were excluded because new fever is usually treated more aggressively in HSCT patients and they frequently receive prophylactic antimicrobials. HSCT patients thus represent an important but distinct patient population. Patients with severe sepsis at presentation were excluded because in this very small subset of patients (<1%), the outcome variable would have occurred independent of the primary predictor variable (i.e., they would go to the intensive care unit [ICU] or receive $\geq$40 ml/kg of fluid resuscitation independent of the time needed to administer antibiotics).

Outcome Variables

Death is a rare event in pediatric patients with FN [23], so we created a composite primary adverse event (AE) outcome including in-hospital mortality and/or its antecedents: admission to the pediatric intensive care unit (PICU) within 24 hours of presentation and/or receipt of $\geq$40 ml/kg of fluid resuscitation within 24 hours of presentation. Fluid resuscitation was defined as normal saline (0.9% NS), Lactated Ringer's solution (Baxter Healthcare, Deerfield, IL), Normosol® solution (Hospira, Lake Forest, IL), or 5% albumin solution administered over 1 hour or less in a volume of $\geq$10 ml/kg or of 1 L in patients weighing over 100 kg. LOS was also used as a primary outcome. The individual components of the composite AE outcome were also analyzed as secondary outcomes.

Predictor Variable

TTA was defined as the time in minutes from presentation to either triage (emergency department [ED]), registration (outpatient clinic), or admitting (direct admission) to the first dose of parenteral antibiotics. TTA was analyzed in intervals varying from 30 to 180 minutes to identify the most appropriate interval for use in subsequent analyses (Supplemental Table I). In these analyses, 60-minute intervals were identified as most strongly associated with the primary outcome and were utilized in all subsequent analyses. TTA was also analyzed as a continuous variable.

Covariates

Relevant covariates were collected including patient age (analyzed as both a continuous variable in months and as a categorical variable including (1) $\leq$12 months, (2) 13–84 months, (3) 85–156 months, and (4) >156 months); gender; diagnosis; temperature; bacteremia; viral infection; initial labs including total white blood cell (WBC) count, ANC, platelet count, and serum creatinine; initial empiric antibiotic(s); presentation location (ED, clinic, or inpatient ward); weekend admission; and year of admission (Supplemental Appendix 2). Because we were unable to control for the duration of fever prior to presentation, we included the distance from the patient's home address to the hospital as a proxy for fever duration.

Study Procedures

All data were manually extracted from the electronic medical record and entered directly into a relational database. The primary predictive variable and all outcome variables were extracted exclusively by the first author or the primary investigator (PI). Accuracy of data extraction for all investigators was evaluated by the PI in a random sample of 20 hospitalizations per extractor in which an accuracy of 98.8% was observed. Additionally, at study completion, the data were examined for extreme or missing values by the PI, and where possible, inconsistencies in static variables (e.g., gender, diagnosis) within individual subjects with multiple hospitalizations were identified.

Analyses

Summary statistics were used to describe the cohort. Univariate mixed regression models (logistic for composite AE outcome and linear for LOS) were utilized to test for association between the predictor and outcome variables. Variables which were statistically significant in the univariate regression models were subsequently evaluated in a multivariate mixed model (logistic for the composite AE outcome and linear for LOS). The final multivariate model was determined using step-wise variable selection in addition to clinical consideration. The mixed models include patient random effects to account for multiple FN admissions from the same patient. A secondary analysis of PICU admission alone as the outcome variable was performed using mixed logistic regression. Additionally, exploratory comparisons of presentation location were performed using Kruskal–Wallis test for continuous variables and χ^2 tests for categorical variables. TTA and total WBC count were log-transformed prior to use in statistical models. Similarly, LOS was transformed by square root prior to statistical modeling. All analyses were performed using SAS 9.2 (SAS Institute, Gary, NC).

