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Pediatric Patients Who Receive Antibiotics for Fever and Neutropenia in Less Than 60 min Have Decreased Intensive Care Needs

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Background. Antibiotic delivery to patients with fever and neutropenia (F&N) in <60 min is an increasingly important quality measure for oncology centers, but several published reports indicate that a time to antibiotic delivery (TTA) of <60 min is quite difficult to achieve. Here we report a quality improvement (QI) effort that sought to decrease TTA and assess associated clinical outcomes in pediatric patients with cancer and F&N. ***Procedure.*** We used Lean-Methodology and a Plan-Do-Study-Act approach to direct QI efforts and prospectively tracked TTA measures and associated clinical outcomes (length of stay, duration of fever, use of imaging studies to search for occult infection, bacteremia, intensive care unit (ICU) consultation or admission, and mortality). We then performed statistical analysis to determine the impact of our QI interventions on total TTA, sub-process times, and clinical outcomes. ***Results.*** Our QI interventions significantly improved TTA such that we are now able to deliver antibiotics in <60 min nearly 100% of the time. All TTA sub-process times also improved. Moreover, achieving TTA <60 min significantly reduced the need for ICU consultation or admission ($P = 0.003$) in this population. ***Conclusion.*** Here we describe our QI effort along with a detailed assessment of several associated clinical outcomes. These data indicate that decreasing TTA to <60 min is achievable and associated with improved outcomes in pediatric patients with cancer and F&N. Pediatr Blood Cancer 2015;62:807–815. © 2015 The Authors. *Pediatric Blood & Cancer*, published by Wiley Periodicals, Inc.

Key words: antibiotics time; fever; neutropenia; quality improvement

INTRODUCTION

Mortality due to sepsis is 1.6 fold higher for pediatric patients with cancer than it is for other children [1], as patients with neutropenia are particularly susceptible to serious bacterial infections and their complications (SBI) [1–4]. Standard of care thus involves intravenous (i.v.) antibiotics and hospital admission for all patients with fever and neutropenia (F&N) associated with cancer or cancer therapy [5,6]. This empiric effort often seems excessive, however, as only 21% of children with F&N have bacteremia [7] and only 11% suffer other serious complications [8].

This low complication rate has made assessment of management interventions aimed at improving outcomes in F&N difficult. Historically, providers have turned to the infectious disease literature for indication of what may work. There, prompt delivery of antibiotics has been associated with improved outcomes in adult patients with meningitis [9–12], sepsis [13–16], community-acquired pneumonia (CAP) [17–20], and solid organ transplant with fever [21]. This association is so strong in adults with sepsis that time to antibiotic delivery (TTA) is the single most important factor for survival, where mortality increases 7.6% with every hour delay [16].

Prompt delivery of antibiotics to patients with F&N has long been considered important [22], but data illustrating this importance have only recently begun to appear in the literature [8,23–26]. The lack of earlier reports indicating significant associations between TTA and outcomes in F&N may be due to small sample sizes and low rates of adverse events, at least in some studies [27], many of which may remain unpublished.

It is apparent that TTA is associated with outcomes in overtly ill adult patients with cancer and F&N, such as patients in the ICU [28], with sepsis [23], or meeting high-risk criteria by the Multination Association of Supportive Care in Cancer score [25]. In more typical, mildly symptomatic adult patients with cancer and F&N, the impacts of TTA on outcomes are less clear, but a small cohort study in Brazil found that a 1 hr delay in TTA is associated with an 18% increase in 28 day mortality, regardless of patient risk category [26].

Evidence that TTA influences outcomes in pediatric F&N has been similarly elusive. A landmark retrospective study reviewed pediatric admissions for F&N at Children's Medical Center Dallas and revealed that TTA <60 min is associated with improved outcomes when a composite adverse event score (including i.v. fluid resuscitation, intensive care unit (ICU) admission, LOS, and death)

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is used [8]. In a smaller study of pediatric patients with F&N in Thailand, multiple outcomes (LOS, mortality, ICU admission, and shock) were improved after a quality improvement (QI) initiative decreased median TTA [24]. Though suggestive of an impact, this study did not directly assess the relationship between TTA and outcomes.

Even though so few studies indicate that TTA improves outcomes for pediatric patients with cancer and F&N, 45% of Children's Oncology Group (COG) centers track TTA, and more than 90% indicate a goal TTA of <60 (or <30) min [29]. The goal of <60 min arises from literature pertaining to adults with sepsis [13,16,30]. This goal has been vaguely propagated such that the accepted goal TTA for pediatric patients with F&N varies from 30 to 120 min [5,6,31,32]. Furthermore, TTA is a Quality of Care (QOC) measure [29,31] for which U.S. News and World Report has been collecting data since 2010.

It is important to note that few centers reliably deliver antibiotics to pediatric patients with F&N in <60 min. In seven published QI reports on TTA in pediatric patients with F&N, none reported a baseline median TTA <60 min [24,31,33–37]. Though most of these studies reported improvement in TTA following their QI efforts [24,31,33,36,37], only two reported a TTA of <60 min in nearly 100% of patients [31,35], and neither allotted time to assess the absolute neutrophil count (ANC) if unknown. Moreover, in a large retrospective study of pediatric patients with cancer and F&N at a major U.S. cancer center, TTA was <60 min only 20% of the time [8]. Reports of TTA in adults are similar. A chart review at Colombia University revealed a median TTA for adults with F&N of 210 min [32]. Moreover, in a multi-site study from Australia, only 16% of patients with F&N received antibiotics in <60 min [38].

