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ORIGINAL ARTICLE

Association of Time to Antibiotic Administration with Hospital Outcomes in Children with Cancer having Febrile Neutropenia: A Prospective Observational Study

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Abstract

Background: *Febrile neutropenia (FN) is a leading cause of morbidity and mortality in children with cancer. Prompt empirical antibiotic therapy is the cornerstone of management of FN and time to antibiotic (TTA) administration has been proposed as a quality of care measure.*

Objective: *To evaluate the association between TTA and hospital outcomes in children with cancer having FN.*

Methods: *This prospective observational study enrolled 40 children with cancer having FN (absolute neutrophil count <500/mm³) admitted in the Department of Pediatric Hematology and Oncology, Bangladesh Medical University (BMU), Dhaka, Bangladesh. TTA was categorized as <60 minutes, 60-120 minutes, 120-180 minutes and >180 minutes (up to 24 hours). The primary outcome was a composite adverse event like- hospital mortality, needed admission in pediatric intensive care unit (PICU) within 24 hours or fluid resuscitation ≥40 mL/kg within 24 hours; the alternative was a good outcome (discharge in stable condition). Associations were assessed using the Chi-square test and Student's t-test; odds ratios (OR) with 95% confidence intervals (CI) were calculated accordingly.*

Results: *Mean age of the study children was 64.2±34.6 months and 62.5% were male. Acute lymphoblastic leukemia (ALL) was the commonest diagnosis (70%). TTA was <60 minutes in 67.5% of children and early TTA (<120 minutes) was achieved in 82.5% cases. The composite adverse outcome occurred in 6 children (15%); hospital mortality was 7.5%. Early TTA was significantly associated with a favorable outcome compared with delayed TTA (χ^2=11.82, df=1, p<0.001). TTA <60 minutes was strongly associated with a good outcome (OR 16.25, 95% CI 1.42-185.7, p=0.003). Urinary tract infection, bacteremia and respiratory tract infection were each significantly associated with adverse outcome (p<0.001), whereas cancer type and laboratory parameters or antibiotic regimen were not associated with outcomes.*

Conclusion: *Early empirical antibiotic administration particularly within 60 minutes of presentation was associated with improved hospital outcomes in children with cancer having FN. The findings support TTA as an actionable quality of care target in pediatric oncology including in resource limited settings.*

Keywords: *Febrile neutropenia, Time to antibiotic, Childhood cancer, Empirical antibiotic therapy, Hospital outcome*

Introduction

Febrile neutropenia (FN) is among the most common oncologic emergencies in children receiving chemotherapy and remains a major cause of morbidity and mortality despite substantial advances in pediatric cancer care[1]. In neutropenic children, fever may be the only manifestation