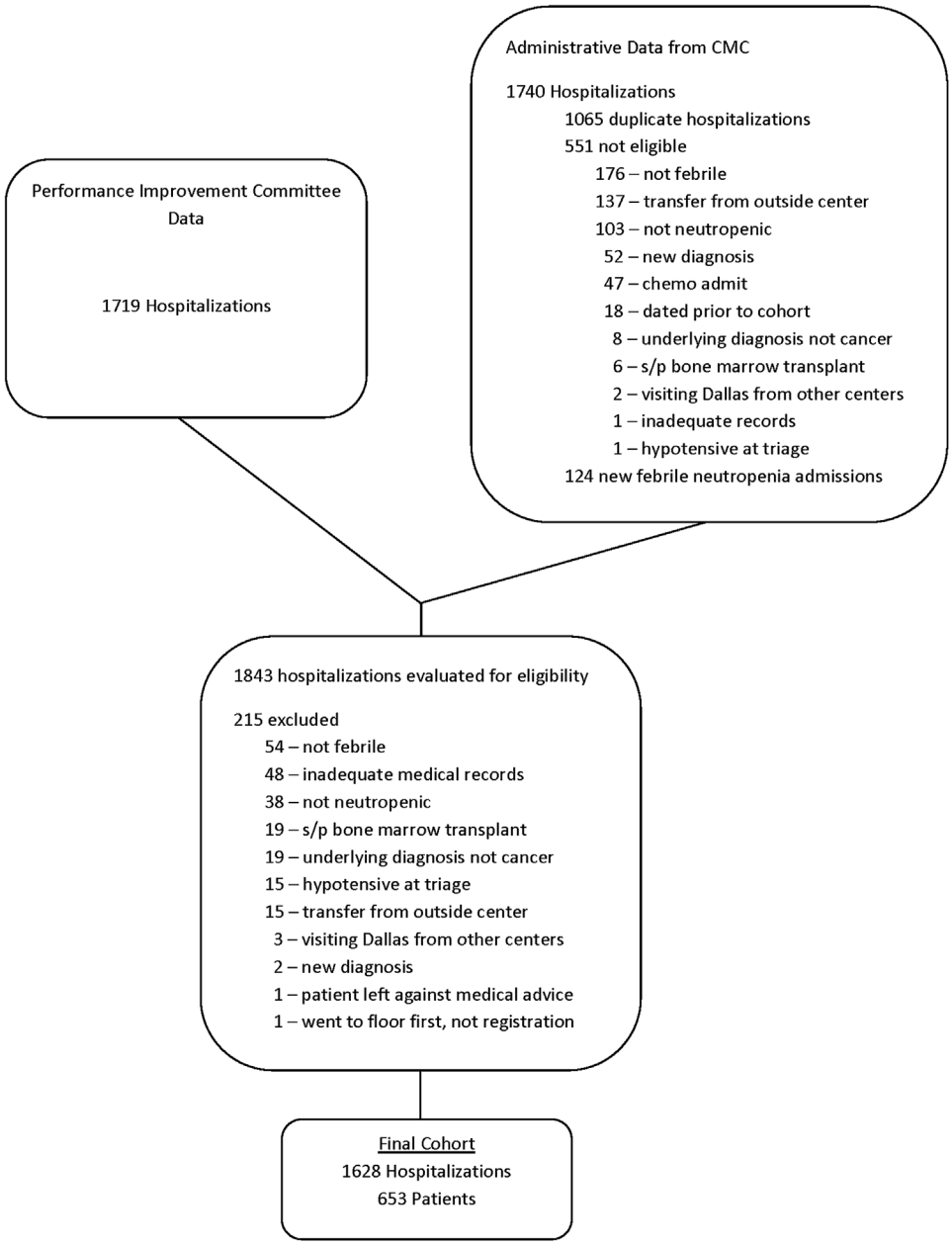

Fig. 1. Cohort identification. Performance Improvement committee hospitalizations were collected prospectively. Administrative records from Children's Medical Center Dallas were reviewed to ensure cohort completeness.