QI projects aimed at decreasing TTA for patients with F&N are being initiated frequently. Emerging data linking TTA to outcomes in patients with F&N emphasize the importance of such efforts, but more studies are needed to fully elucidate the impact of a TTA <60 min. Here we report a QI effort at Children's Hospital Colorado (CHCO) which successfully decreased TTA to <60 min in nearly 100% of pediatric patients with cancer and F&N. Moreover, patients who received antibiotics in <60 min had a decreased need for ICU level care when compared to patients with a TTA >60 min. We discuss our QI methodology, including what worked and what did not, to aid similar efforts at other hospitals, and describe the ongoing maintenance phase of our project which has continued to yield success.

METHODS

The Organizational Research Risk & Quality Improvement Review Panel (ORRQIRP) of the Institutional Review Board at the University of Colorado Denver approved this 15 month study which aimed to streamline the process of delivering i.v. antibiotics to patients with cancer and F&N in Center for Cancer and Blood Disorders (CCBD) clinics at CHCO. Details regarding our QI methodology are provided in the supplement. Briefly, we applied Lean Methodology [39,40] and used a Plan-Do-Study-Act (PDSA) approach [41]. PDSA cycles began roughly every 4 weeks and process measures were analyzed with each cycle. Sub-process measures were added partway through the study; thereby defining the end of the later-termed Empiric Phase (4 months) and the beginning of the Data-based Phase (4 months) of our project.

Electronic medical record (EMR) data for all patients who received i.v. antibiotics in a CCBD clinic during the study period were individually assessed for inclusion criteria of (i) oncologic diagnosis; (ii) ANC < 500 or <580 and expected to fall; (iii) new fever >38.3C or multiple fevers >38.0C over a 24 h period; and (iv) patient admitted for further management (Supplemental Figure S1). TTA was defined as time from check-in to the start of i.v. antibiotic administration. For patients who developed a new fever in clinic, the check-in time was modified to reflect the time of first fever. Sub-process times were similarly calculated and evaluated to assure that the sum of sub-processes was equal to TTA. For outcomes analysis, EMR data pertaining to duration of fever, bacteremia, imaging studies, ICU level care, LOS and disposition were assessed. All time stamps and outcome data were evaluated by chart review to ensure accuracy. Statistical calculations were performed using Minitab software (Minitab Inc.).

RESULTS

Retrospective analysis of patients treated for F&N in the baseline period (7 months) revealed significant room for improvement (Fig. 1, Table I) with only 19% of patients receiving antibiotics in <60 min. Analysis of clinic flow revealed several potential barriers to TTA <60 (Fig. 2) and the most important of these were thought to be (i) waiting for the ANC; (ii) transferring the patient from an exam room to the infusion center; and (iii) finding a provider to write the antibiotic orders. We first worked to increase awareness about the project within CCBD clinics, and then addressed these barriers with sequential PDSA cycles.

We started with the Sign&Hold PDSA which involved having a provider write antibiotic orders for any patient presenting with fever prior to knowing the ANC. The orders were to be written, signed, and held such that they would not be released and sent to pharmacy until the ANC was resulted and then only if ANC <500 cells/microliter. Anybody with access to the EMR could release the orders, thereby eliminating the need to find a provider once ANC was known. There were no incidents where sign and hold orders were inappropriately released.

Real-time P-chart evaluation indicated that the percent of patients who received antibiotics in <60 min was higher after implementation of the Sign&Hold PDSA than it was during the baseline period (Fig. 3, Table I), but the Sign&Hold PDSA did not improve TTA <60 percentage when compared to the previous month alone (Fig. 3). This suggested that simply increasing awareness, which occurred prior to implementation of the Sign&-Hold PDSA, improved our TTA <60 percentage. Notably, however, TTA mean, median, and variance decreased markedly in the month following implementation of the Sign&Hold PDSA (Fig. 1), indicating improvement in the process, despite a lack of change in the TTA <60 goal measure.

The next two PDSA cycles (Add-on Fever and CBC Sepsis) were similarly devised to combat identified barriers to TTA <60 (Fig. 2). The goal of the Add-on Fever PDSA was to decrease the time required to move a patient from an exam room to the infusion center by designating a special appointment type which would define patients with potential F&N as patients who may ultimately need an infusion room. Team discussions importantly identified that this PDSA was essentially ignored and therefore had little impact on clinic flow or TTA (Fig. 3).