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of infection, because the inflammatory response that produces visible signs is attenuated by the low neutrophil count and the neutropenic state itself is asymptomatic until fever develops. Chemotherapy-induced neutropenia compromises innate immune defenses, predisposing affected children to rapidly progressive bacterial and fungal infections that may culminate in severe sepsis, septic shock, multiorgan dysfunction and death if not promptly treated[2]. In addition to its clinical consequences, FN contributes to prolonged hospitalization, increased healthcare expenditure, interruptions or dose reductions in chemotherapy and deterioration in quality of life among pediatric oncology patients[3]. The introduction of empirical broad-spectrum antibiotic therapy has dramatically improved outcomes in neutropenic patients over the past several decades. Since the pioneering work of Pizzo and colleagues, early initiation of antibiotics in febrile neutropenic episodes has become the cornerstone of management because delaying treatment may permit rapid progression of occult infection[3]. Contemporary international guidelines continue to strongly recommend immediate administration of empirical broad-spectrum antibiotics to all children with cancer presenting with FN, preferably immediately after clinical assessment and blood culture collection[4,5]. Many institutions have therefore adopted the concept of the "golden hour," aiming to administer the first dose of antibiotics within 60 minutes of patient presentation, while even shorter intervals are recommended for children with suspected sepsis[6]. The promptness of initial antibiotic administration, expressed as the time-to-antibiotic (TTA) has been proposed as a quality-of-care (QOC) measure for several infectious conditions[7]. Although prompt antibiotic administration is widely accepted as best practice, the precise relationship between TTA and clinical outcomes remains an area of active investigation. Earlier studies demonstrated that adherence to guideline-based management was associated with improved outcomes and fewer complications among patients with FN[8]. Nevertheless, the investigators emphasized that minimizing delays remains prudent because children with occult bacteremia may deteriorate unexpectedly and are often clinically indistinguishable at presentation[9]. Despite these recommendations, timely antibiotic administration remains challenging in many healthcare settings. Overcrowded emergency departments, delayed recognition of FN, limited availability of trained personnel, diagnostic constraints and logistical barriers to drug delivery may all contribute to prolonged TTA. Such challenges are often more pronounced in low- and middle-income countries, where healthcare resources are limited. In Bangladesh and other resource-constrained settings, data examining the relationship between early empirical antibiotic administration and hospital outcomes in children with cancer having FN remain scarce. The absence of context-specific evidence limits the ability of healthcare institutions to establish effective protocols tailored to local realities. Determining whether prompt antibiotic administration influences outcomes such as duration of hospitalization, requirement for intensive care support, microbiologically documented infections, treatment-related complications and mortality is therefore of considerable clinical importance. Such evidence may strengthen antimicrobial stewardship efforts, enhance adherence to evidence-based guidelines, optimize utilization of limited healthcare resources and support the development of interventions aimed at reducing delays in antibiotic delivery. We therefore conducted this prospective observational study to evaluate the effect of early empirical antibiotic administration on hospital outcomes in children with cancer having FN and to identify the TTA interval most strongly associated with a favorable outcome.

Methodology

Study Design and Setting

This prospective observational study was conducted in the inpatient Department of Paediatric Hematology and Oncology, Bangladesh Medical University (BMU) former Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, over a six-month period from November 2014 to July 2015. All children with a diagnosis of cancer admitted to the department during the study period were screened for eligibility.

Study participants, sample size and sampling technique

Children were eligible if they had a confirmed diagnosis of cancer together with febrile neutropenia, defined as new-onset fever (a single oral/axillary-equivalent temperature >38.5°C, or 38.0 - 38.4°C on two occasions one hour apart) and an absolute neutrophil count (ANC) <500/mm³ [10]. Children were excluded if time-to-antibiotic (TTA) exceeded 24 hours; if fever or neutropenia developed after the initial presentation; if they presented with severe sepsis (FN with systolic hypotension below the fifth percentile for age) [10]; if they required admission in pediatric intensive care unit (PICU) at initial presentation; or if they received ≥40 mL/kg of fluid resuscitation at presentation independent of the timing of antibiotics. Using the formula $n = Z^2pq/e^2$ ($Z = 1.96$, expected prevalence of adverse events $p = 12\%$,8 acceptable error $e = 10\%$), the required sample size was 40. A purposive sampling technique was employed to recruit eligible participants consecutively during the study period.

Operational definitions and study variables

TTA was defined as the time in minutes from presentation (triage in the emergency department, registration in the

outpatient clinic, or admission for direct observation) to administration of the first dose of empirical parenteral antibiotics and was analyzed in four intervals: <60 minutes, 60-120 minutes, 120-180 minutes and >180 minutes up to 24 hours [7]. For dichotomous analysis, early TTA was defined as <120 minutes and delayed TTA as 120 minutes to 24 hours. The primary outcome was a composite adverse event (CAE) comprising hospital mortality, needed admission in PICU within 24 hours of presentation or fluid resuscitation e"40 mL/kg within 24 hours of presentation; the alternative outcome was a good outcome defined as discharge from hospital in stable condition. Covariables recorded included age, sex, anthropometry, type of cancer, temperature, any systemic infection, bacteremia, total white blood cell (WBC) count, ANC, platelet count, serum creatinine, serum albumin and the initial empirical antibiotic regimen.