RESULTS

The cohort included 1,628 FN hospitalizations from 653 unique patients. Clinical characteristics of the patients and their hospitalizations are presented in Tables I and II. Notably, nearly half of hospitalizations occurred in patients with acute lymphoblastic leukemia (ALL). The emergency room was the most common presentation location accounting for 54.4% of hospitalizations. Additionally, the median neutrophil count and platelet count revealed profound myelosuppression. Bacteremia occurred in 12.1% of hospitalizations, and viral infections were documented in 8.4% of hospitalizations. Both bacteremia and viral infection were observed in 1.5% of hospitalizations.

Composite AE Outcome

The composite AE outcome occurred in 11.1% of admissions with in-hospital mortality occurring in 0.7%, PICU admission occurring in 4.7%, and fluid resuscitation $\geq$40 ml/kg occurring in 10.1%. Of the patients who died or were admitted to the PICU, 91% had fluid resuscitation $\geq$40 ml/kg. In univariate analyses (Tables I and II), admissions with the composite AE outcome

TABLE I. Categorical Predictor Variables—Descriptive Analysis and Univariate Analysis With the Composite AE Outcome

Categorical variables	% of all hospitalizations (N = 1,628)	% with composite AE outcome (composite occurred in 11.1% of total)	OR	95% CI	*P*
Primary predictor					
TTA 60-minute intervals (minutes)					
≤60	20.0	5.2	(Ref)	(Ref)	(Ref)
61–120	32.9	14.2	2.88	1.70–4.89	<0.001
121–180	25.6	12.7	2.56	1.51–4.35	<0.001
>181	21.5	10.0	2.00	1.10–3.62	0.02
Covariates					
Gender					
Male	51.2	11.4	(Ref)	(Ref)	(Ref)
Female	48.8	10.8	0.94	0.68–1.31	0.73
Oncology diagnosis					
ALL not in induction or DI	12.2	6.7	(Ref)	(Ref)	(Ref)
ALL in induction or DI	26.5	12.1	1.88	1.07–3.31	0.03
Very high risk or relapsed ALL	10.4	14.2	2.33	1.30–4.19	0.005
AML	7.5	23.0	4.11	2.33–7.24	<0.001
Sarcoma	15.0	11.9	1.83	1.07–3.13	0.03
CNS tumor	11.1	11.1	1.66	0.89–3.12	0.11
Non-Hodgkin's lymphoma	7.9	9.4	1.42	0.62–3.26	0.40
Neuroblastoma	3.0	10.2	1.55	0.61–3.92	0.35
Other	6.5	9.4	1.38	0.60–3.16	0.45
Presentation location					
Clinic	30.3	6.5	(Ref)	(Ref)	(Ref)
Emergency department (ED)	54.4	15.7	2.66	1.74–4.09	<0.001
Inpatient unit	15.4	4.0	0.62	0.25–1.49	0.28
Weekend presentation					
Weekday presentation	65.6	9.5	(Ref)	(Ref)	(Ref)
Weekend presentation	34.4	14.3	1.59	1.16–2.19	0.004
Initial empiric antibiotics					
Monotherapy—third-generation cephalosporin	26.1	14.6	(Ref)	(Ref)	(Ref)
Other monotherapy	6.5	9.5	0.56	0.28–1.12	0.10
Dual-therapy—anti-PSDMN, AG	14.4	5.1	0.70	0.49–1.01	0.05
Triple-therapy—anti-PSDMN, AG, Anti-GP	48.5	10.5	0.31	0.16–0.62	0.001
Other combination therapy	4.6	18.9	1.39	0.76–2.58	0.28
Bacteremia					
Without bacteremia	87.9	8.3	(Ref)	(Ref)	(Ref)
With bacteremia	12.1	32.0	5.15	3.51–7.57	<0.001
Viral infection					
Without viral infection	91.6	10.4	(Ref)	(Ref)	(Ref)
With viral infection	8.4	19.0	2.05	1.30–3.23	0.002
Year of admission					
2001–2003	27.1	7.0	(Ref)	(Ref)	(Ref)
2004–2006	32.8	8.4	1.26	0.78–2.04	0.341
2007–2009	40.1	16.1	2.62	1.72–4.01	<0.001