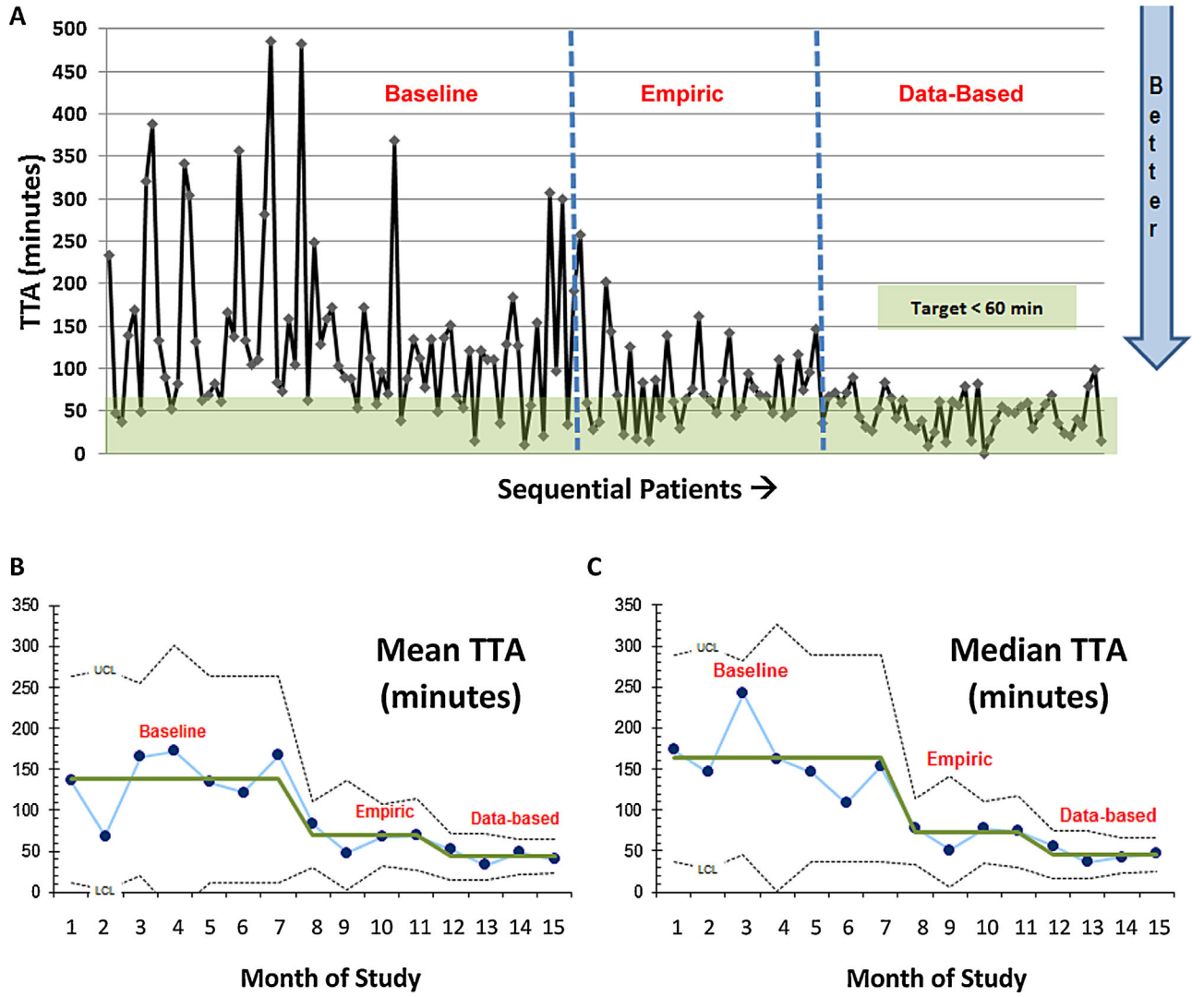

Fig. 1. Changes in TTA over time. TTA: time to antibiotic delivery. (**A**) Run Chart indicates TTA for each consecutive patient included in the study (N = 116). Phase of study is shown in Red. Target TTA of <60 min is shaded in green. Control Charts for Mean (**B**) and Median (**C**) TTA are also shown. Upper (UCL) and Lower (UCL) control limits are shown as dashed lines. The green line indicates the overall mean (**B**) or median (**C**) for the phase of study. The blue line connects the mean (**B**) or median (**C**) for each month of study.

The CBC Sepsis PDSA aimed to decrease time spent waiting for an ANC result and required collaboration with laboratory staff. Typically, ANC results would come from complete blood count (CBC) with Differential orders after manual verification of the ANC by a technician. During the baseline period, such orders were processed in 45 min (Table I). To decrease this time, we worked with the laboratory to develop a new order type (CBC Sepsis) that would designate a request to immediately release machine ANC results as preliminary. Analysis of 200 CBC Sepsis orders revealed that preliminary results of ANC >500 are converted to final results of ANC <500 less than 0.5% of the time. Preliminary CBC Sepsis results are available in 10 (+/− 4.6) minutes, a 65–75% improvement over CBC with Differential orders (Table I). The CBC Sepsis PDSA was not reliably followed in the initial weeks after its implementation, however, and therefore did not significantly impact clinic flow or TTA (Fig. 3).

Taken together, our first three PDSA cycles made up the Empiric phase of our project and improved mean TTA, median TTA, and variance within the process (Fig. 1, Table I), but failed to improve our TTA <60 percentage (Fig. 3, Table I). To identify further barriers to TTA <60, we turned to sub-process analysis. We immediately found that logical breaks in clinic flow (first vitals, roomed, lab drawn, etc.) could not be reliably assessed, as time stamps were manually entered and often inaccurate. We therefore identified reliable EMR time stamps and divided our process into four sub-processes (Fig. 2) based on these. The four sub-processes were (i) Check-in to Specimen Received; (ii) Specimen Received to Lab Resulted; (iii) Lab Resulted to Order Released; and (iv) Order Released to Antibiotics Given. As expected, variance was high in the baseline period for all four sub-processes (Fig. 4, Table I). The Empiric phase of our project appeared to improve mean, median, and standard deviation for each sub-process, but these comparisons did not reach statistical significance (Fig. 4, Table I).