Study procedures

Following enrollment sociodemographic data, cancer diagnosis and history of prior antibiotic exposure were recorded on a structured questionnaire. Then anthropometry and temperature were documented. Laboratory evaluation included complete blood count (CBC) with differential and ANC, erythrocyte sedimentation rate (ESR), platelet count, serum creatinine, serum albumin, blood culture, urine routine microscopic examination and culture. Chest radiography and abdominal ultrasonography (USG) were also performed. TTA was recorded for every patient, who was then monitored and followed up until a study outcome was reached.

Ethical considerations

Ethical approval of this study was obtained from the Institutional Review Board (IRB) of BMU. Written informed consent was obtained from the parents or legal guardians of all participants before enrollment. Confidentiality of patient information was strictly maintained throughout the study.

Statistical analysis

Statistical analysis was performed by windows-based software the Statistical Package for the Social Sciences (SPSS) version 13.0. Descriptive statistics were used to summarize the baseline characteristics of the study participants. Continuous variables were expressed as mean with standard deviation (±SD), whereas categorical variables were summarized using frequency with percentage. The chi-square test (with Fisher's exact test where appropriate) was used to compare categorical variables and Student's t-test to compare continuous variables. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the association between TTA categories and the composite outcome. A p value <0.05 was considered as statistically significant.

Results

This study was intended to evaluate the association of early empirical antibiotic administration with hospital outcomes in children with cancer having febrile neutropenia (FN). Total 40 children with cancer having FN were included in the study following selection criteria.

Baseline characteristics

The mean age of the study children was 64.2±34.6 months (range 15-144 months), with 70.0% aged 13-84 months and 30.0% aged 85-156 months. Of them, twenty-five children (62.5%) were male and 15 (37.5%) were female (male-to-female ratio 1.7:1); their mean body surface area (BSA) was 0.72 ± 0.26 m^2, mean hemoglobin level was 8.95 ± 2.45 g/dL and mean ANC was144.7 ± 143.0 /mm^3. Acute lymphoblastic leukemia (ALL) was the commonest underlying malignancy (70.0%), followed by lymphoma (10.0%), Wilms tumor (7.5%), acute myeloid leukemia (AML, 5.0%), and other tumors including hepatoblastoma and Ewing sarcoma (7.5%) (Table-I).

Table-I

Baseline demographic, clinical and laboratory characteristics of the study population (N= 40)

Characteristic	n (%) /mean ± SD	Range
Age (months)		
13–84	28 (70.0)	-
85–156	12 (30.0)	-
Mean ± SD	64.2 ± 34.6	15-144
Sex		
Male	25 (62.5)	-
Female	15 (37.5)	-
Anthropometry		
Weight (kg)	17.3 ± 7.7	4-45
Height (cm)	102.6 ± 22.1	55-152
Body surface area (m^2)	0.72 ± 0.26	0.30-1.46
Primary malignancy		
Acute lymphoblastic leukemia	28 (70.0)	-
Lymphoma	4 (10.0)	-
Wilms tumor	3 (7.5)	-
Acute myeloid leukemia	2 (5.0)	-
OtherC"	3 (7.5)	-
Laboratory parameters		
Hemoglobin (g/dL)	8.95 ± 2.45	5.90-14.60
ESR (mm/1st hour)	37.5 ± 16.4	15-78
Total WBC count (/mm^3)	1096 ± 1173	110-6960
ANC (/mm^3)	144.7 ± 143.0	10-500
Serum creatinine (mg/dL)	0.60 ± 0.17	0.26-1.0
Serum albumin (g/L)	36.2 ± 5.3	24-48

SD= Standard deviation; ESR= Erythrocyte sedimentation rate; WBC= White blood cell; ANC= Absolute neutrophil count.