AE, adverse event; ALL, acute lymphoblastic leukemia; DI, delayed intesnification; AML, acute myelogenous leukemia; CNS, central nervous system; TTA, time to antibiotics; Anti-PSDMN, anti-pseudomonal agent; AG, aminoglycoside; Anti-GP, anti-gram-positive agent.

had a higher median TTA at 119 minutes compared to 113 minutes in the group without the composite AE outcome (Log TTA, Odds Ratio [OR] 1.29 [95% Confidence Interval, CI, 1.02–1.64], $P = 0.03$). We analyzed TTA intervals from 30 to 180 minutes (Supplemental Table I) and identified 60-minute intervals (TTA60) as most strongly associated with the composite AE outcome (61–120 minutes vs. ≤60 minutes; OR 2.88, [95%CI 1.70–4.89], $P < 0.001$).

In multivariate analysis (Table III), TTA was not associated with the composite AE outcome when analyzed as a continuous variable (OR 0.89, 95% CI 0.65–1.24); however, 60-minute TTA intervals were independently associated with increasing likelihood of the composite AE outcome (61–120 minutes vs. ≤60 minutes; OR 1.81 [95% CI 1.01–3.26], $P = 0.048$). Bacteremia, the diagnosis of acute myelogenous leukemia (AML), presentation to the ED, decreasing total WBC count, increasing initial creatinine, and later year of admission were also associated with the composite AE outcome.

In an analysis of a secondary outcome, TTA and TTA60 intervals were not associated with PICU admission

TABLE II. Continuous Predictor Variables—Descriptive Analysis and Univariate Analysis With the Composite AE Outcome

Continuous variables	All hospitalizations (N = 1,628)	With composite AE outcome (N = 181)	Without composite AE outcome (N = 1,447)	OR	95% CI	*P*
Time to antibiotics[a] (minutes), median (intra-quartile range [IQR])	114 (71, 167)	119 (86, 165)	113 (66, 168)	1.29	1.02–1.64	0.03
Age (months), median (IQR)	80 (42, 142)	103 (42, 162)	78 (42, 139)	1.004	1.001–1.006	0.008
Distance from home to hospital (miles), median (IQR)	19 (13, 33)	19 (12, 32)	19 (14, 35)	1.03	0.85–1.25	0.74
Initial temperature (°C), median (IQR)	38 (37.3, 38.6)	38.2 (37.5, 39)	38 (37.3, 38.5)	1.49	1.24–1.79	<0.001
Initial total WBC[a] ($\times 10^3$/mm^3), median (IQR)	0.5 (0.2, 1)	0.3 (0.1, 0.7)	0.6 (0.3, 1)	0.60	0.50–0.72	<0.001
Initial ANC (/mm^3), median (IQR)	32 (0, 137)	14 (0, 81)	34 (1, 144)	0.998	0.996–0.999	0.02
Initial platelets ($\times 10^3$/mm^3), median (IQR)	44 (16, 112)	22 (8, 52)	50 (17, 120)	0.993	0.989–0.996	<0.001
Initial creatinine, (serum, mg/dl), median (IQR)	0.4 (0.3, 0.6)	0.5 (0.4, 0.7)	0.4 (0.3, 0.6)	4.76	2.12–10.71	<0.001

AE, adverse event; WBC, white blood cell; ANC, absolute neutrophil count. [a]Time-to-antibiotics and initial total white blood cell count were log-transformed.