TABLE I. Patient Data by Phase of Study

Category	Statistic	Baseline	Empiric	Data-based	Combined
Descriptive Statistics	Sample Size (N (% of Total=116))	53 (45.7)	24 (20.7)	39 (33.6)	63 (54.3)
	Mean TTA (min)	164.0	73.8 ***	45.2 ***	56.1 ***
	Median TTA (min)	134.0	68.0 ***	43.0 ***	54.0 ***
	Standard Deviation	118.6	34.2 ***	24.3 ***	31.5 ***
	Percent TTA <60 min	19	29 NS	74 ***	57 ***
Sub-Processes	Check-in to Specimen Received				
	Mean (min)	67.3	42.2 **	34.6 ***	37.6 ***
	Median (min)	57.3	35.9 NS	33.9 ***	33.9 ***
	Standard Deviation	36.4	25.8 NS	14.9 NS	20.0 NS
	Specimen Received to Lab Resulted				
	Mean (min)	51.3	41.7 NS	18.7 ***	28.1 ***
	Median (min)	43.5	36.0 NS	15.0 ***	22.5 ***
	Standard Deviation	32.3	25.4 NS	13.1 NS	22.1 NS
	Lab Resulted to Order Released				
	Mean (min)	101.0	21.2 ***	10.2 ***	14.8 ***
	Median (min)	63.0	10.0 **	1.0 **	5.0 ***
	Standard Deviation	104.6	31.5 *	19.3 **	25.3 ***
	Order Released to Antibiotics Given				
	Mean (min)	42.2	38.5 NS	25.6 **	30.5 NS
	Median (min)	34.0	26.0 NS	18.0 ***	21.0 ***
	Standard Deviation	30.8	46.0 NS	20.4 NS	32.9 NS
Outcomes	Length of Stay				
	Mean (days)	5.6	10.2 NS	6.4 NS	7.8 NS
	Median (days)	3.9	3.9 NS	3.9 NS	3.9 NS
	Standard Deviation	5.7	17.0 NS	6.4 NS	11.6 NS
	Duration of Fever				
	Mean (days)	3.5	7.3 NS	4.0 NS	5.3 NS
	Median (days)	2.0	2.5 NS	2.0 NS	2.0 NS
	Standard Deviation	3.3	12.9 NS	4.7 NS	9.0 NS
	Need for Imaging Workup (N (%))	6 (11.3)	3 (12.5) NS	2 (5.1) NS	5 (7.9) NS
	Bacteremia (N (%))	9 (16.9)	3 (12.5) NS	8 (20.5) NS	11 (17.4) NS
	Need for ICU Level Care (N (%))	18 (34.0)	9 (37.5) NS	5 (12.8) *	14 (22.2) NS
	Mortality (N (%))	1 (1.9)	2 (8.3) NS	1 (2.6) NS	3 (4.8) NS
Process Variation	Process Followed (N (%))	22(41.5)	12 (50.0) NS	15 (38.5) NS	27 (42.9) NS
	Waited for ANC (N (%))	39 (73.6)	19 (79.2) NS	31 (79.5) NS	50 (79.4) NS
Patient Characteristics	Gender Male (N (%))	31 (58.5)	7 (29.2) *	14 (35.9) *	21 (33.3) **
	Age (N (%))				
	<2 years	5 (9.4)	1 (4.2) NS	2 (5.1) NS	3 (4.8) NS
	2–12 years	28 (52.8)	14 (58.3) NS	25 (64.1) NS	39 (61.9) NS
	>12 years	20 (37.7)	9 (37.5) NS	12 (30.8) NS	21 (33.3) NS
	Primary Diagnosis (N (%))				
	Lymphoid Leukemia	29 (54.7)	13 (54.2) NS	20 (51.3) NS	33 (52.4) NS
	Myeloid Leukemia	5 (9.4)	2 (8.3) NS	1 (2.6) NS	3 (4.8) NS
	Lymphoma	0 (0)	1 (4.2) NS	2 (5.1) NS	3 (4.8) NS
	Extracranial Solid Tumor	9 (17.0)	7 (29.2) NS	11 (28.2) NS	18 (28.6) NS
	Brain Tumor	9 (17.0)	1 (4.2) NS	4 (10.3) NS	5 (7.9) NS
	Other	1 (1.9)	0 (8.3) NS	1 (2.6) NS	1 (1.6) NS

TTA, time to antibiotic delivery; ANC, absolute neutrophil count; ICU, intensive care unit. Statistics for Mean, Median, Standard Deviation, and Percent calculated using 2-sample *t*-test, Moods Median, Levene's Test, or Fisher's exact test, respectively. *P* values represented by asterisks where ***<0.001, **<0.01, *<0.05, and NS, not significant when compared to baseline. % indicates percent of patients in that study period unless otherwise indicated. ICU level care includes ICU consultation and/or admission.

To address the Check-in to Specimen Received sub-process, we implemented the Designated Room PDSA. This PDSA required reserving a room in clinic for patients with potential F&N, a concept which was met with much resistance from clinic staff. Sub-process data was used to convincingly illustrate the need, however, and this PDSA was eventually approved. P-chart analysis revealed that this PDSA led to a steady increase in the TTA <60 percentage (Fig. 3). A similar approach was taken to address the Order Released to Antibiotics Given sub-process. We argued that antibiotics needed to be stocked in the clinic Omnicell in order to decrease the time required to prepare the drugs. We used sub-process data to convince hospital administration that this change was necessary. The Omnicell Dispense PDSA also improved TTA <60 percentage (Fig. 3), though it was initially difficult to tell if this change was due to continued improvement from the Designated Room PDSA or to new improvement from