Microbiological and radiological findings

Among the study children urine culture yielded a pathogen in 4 children (10.0%): Escherichia coli in 3 (7.5%) and Acinetobacter species in 1 (2.5%); the remaining 90.0% showed no growth. Blood culture was positive in a single child (2.5%), who grew Klebsiella species. Chest radiography was normal in 34 children (85.0%); pneumonitis was identified in 5 (12.5%) children and pleural effusion in 1 (2.5%) child (Table-II).

Table- II

Distribution of urine culture, blood culture, and chest radiography findings among the study participants (N= 40)

Variables	Frequency (n)	Percentage (%)
Urine culture		
No growth	36	90.0
Escherichia coli	3	7.5
Acinetobacter species	1	2.5
Blood culture		
No growth	39	97.5
Klebsiella species	1	2.5
Chest radiography		
Normal	34	85.0
Pneumonitis	5	12.5
Pleural effusion	1	2.5

Empirical antibiotic therapy and time-to-antibiotic

In this study empirical therapy comprised a carbapenem-based regimen in all children: monotherapy (carbapenem) in 6 (15.0%) children, dual therapy (carbapenem plus vancomycin or clindamycin) in 29 (72.5%) children and triple therapy (carbapenem plus vancomycin/clindamycin plus metronidazole) in 5 (12.5%) children (Table-III).

Table-III

Distribution of Empirical Antibiotic Regimen and Time to Antibiotic (TTA) Among Study Participants (N = 40)

Empirical therapy regimen	Frequency (n)	Percentage (%)
Carbapenem monotherapy	6	15.0
Carbapenem + Vancomycin/ Clindamycin	29	72.5
Carbapenem + Vancomycin/ Clindamycin + Metronidazole	5	12.5

TTA was <60 minutes in 27 children (67.5%), 60-120 minutes in 6 (15.0% children), 120-180 minutes in 5 (12.5%) children and >180 minutes up to 24 hours in 2 (5.0%) children. Overall, early TTA (<120 minutes) was achieved in 33 children (82.5%) and delayed TTA (120 minutes to 24 hours) in 7 (17.5%) children (Table-IV).

Table-IV

Distribution of Empirical Antibiotic Regimen and Time to Antibiotic (TTA) Among Study Participants (N= 40)

Variable	Frequency (n)	Percentage (%)
Time to antibiotic (TTA)		
<60 minutes	27	67.5
60-120 minutes	6	15.0
120-180 minutes	5	12.5
>180 minutes - 24 hours TTA category	2	5.0
Early TTA (<120 minutes)	33	82.5
Delayed TTA (120 minutes - 24 hours)	7	17.5

Outcomes of the study

It was observed that, a good outcome (discharge in stable condition) was achieved in 34 children (85.0%). The composite adverse event occurred in 6 children (15.0%): hospital mortality in 3 (7.5%), PICU admission within 24 hours in 1 (2.5%) and fluid resuscitation e”40 mL/kg within 24 hours in 2 (5.0%) children (Table-V).

Table-V

Outcomes of the study (N= 40)

Outcomes of the study	
Good (discharge in stable condition)	34 (85.0)
Composite adverse event	6 (15.0)
Hospital mortality	3 (7.5)
PICU admission within 24 h	1 (2.5)
Fluid resuscitation ≥40 mL/kg within 24 h	2 (5.0)

PICU= Pediatric intensive care unit.

Factors associated with the composite adverse outcome

On univariate analysis, the type of malignancy was not significantly associated with outcome (p>0.05). In accordance any of the hematological or biochemical parameters including hemoglobin, ESR, total white-cell count, ANC, serum creatinine and serum albumin were not significantly associated with outcome ((p>0.05 in all instances). The empirical antibiotic regimen was likewise not associated with outcome (monotherapy p=0.90, dual therapy p=0.18 and triple therapy p=0.09). In contrast, urinary tract infection, bacteremia, and respiratory tract infection were each strongly associated with the composite adverse outcome (p<0.001 in all instances) (Table- VI).