(Supplemental Table II). Predictors of PICU admission included bacteremia, diagnosis of AML, presentation to the ED, decreasing total WBC count, and increasing initial creatinine. Within TTA60 intervals, the relative proportion of PICU admission and composite AE outcome were similar (Supplemental Table III).

Length of Stay

The median LOS was 4 days with an intraquartile range of 2–7 days and a maximum LOS of 267 days. TTA was not associated with LOS in univariate analysis (β coefficient = −0.09 [95% CI −0.19, 0.01], $P = 0.07$). TTA60 intervals were also not associated with LOS in univariate analysis (Supplemental Table IV). In a multivariate analysis of LOS (Table IV), age ≤12 months, diagnosis of ALL in induction or delayed intensification (DI), diagnosis of AML, decreasing total WBC count, bacteremia, and later year of admission were associated with increased LOS. The diagnoses of sarcoma, CNS tumor, and neuroblastoma were associated with decreased LOS.

Presentation to the ED

We further explored the unexpected independent association between presentation to the ED and the occurrence of the composite AE outcome. We compared the presenting features of patients presenting to clinic, ED, and inpatient ward (Table V). No differences in presenting features including age, high-risk oncology diagnosis (AML or ALL in induction or DI), bacteremia, viral infection, initial creatinine, ANC, or platelets were identified to explain the difference in composite AE outcome. The difference in temperature between groups was statistically significant but is likely attributable to the decreased temperature observed in patients presenting for direct admission and seems unlikely to fully explain the difference in outcomes between admission sources.

TABLE III. Multivariate Analysis of Composite AE Outcome*

Predictor variable	OR	95% CI	*P*
Primary predictor			
TTA 60-minute intervals (referent = ≤ 60 minutes)			
61–120 minutes	1.81	1.01 to 3.26	0.048
121–180 minutes	1.44	0.77 to 2.71	0.26
>181 minutes	1.16	0.59 to 2.27	0.67
Covariates			
Bacteremia	3.99	2.51 to 6.34	<0.001
Initial creatinine	3.56	1.56 to 8.13	0.004
Presentation location (referent = clinic)			
Emergency department (ED)	3.15	1.95 to 5.09	<0.001
Inpatient unit	0.73	0.29 to 1.83	0.50
Oncology diagnosis (referent = ALL not in induction or DI)			
AML	2.27	1.22 to 4.24	0.01
Year of admission (referent = 2001–2003)			
2004–2006	0.91	0.54 to 1.52	0.72
2007–2009	2.00	1.27 to 3.13	0.002
Initial total WBC[a]	0.76	0.62 to 0.94	0.01

AE, adverse event; ALL, acute lymphoblastic leukemia; DI, delayed intensification; AML, acute myelogenous leukemia; WBC, white blood cell; TTA, time to antibiotics. *Composite AE outcome = in-hospital mortality, PICU admission within 24 hourrs of presentation, or fluid resuscitation ≥40 ml/kg within 24 hours of presentation. [a]Initial total white blood cell count was log-transformed.

TABLE IV. Multivariate Analysis of Length of Stay*

Predictor variable	β coefficient	95% CI	*P*
Primary predictor			
TTA60 intervals (referent = ≤60 minutes)			
61–120 minutes	0.06	−0.10 to 0.22	0.44
121–180 minutes	−0.04	−0.17 to 0.10	0.55
>181 minutes	0.07	−0.10 to 0.23	0.43
Covariates			
Bacteremia	0.80	0.58 to 1.03	<0.001
Oncology diagnosis (referent = ALL not in induction or DI)			
ALL in induction or DI	0.61	0.37 to 0.85	<0.001
AML	1.10	0.82 to 1.37	<0.001
Sarcoma	−0.39	−0.55 to −0.24	<0.001
CNS tumor	−0.20	−0.35 to −0.04	0.01
Neuroblastoma	−0.33	−0.52 to −0.14	<0.001
Year of admission (referent = 2001–2003)			
2004–2006	0.15	0.01 to 0.30	0.04
2007–2009	0.22	0.08 to 0.35	0.001
Initial total WBC[a]	−0.21	−0.28 to −0.14	<0.001
Age (referent = 13–84 months)			
≤12 months	0.47	0.09 to 0.85	0.02
85–156 months	−0.02	−0.14 to 0.11	0.81
>156 months	0.13	−0.06 to 0.32	0.18