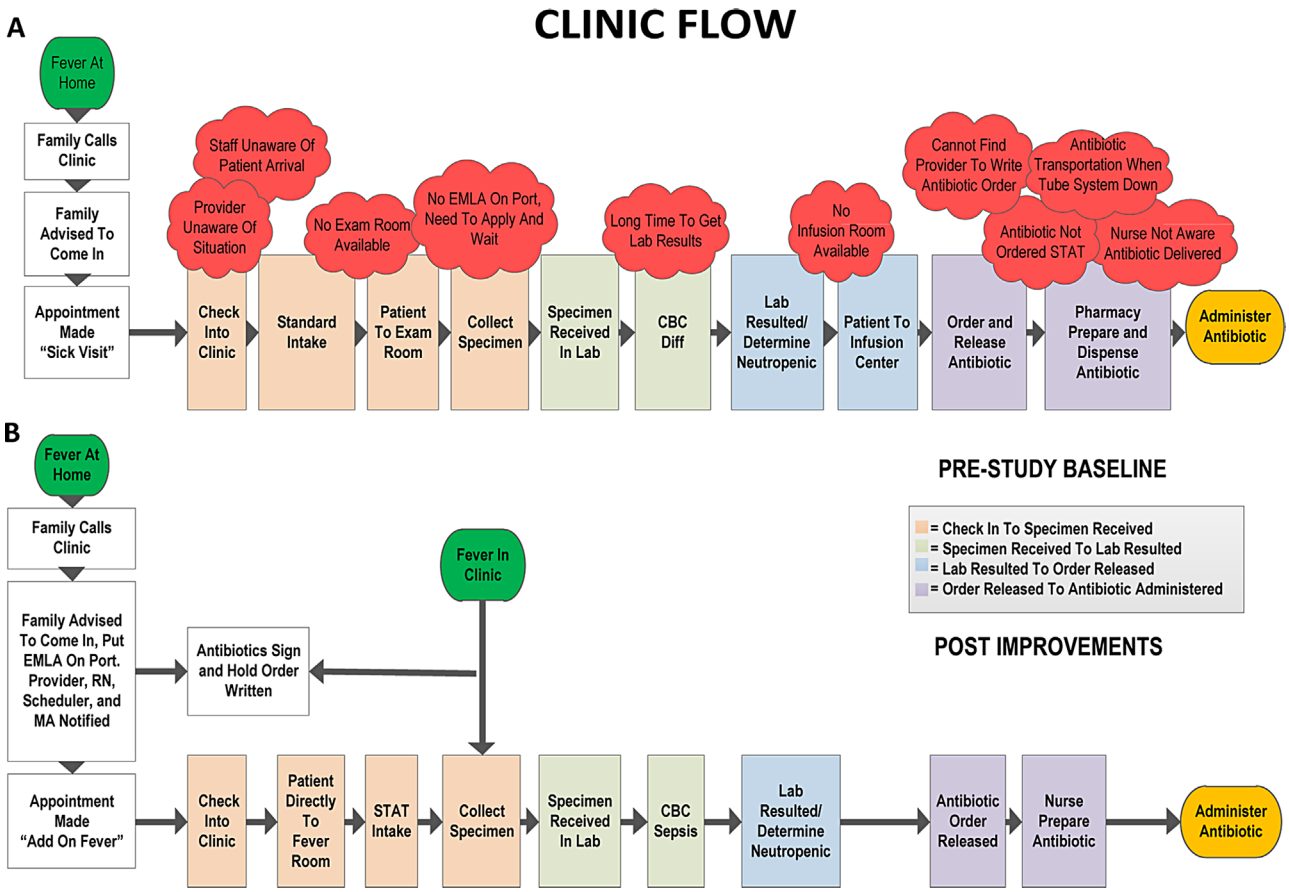

Figure 2. Clinic flow for patients presenting with fever and possible neutropenia. TTA: time to antibiotic delivery. The top panel (**A**) represents flow prior to the start of this project and during the baseline period. Perceived barriers to a TTA <60 min identified by Lean Methodology and team brainstorming are indicated in red. The bottom panel (**B**) represents flow after project improvements were implemented. Individual steps of the process were grouped into four sub-processes for analysis and are color-coded as indicated in the legend. Non-value-added steps were eliminated by project improvements. There was no defined process for patients who developed a fever in clinic prior to project interventions.

the Omnicell Dispense PDSA. Sub-process analysis revealed that both contributed (Fig. 4).

Drivers of success and failure were identified and addressed in real-time throughout. During the last few months of the project, such analysis revealed that TTA <60 was achievable when providers and staff adhered to project interventions and cases where TTA was >60 min were universally associated with a failure to follow the process. This led to our final two PDSA efforts, Re-Education and EMLA. The Re-Education effort reminded all providers and staff of the new process for patients with potential F&N (Fig. 2) and notably led to continued improvement in the TTA <60 percentage (Fig. 3). The EMLA PDSA targeted families and reminded them to apply Eutectic Mixture of Local Anesthetics (EMLA) cream to their child's mediport prior to presenting to clinic so that i.v. access could be obtained immediately upon arrival.

The Data-Based phase of our project ended upon assessment of our global aim which was to deliver antibiotics to 100% of patients with cancer and F&N within 59 min of check-in by the end of our 15 month study. Though this aim was not met (Fig. 3, Table I), the Data-Based phase of the project significantly improved TTA mean, median, and variance (Fig. 1, Table I). The mean and median times for all four sub-processes were also improved (Fig. 4, Table I). Moreover, our TTA <60 percentage improved from a baseline of 19–74% in the Data-Based phase (Table I). This project then continued into a Maintenance phase which continued to yield improvement, resulting in a TTA <60 percentage of 100% for several months (Fig. 3). The Maintenance phase of this project involved continued real-time data analysis, but, importantly, no further PDSA efforts were implemented or indicated.