Table-VI

Univariate association between clinical, laboratory, and infection-related factors and the composite adverse outcome (N= 40)

Factors	Good (n = 34)	Adverse event (n = 6)	p-value
Type of malignancy			
ALL	25 (62.5%)	3 (7.5%)	0.246
AML	1 (2.5%)	1 (2.5%)	0.155
Wilms tumor	2 (5.0%)	1 (2.5%)	0.355
Lymphoma	4 (10.0%)	0	0.376
Other	2 (5.0%)	1 (2.5%)	0.355
Hematological / biochemical (mean ± SD)			
Hemoglobin (g/dL)	8.79 ± 2.43	9.78 ± 2.59	0.370
ESR (mm/1st h)	36.7 ± 17.7	38.3 ± 8.3	0.825
Total WBC (/mm³)	1234 ± 1227	462 ± 255	0.137
ANC (/mm³)	165.2 ± 150.9	61.7 ± 41.7	0.107
Creatinine (mg/dL)	0.60 ± 0.16	0.59 ± 0.22	0.931
Albumin (g/L)	36.0 ± 5.2	36.3 ± 5.9	0.888
Infection-related factors			
Urinary tract infection (n= 4)	1 (2.5%)	3 (7.5%)	<0.001
Bacteremia (n= 1)	0	1 (2.5%)	<0.001
Respiratory tract infection (n= 6)	1 (2.5%)	5 (12.5%)	<0.001
Empirical antibiotic regimen			
Monotherapy	5 (14.7%)	1 (16.7%)	0.90
Dual therapy	26 (76.5%)	3 (50.0%)	0.18
Triple therapy	3 (8.8%)	2 (33.3%)	0.09

Chi-square test (Fisher's exact test for infection-related factors) for categorical variables and Student's t-test for continuous variables. Bold p-values denote statistical significance (p<0.05). ALL= Acute lymphoblastic leukemia; AML= Acute myeloid leukemia.

Association of Time-to-antibiotic (TTA) and outcome

Early TTA (<120 minutes) was significantly associated with a good outcome compared with delayed TTA (÷²=11.82, df=1, p=0.001). When the four TTA intervals were examined individually, TTA <60 minutes showed a strong, statistically significant association with a good outcome (OR 16.25, 95% CI 1.42–185.7, p=0.003), whereas the associations for the 60–120-minute (p=0.17), 120–180-minute (p=0.09), and >180-minute (p=0.15) intervals were not significant. The relationship between TTA and the composite outcome is presented in Table VII.

Table-VII

Association between time-to-antibiotic (TTA) and the composite adverse outcome (N= 40)

TTA	Good (n = 34)	Adverse (n = 6)	OR (95% CI)	p-value
Dichotomous category ($\chi^2 = 11.82$, df = 1)				
Early (<120 min)	30 (75.0%)	3 (7.5%)	-	<0.001
Delayed (120 min–24 h)	4 (10.0%)	3 (7.5%)	-	
By TTA interval				
<60 minutes	26 (76.5%)	1 (16.7%)	16.25(1.42–185.7)	0.003
60-120 minutes	4 (11.8%)	2 (33.3%)	0.27(0.02–2.96)	0.17
120-180 minutes	3 (8.8%)	2 (33.3%)	0.19(0.02–2.33)	0.09
>180 minutes - 24 hours	1 (2.9%)	1 (16.7%)	0.15(0.00–6.71)	0.15

Chi-square test. OR, odds ratio; CI, confidence interval. Bold p-values denote statistical significance (p<0.05). The wide confidence interval for the <60-minute interval reflects the small sample size and low event count.

Discussions

Febrile neutropenia (FN) remains a common and potentially life-threatening complication of chemotherapy in patients with cancer despite advances in infection prevention. Because fever may be the only sign of infection in neutropenic patients, FN is considered an oncologic emergency. Prompt administration of empirical broad-spectrum parenteral antibiotics is therefore the cornerstone of initial management and is essential to reduce morbidity, mortality and adverse clinical outcomes[11].