ALL, acute lymphoblastic leukemia; DI, delayed intensification; AML, acute myelogenous leukemia; CNS, central nervous system; WBC, white blood cell; TTA, time to antibiotics. *Length of stay in days was tranformed by square root. [a]Initial total white blood cell count was log-transformed.

DISCUSSION

In a large cohort of children with cancer and FN, we found that TTA is independently associated the composite AE outcome of in-hospital mortality, PICU admission within 24 hours of presentation, or fluid resuscitation ≥40 ml/kg within 24 hours of presentation but not LOS. We also identified the expected risk factors for poor outcome of FN including underlying oncologic diagnosis, degree of myelosuppression as reflected in the total WBC count, the presence of bacteremia, and initial serum creatinine. Additionally, we found an unexpected, independent association of presentation location (ED vs. clinic) with the composite AE outcome. Finally, independent predictors of increased LOS included the presence of bacteremia, underlying oncologic diagnosis, patient age, degree of myelosuppression, and year of admission.

No published reports have examined the relationship between TTA and outcomes in pediatric patients with FN. In a small study (N = 68) of adult oncology patients, prolonged TTA was not associated with increased mortality or LOS [24]; however, among adult cancer patients admitted to the ICU, prolonged TTA (>2 hours) was associated with mortality [25]. Similarly, among

TABLE V. Exploratory Analysis of Presentation Location

	Presentation location			
Variable	ED (N = 886)	Inpatient unit (N = 251)	Clinic (N = 491)	*P*
Composite AE outcome (%)	15.7	4	6.5	<0.0001
Time to antibiotics (TTA, minutes), median	145	60	93	<0.0001
Age, months, median	75	85	82	0.51
Oncology diagnosis (%)				0.06
AML	6.6	11.6	7.1	
ALL in induction or DI	10.5	14.4	14.2	
Bacteremia (%)	11.8	11.2	13.2	0.66
Viral infection (%)	8.7	5.2	9.5	0.12
Temperature on presentation (°C), median	38.0	37.8	38.0	<0.0001
Initial creatinine (mg/dl), median	0.4	0.4	0.5	0.46
Initial ANC (/mm^3), median	30	26	36	0.15
Initial platelets ($\times 10^3$/mm^3), median	44	39	46	0.43

AE, adverse event; ED, emergency department; ALL, acute lymphoblastic leukemia; DI, delayed intensification; AML, acute myelogenous leukemia.

adult FN patients with septic shock, prolonged time-to-effective antibiotics (over 24 hours) was associated with mortality [26]. In patients with bacteremia, time-to-effective antibiotics measures the time from presentation to delivery of antibiotics which provide coverage against the isolated organism after accounting for susceptibilities. An analysis of time-to-effective antibiotics from this cohort will be reported separately. When TTA has been associated with outcomes in other infectious diseases, the cutpoints which have been analyzed include 3 hours [27] and 6 hours [7,28] in bacterial meningitis, 4 hours [13] and 8 hours [12,14] in CAP, 3 hours [11] in solid organ transplant patients, and 1 hour in septic shock [9,10]. In this study, the identification of 1 hour for TTA as predictive of outcome in children with FN is consistent with previous literature for adults with sepsis and is not surprising given the frequent occurrence of septic shock in the FN population [10]. Importantly, in a recent survey, of the 45% of pediatric cancer centers that track TTA, over 90% reported using either 30 or 60 minutes as their cutpoint [15], so many pediatric oncology centers are well positioned to intervene and improve TTA.