With the exception of gender, patient characteristics were equivalent across all phases of study (Table I). We had a high proportion of males in the baseline period, resulting in statistically significant gender differences between the Empiric phase and the Data-Based phase when compared to baseline (Table II). Importantly, the gender difference between the Empiric phase and the Data-Based phase was not statistically significant. Patients were treated equivalently across all phases of study, with providers waiting for the ANC result prior to delivering antibiotics in roughly 70–80% of patients, and providers adhering to all project interventions (process followed) roughly 40–50% of the time (Table I).

To determine if achieving a TTA <60 min was associated with improved outcomes, we collected EMR data on LOS, duration of fever, need for imaging to search for occult infection, bacteremia,

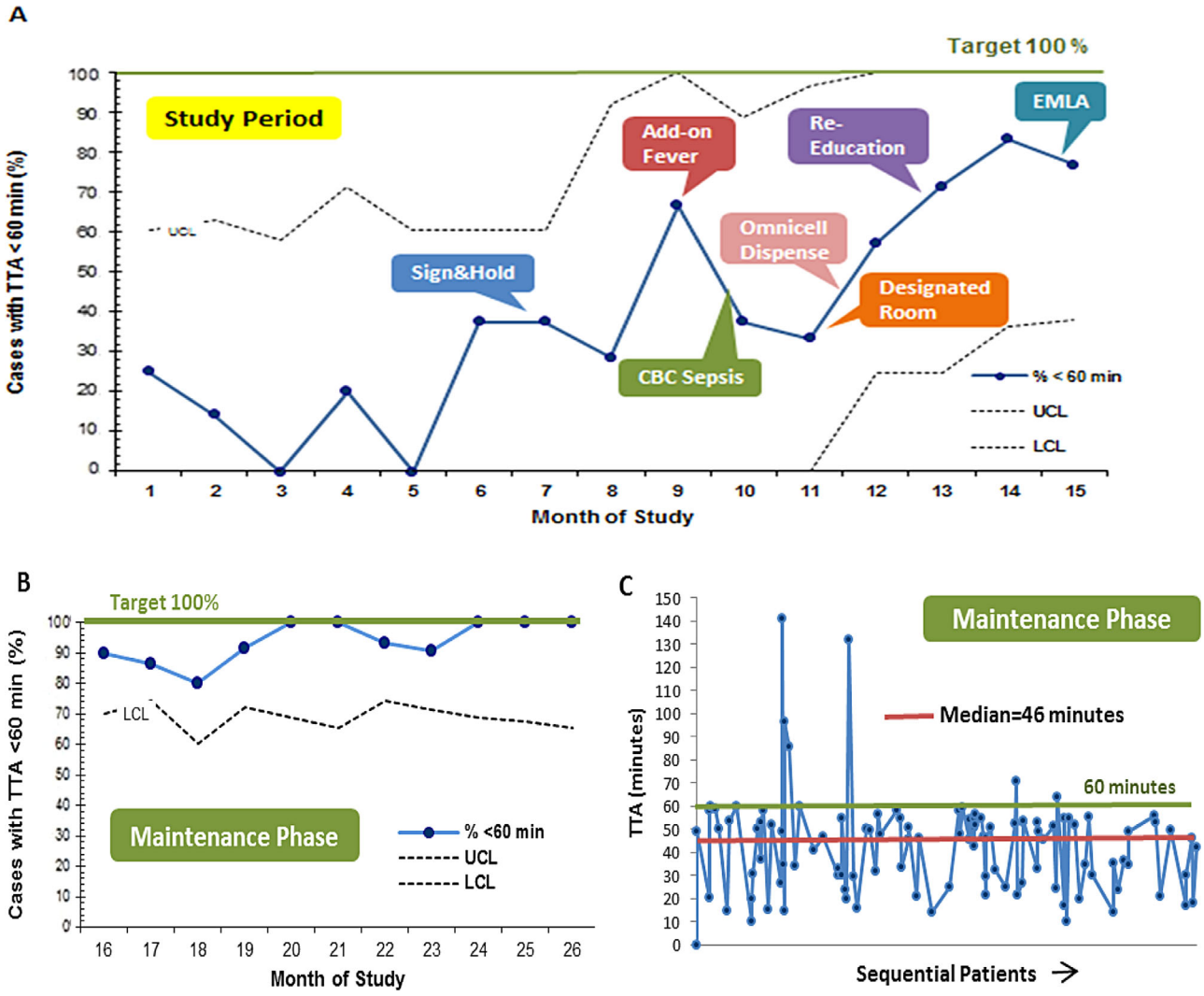

Figure 3. Percent of cases with TTA <60 min. TTA, time to antibiotic delivery. (**A**) P-Chart indicates the percent of patients who received antibiotics in <60 min during the study period. Target TTA <60 of 100% is shown in green. Upper (UCL) and Lower (UCL) control limits are shown as dashed lines. The blue line connects the percent of cases with TTA <60 min for each month of study. Colored bubbles designate Plan-Do-Study-Act (PDSA) cycles. (**B**) Continuation of chart A representing the Maintenance Phase wherein no further PDSA cycles occurred. (**C**) Run-chart showing TTA for all consecutive patients in the Maintenance phase (N = 104). The green line marks TTA of 60 min and the red line marks the median TTA for the Maintenance phase.

need for ICU consultation or admission, and mortality. Though most of these measures appeared to improve with a TTA <60, none of the differences reached statistical significance during the study period (Table II). Suspecting the lack of statistical significance was due to sample size, we included Maintenance Phase data in our analysis, resulting in a sample size of 220 patients. This analysis revealed a statistically significant 20% decrease in the need for ICU level care when TTA is <60 min (Table II). Interestingly, this outcomes measure also reached statistical significance when analyzed by phase of study (Table I). Achieving a TTA <60 min was also associated with decreased mortality; mortality was 3.9% if TTA >60 min and 0.7% if TTA <60 min (Table II). Though this change did not reach significance by Fisher's Exact Test, these data represent an absolute risk reduction of 3.2%, a relative risk reduction of 82.1%, and a number needed to treat of 31.