In this prospective observational study of 40 children with cancer and FN, early empirical antibiotic administration was significantly associated with improved outcomes. A good outcome was achieved in 85% of children, while the composite adverse events- hospital mortality, PICU admission or fluid resuscitation e”40 mL/kg within 24 hours occurred in 15%, with an overall hospital mortality of 7.5%. Children who received antibiotics within 120 minutes had significantly better outcomes than those treated later ($p<0.001$), and the strongest protective association was observed when antibiotics were given within 60 minutes (OR 16.25, $p= 0.003$). These findings are consistent with previous work across diverse patient populations. Prolonged TTA has been linked to increased mortality in adult bacterial meningitis[12,13], in severe sepsis and septic shock[14, 15], and in febrile solid-organ transplant recipients [16]. In a large retrospective cohort of children with cancer having FN, Fletcher and colleagues demonstrated that TTA d”60 minutes, compared with 61 - 120 minutes, was associated with a lower incidence of a composite adverse outcome, and proposed 60 minutes as the benchmark for pediatric FN[17]. Our results, derived from a prospective observational cohort, reinforce this benchmark and extend it to a resource-limited setting.

When the TTA intervals were analyzed individually, only the <60-minute interval was significantly associated with a favorable outcome, while the 60 -120, 120-180, and >180-minute intervals were not significantly associated with outcomes. This dose-response pattern echoes data from sepsis, where Gaieski and colleagues reported a 70% relative reduction in mortality among patients in intensive care unit (ICU), treated within one hour of triage[18], and from adult patients with FN, where Rosa and Goldani found that each hour of delay in TTA increased the risk of death by 18%[19]. Together these observations support the prioritization of antibiotic delivery within the first hour of presentation in neutropenic children with cancer.

Among the factors examined for association with adverse outcome, urinary tract infection, bacteremia and respiratory tract infection were each statistically significant ($p<0.001$), underscoring the prognostic weight of a documented focus of infection. In contrast, the type of malignancy, hematological and biochemical parameters (hemoglobin, ESR, total white-cell count, ANC, creatinine, and albumin), and the empirical antibiotic regimen were not significantly associated with outcome ($p>0.05$). Other authors have reported that bacteremia, a diagnosis of AML, a falling white-cell count, and rising creatinine are associated with adverse events[17], and that prolonged neutropenia, slow neutrophil recovery, multi-bacterial infection, and respiratory infection predict a poor course[20]. The absence of significant associations for these variables in our cohort most likely reflects the small sample size rather than a true lack of effect.

Empirical broad-spectrum antibiotic therapy remains standard in FN even before microbiological confirmation, although rising antimicrobial resistance and shifting pathogen epidemiology continue to challenge initial regimen selection [20]. We found no significant difference in outcome between mono- antibiotic, dual- antibiotic, and triple-antibiotic regimens, a finding consistent with several previous reports that did not detect an association between the specific empirical antibiotic regimen and outcome[17,18,19]. This suggests that, within an appropriate guideline-based framework, the timeliness of the first dose may be more decisive than the precise combination chosen.

Conclusion

In children with cancer having febrile neutropenia, early empirical antibiotic administration, particularly within 60 minutes of presentation was associated with significantly better hospital outcomes than delayed administration. Documented urinary tract infection, bloodstream infection and respiratory tract infection were associated with adverse events; whereas the type of malignancy, baseline laboratory parameters (hematological and biochemical) and the specific antibiotic regimen were not associated with outcomes. These results support the adoption of time-to-antibiotic as an actionable quality-of-care target in pediatric oncology, including in resource-limited settings and call for larger multicenter studies to refine the optimal threshold.

Limitations

This study had several limitations. It was conducted at a single center, which may limit generalizability. The sample size was relatively small and the number of adverse events were few, producing wide confidence intervals and limiting the power to detect associations for secondary variables and to perform multivariable adjustment.

Recommendation

Larger, multicenter studies are needed to confirm the findings of this study and to define the optimal TTA threshold for pediatric FN in this setting.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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