Several QOC implications are apparent from this study. In considering TTA for pediatric patients with FN within Donabedian's QOC model of structure-process-outcome [29], TTA is a process measure. The validity of TTA as a process measure for FN is grounded in its focus on the quality domains of efficiency, timeliness, and patient centeredness [30]. The association of TTA with outcomes of FN suggests that TTA also reflects the safety and effectiveness domains of QOC. The association of TTA with outcomes of FN in this study greatly strengthens the appeal of TTA as a QOC measure and helps justify the use of TTA for the purpose of comparing and ranking pediatric cancer centers. As a result, pediatric cancer centers will be further compelled to track TTA and to implement process improvement techniques to ensure the timely delivery of antibiotics to children with FN.

The lack of dose effect of TTA on FN outcomes is intriguing. The distribution of relevant clinical attributes (e.g., high-risk diagnosis, bacteremia) was skewed toward the earliest TTA intervals (0–60 and 61–120 minutes). The over-representation of low risk attributes in patients in the later TTA intervals (121–180 and $>$180 minutes) likely explains the lack of TTA dose effect. Therefore, we hypothesize that, within pediatric patients with FN, three distinct patient populations may exist: (1) those who present with severe sepsis and are very likely to have poor outcomes in spite of prompt antibiotic administration, (2) those who present with ''mild'' FN in whom TTA will not influence the likelihood of poor outcome because that likelihood is so low, and (3) those who present with FN and other risk factors for poor outcome in whom TTA may meaningfully contribute to outcome. This study intentionally excluded the group of patients who presented with severe sepsis prior to receiving antibiotics. We considered using the recently published risk prediction score for children with FN in our cohort [31], but it was not feasible for us to retrospectively collect all of the necessary data elements. Therefore it will be important both to confirm our finding in other patient cohorts and to evaluate whether risk prediction will be able to further refine the role of TTA in pediatric patients with FN. Furthermore, prospective studies are needed to examine the impact on outcomes for interventions aimed at decreasing TTA.

The finding that presentation to the ED increases the risk of poor outcome may be attributable to increasingly high patient volumes in the ED setting [32], experience of personnel, unmeasured differences between patients presenting to the ED (vs. clinic), or other factors. Importantly, during working hours at our institution, all potential FN patients with new fever are directed to the oncology outpatient clinic regardless of disease severity (unless a ''true medical emergency'' is identified by phone triage.) Similarly, during nights and weekends, potential FN patients with known or likely neutropenia are preferentially directly admitted to the inpatient oncology unit pending bed availability. Therefore, no system bias can be identified that would send the sickest FN patients to the ED, and our analysis shows no apparent differences in the measured clinical features of patients in the ED compared to other care settings. This finding needs to be evaluated in other centers before concluding that presentation to the ED is truly a risk factor for adverse outcomes in FN.

Limitations of this study include those inherent to its single-center, retrospective design particularly selection bias and information bias. During the prolonged study timeframe, treatment protocols for many cancers may have changed which we did not account for other than including the year of admission. We were also unable to account for the duration of fever/illness at home though we included a measure of the distance of the patient's home address from the hospital as a proxy. Additionally, we did not collect physiologic data (heart rate and blood pressure), which may have furthered our understanding of the poor outcome of children admitted from the ED, nor did we account for any prophylactic antibiotics with which patients may have been treated. Finally, we did not attempt to account for baseline level of illness, existing comorbidities, or for sources of infection other than bacteremia and viral infection (e.g., pneumonia).

In conclusion, this report describes novel, independent associations of TTA and presentation to the ED with poor outcome in a large cohort of pediatric patients with FN. Subsequent investigation should evaluate TTA prospectively in other FN patients, identify risk factors for prolonged FN, and establish interventions that reduce TTA. Most pediatric cancer centers that routinely measure TTA in their patients use a 60-minute benchmark [15], and based on our findings, we propose 60 minutes as the TTA benchmark for pediatric patients with FN (vs. 30 minutes or other). Moreover, our findings should compel a concerted effort by all pediatric cancer centers and associated ED's to both measure TTA and to intervene when TTA is prolonged.