DISCUSSION

Many attempts to devise risk stratification algorithms aimed at differentiating high-risk from low-risk F&N have been undertaken, and a meta-analysis of these methods showed none to be better than the others [42]. Still, no single algorithm has been adopted for use in pediatric patients with F&N. Leaders in the field have called for pediatric F&N management guidelines several times [43–47], but we still do not have an accepted protocol. In the absence of a consensus, improving outcomes is the only way to control cost.

F&N admissions for pediatric patients cost roughly $12,000 per event [48,49]. Costs increase, and in some cases immeasurably, with adverse events including prolonged LOS, need for imaging to search for occult infection, bacteremia requiring full-course i.v. antibiotics, need for ICU consultation or admission, and mortality. Due to the rarity of such events [8], assessing the ability of F&N

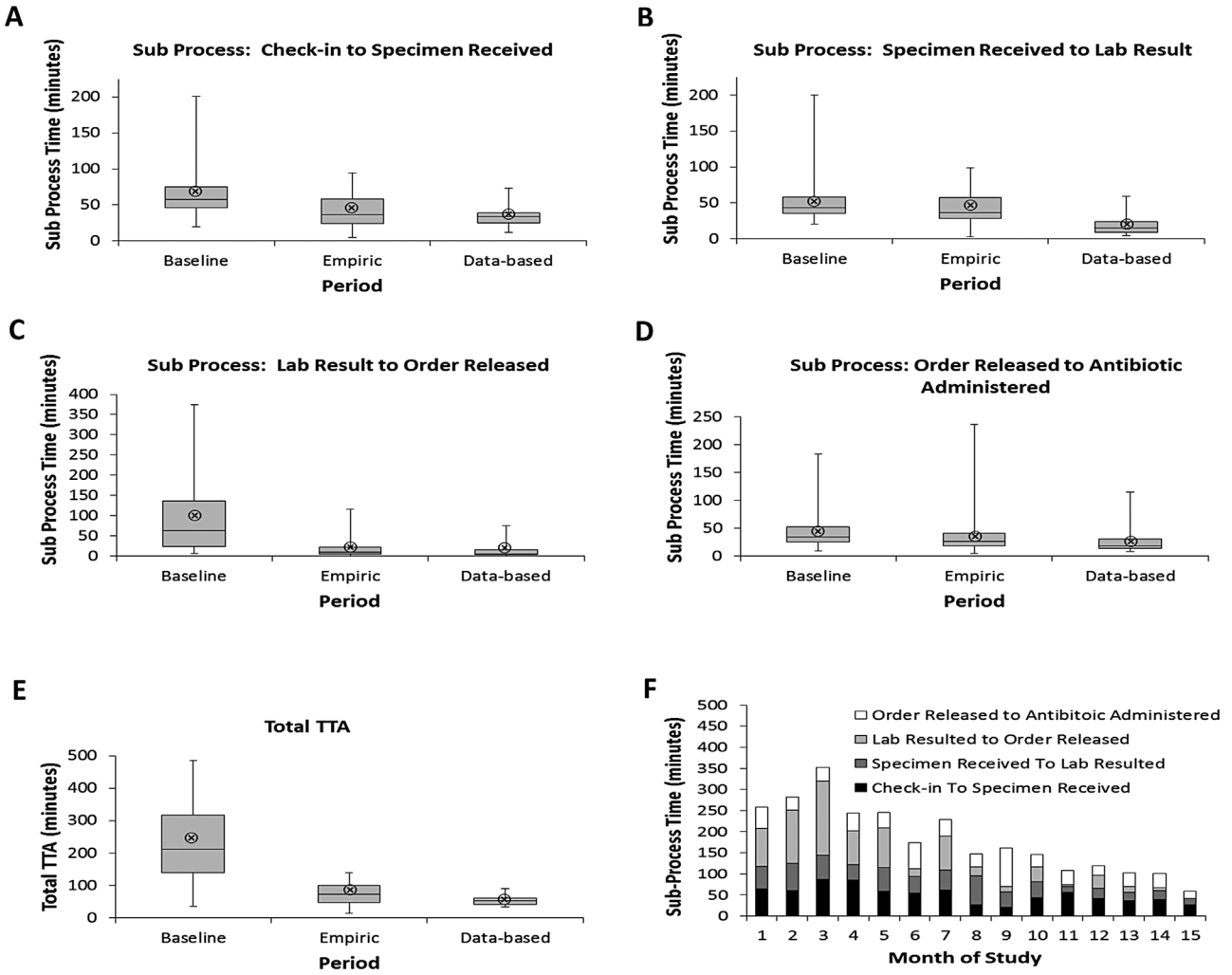

Figure 4. Sub-process analysis. TTA, time to antibiotic delivery. Total TTA was divided into four sub-processes: (**A**) Check-in to Specimen Received, (**B**) Specimen Received to Lab Resulted, (**C**) Lab Resulted to Order Released, and (**D**) Order Released to Antibiotic Administered, which sum to yield TTA (**E**) Box and Whisker plots (**A**–**E**) show minimum to maximum values (whiskers), mean (asterisk), and median (horizontal line) by study period. In **F**, stacked bars designate average sub-process times for each month regardless of study period.

TABLE II. Clinical Outcomes by TTA

	Study period alone			With maintenance phase		
	TTA>60	TTA < 60	*P*-Value	TTA > 60	TTA < 60	*P*-Value
Sample Size N (%)	68 (58.6)	48 (41.4)	n/a	77 (35.0)	143 (65.0)	n/a
Length of Stay						
Mean (days)	7.1	6.4	NS	6.9	5.7	NS
Median (days)	3.9	3.9	NS	3.9	3.8	NS
Standard Deviation	11.2	6.3	NS	10.7	6.1	NS
Duration of Fever						
Mean (days)	3.2	2.6	NS	3.0	2.0	NS
Median (days)	2.0	1.0	NS	2.0	1.0	NS
Standard Deviation	6.9	4.3	NS	6.6	3.4	NS
Need for Imaging Workup (N (%))	4 (5.9)	7 (14.6)	NS	4 (5.2)	13 (9.1)	NS
Bacteremia (N (%))	8 (11.8)	12 (25.0)	NS	10 (13.0)	22 (15.4)	NS
Need for ICU Level Care (N (%))	22 (32.4)	10 (20.8)	NS	23 (29.9)	18 (12.6)	0.003
Mortality (N (%))	3 (4.4)	1 (2.1)	NS	3 (3.9)	1 (0.7)	NS

TTA, time to antibiotic delivery; ICU, intensive care unit; Statistics for Mean, Median, Standard Deviation, and Percent calculated using 2-sample T-test, Moods Median, Levene's Test, or Fisher's exact test, respectively. NS, not significant.

management interventions to improve outcomes and reduce costs is incredibly difficult. Notably, two recent studies indicate that a TTA <60 min is associated with improved outcomes in pediatric patients with cancer and F&N [8,24].

Here we add to this growing body of literature by demonstrating that achieving a TTA <60 min in pediatric patients with cancer and F&N is associated with a decreased need for ICU consultation or admission (Table II). At our institution, ICU admissions for patients from the CCBD cost, on average, $4,607 per day. Patients that required ICU admission in our study spent an average of 4.5 days in the ICU, resulting in a cost exceeding $20,000 per patient. Decreasing the need for ICU level care therefore provides a significant cost savings.

Mortality was also impacted by achieving a TTA <60 min. TTA <60 min was associated with a relative risk reduction for mortality of 82.1% when compared to TTA >60 min. Furthermore, we experienced zero mortality in the Maintenance phase of our project (N = 104) which is clinically relevant even if not statistically significant. Though likely substantial, the cost savings associated with decreased morbidity and mortality could not be accurately assessed in our study.

TTA is an established QOC measure [31] with <60 min being accepted as an appropriate TTA guideline [29]. With increasing evidence that meeting this guideline is associated with improved outcomes for pediatric patients with F&N, QI efforts aimed at decreasing TTA become particularly important. An analysis of seven published QI reports on TTA in pediatric F&N [24,31,33–37] indicated that QI methods vary and success is rare. Moreover, in the studies where a TTA of <60 min was achieved [31,35], process algorithms did not allow for assessment of the ANC if unknown. Being aware of the challenges associated with previous TTA QI efforts aided our own. Accordingly, we successfully decreased TTA (Fig. 1, Table I) leading to a TTA <60 percentage of 100% over several months during the Maintenance phase of our project (Fig. 3). Importantly, we continued to allow for assessment of the ANC in patients where it was unknown, thereby avoiding unnecessary delivery of antibiotics to febrile patients with an ANC >500. Our efforts also decreased TTA mean, median, and variation (Fig. 1, Table I), indicating notable improvement in our clinic process.

Reports of QI projects rarely address associated expense, even though expense is particularly relevant if endpoints are rare. The QI effort and all interventions described herein involved only subtle changes to routine procedures at our institution. Associated expenses were deemed minimal and essentially unmeasurable, as they could not be separated from daily operating procedure. Cost benefits discussed above can therefore be considered absolute benefits, without the caveat of expensive interventions required to attain them.

Real-time analysis of our data revealed that increasing awareness alone improved TTA measures (Fig. 1, Fig. 3). Still, we learned that an intuitive approach was not enough, as the Empiric phase of our project did not improve our goal measure (Fig. 3, Table I). Careful data analysis in the Data-based phase of our project produced more notable improvements across all measures of TTA and TTA sub-processes (Fig. 1, Fig. 4, and Table I). Importantly, we also discovered that process improvements can be sustained (and even further improved) long after active QI efforts cease, as evidenced by our Maintenance phase data (Fig. 3).

We have included details regarding each PDSA in this report to demonstrate an ability to overcome perceived barriers with a multidisciplinary approach, data-based interventions, and persistence. We found that a multidisciplinary team was essential to understand the clinic process and facilitate needed interventions (Fig. 2). Data analysis provided the justification for each intervention and ample opportunity to sway naysayers, as evidenced by the Omnicell Dispense PDSA. Finally, persistence to re-address previously targeted barriers and failed PDSA cycles resulted in remarkable improvement (Fig. 3).

Although we significantly improved TTA (Table I) and demonstrated that TTA <60 min is associated with a decreased need for ICU level care (Table II), the majority of outcomes measures did not reach statistical significance in this study (Table II). Similar results have been noted by others [8] and are a reflection of the rarity of adverse outcomes in F&N. Large scale multicenter studies will therefore be required to determine the effects of decreasing TTA for pediatric patients with cancer and F&N. The ongoing Maintenance phase of our project will contribute to this effort, but small sample size remains a caveat.

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