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REFERENCES

1. Pizzo PA, Poplack DG. Principles and practice of pediatric oncology. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010, 1531 pp.
2. Rolston KV. New trends in patient management: Risk-based therapy for febrile patients with neutropenia. Clin Infect Dis 1999;29:515–521.
3. Picazo JJ. Management of the febrile neutropenic patient: A consensus conference. Clin Infect Dis 2004;39:S1–S6.
4. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730–751.

5. Freifeld AG, Bow EJ, Sepkowitz KA, et al. 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:e56–e93.
6. Lepur D, Barsic B. Community-acquired bacterial meningitis in adults: Antibiotic timing in disease course and outcome. Infection 2007;35:225–231.
7. Proulx N, Frechette D, Toye B, et al. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM 2005;98:291–298.
8. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–1377.
9. 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;34:1589–1596.
10. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296–327.
11. 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;9:1657–1665.
12. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. JAMA 1997;278:2080–2084.
13. Houck PM, Bratzler DW, Nsa W, et al. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 2004;164:637–644.
14. 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;162:682–688.
15. 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;58:303–305.
16. Corey AL, Snyder S. Antibiotics in 30 minutes or less for febrile neutropenic patients: A quality control measure in a new hospital. J Pediatr Oncol Nurs 2008;25:208–212.
17. Amado VM, Vilela GP, Queiroz A, Jr, et al. Effect of a quality improvement intervention to decrease delays in antibiotic delivery in pediatric febrile neutropenia: A pilot study. J Crit Care 2011;26:e9–e12.
18. Burry E, Punnett A, Mehta A, et al. Identification of educational and infrastructural barriers to prompt antibiotic delivery in febrile neutropenia: A quality improvement initiative. Pediatr Blood Cancer 2012;59:431–435.
19. Breitfeld PP, Dale T, Kohne J, et al. Accurate case finding using linked electronic clinical and administrative data at a children's hospital. J Clin Epidemiol 2001;54:1037–1045.
20. Madsen K, Rosenman M, Hui S, et al. Value of electronic data for model validation and refinement: Bacteremia risk in children with fever and neutropenia. J Pediatr Hematol Oncol 2002; 24:256–262.
21. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.
22. Gebara BM. Values for systolic blood pressure. Pediatr Crit Care Med 2005;6:500, author reply 500–501.
23. Santolaya ME, Alvarez AM, Aviles CL, et al. Admission clinical and laboratory factors associated with death in children with cancer during a febrile neutropenic episode. Pediatr Infect Dis J 2007;26: 794–798.
24. 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;18:280–284.
25. Larche J, Azoulay E, Fieux F, et al. Improved survival of critically ill cancer patients with septic shock. Intensive Care Med 2003;29:1688–1695.
26. Lin MY, Weinstein RA, Hota B. Delay of active antimicrobial therapy and mortality among patients with bacteremia: Impact of severe neutropenia. Antimicrob Agents Chemother 2008;52:3188–3194.
27. Auburtin M, Wolff M, Charpentier J, et al. Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study. Crit Care Med 2006;34:2758–2765.
28. Koster-Rasmussen R, Korshin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. J Infect 2008;57:449–454.
29. Donabedian A. The quality of care. How can it be assessed? JAMA 1988;260:1743–1748.
30. Institute of Medicine (U.S.). Committee on Quality of Health Care in America. Crossing the quality chasm: A new health system for the 21st century. Washington, DC: National Academy Press; 2001, 337 pp.
31. Ammann RA, Bodmer N, Hirt A, et al. Predicting adverse events in children with fever and chemotherapy-induced neutropenia: The prospective multicenter SPOG 2003 FN study. J Clin Oncol 2010;28:2008–2014.
32. Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. Adv Data 2007;386:1–32.