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Hospital Outcome of Febrile Neutropenia Following Early Administration of Antibiotic in Children with Cancer

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Abstract

Background: Febrile neutropenia (FN) is a major source of morbidity and mortality among pediatric patients with cancer. Prompt administration of antibiotics or early time to antibiotic (TTA) is associated with improved outcomes in febrile neutropenic children with cancer. **Objective:** To compare hospital outcomes between children with cancer receiving early versus delayed antibiotic administration for febrile neutropenia. **Methods:** This observational study was conducted at the Department of Paediatrics Haemato-oncology, Bangladesh Medical University (BMU), Dhaka, Bangladesh. Total 40 children with cancer who developed febrile neutropenia were evaluated. Data were collected by interview, physical examination and evaluation of laboratory reports. Age, primary disease, neutropenia, time to antibiotic (TTA), etiologies and outcomes were recorded accordingly. **Results:** Out of 40 children, majority 28 (70.0%) belonged to age ≤ 7 years. Of them, 28 (70.0%) children had acute lymphoblastic leukemia (ALL), 4 (10.0%) had lymphoma, 3 (7.5.0%) had Wilm's tumor, 2 (5.0%) had acute myeloblastic leukemia (AML) and 3 (7.5%) had other cancer. Early TTA (<60 minutes) was found in 27 (67.5%) children and delayed TTA (60 minutes to 24 hours) was found in 13 (32.5%) children. Composite adverse events (AE) occurred in only 15% study children

whereas good outcome observed in 85% children. Children with early antibiotic therapy (<60 minute) had better outcome than those with delayed antibiotic therapy ($p < 0.001$). Regarding the different TTA; <60 minutes TTA had significant better outcomes than other time intervals ($p < 0.05$). Presence of urinary tract infection (UTI), bacteremia, respiratory tract infection (RTI) and early TTA were significantly associated with outcomes of FN in children with cancer ($p < 0.05$). **Conclusion:** Early TTA had better outcome of FN in children with cancer than those with delayed TTA. Presence of UTI, bacteremia, RTI and early TTA were significantly associated with outcomes of FN in children with cancer.

Keywords

Children with Cancer, Febrile Neutropenia (FN), Time to Antibiotic (TTA), Outcomes

1. Introduction

Febrile neutropenia (FN) is a major source of morbidity and mortality among pediatric patients with cancer [1]. Children with cancer, fever during neutropenia may be the only sign of infection because the inflammatory response that causes visible signs of infection (erythema, edema, swelling, or drainage) does not occur [1]. The time of the patient's presentation with fever may not reflect the time of onset of illness, as the state of neutropenia is asymptomatic until the patient becomes febrile. Neutropenia is a major risk factor for the development of an infection. The risk of infection is greatly affected by the severity and duration of the neutropenia [1]. Fever is still the most common complication of antineoplastic therapy and is likely to remain so until the development of tumor specific therapies that are not myeloablative [1]. A substantial proportion of febrile episodes are caused by opportunistic bacterial and fungal pathogens and are associated with a considerable risk of complications, such as overwhelming sepsis and death, unless prompt therapy is administrated [2]. Although bacteremia is documented in only 15% to 20% of neutropenic patients, it remains a significant cause of mortality in the febrile neutropenic patient [3]. Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer [4]. 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 [5]. TTA is defined as the time in minutes from presentation of either triage [emergency department (ED)], registration (outpatient clinic), or admitting (direct admission) to the first dose of parenteral antibiotics [5]. TTA was analyzed in intervals varying from 30 to 180 minutes to identify the most appropriate interval for use in subsequent analyses [4]. Decreased TTA is associated with improved outcomes of pediatric patients with FN [6]. In a study of 1523 monomicrobial bacteremia episodes in hospitalized patients, the impact of delay of active

antimicrobial therapy on mortality was found to vary by level of neutropenia [7]. In adjusted analysis, delay was not significantly associated with increased mortality among patients who were nonneutropenic [7]. In another study of a large cohort of children with cancer and FN found that delayed TTA is independently associated the poor adverse event (AE) outcome of in-hospital mortality, pediatric intensive care unit (PICU) admission within 24 hours of presentation, or fluid resuscitation > 40 ml/kg within 24 hours of presentation [4]. Other published reports also describe quality improvement initiatives designed to decrease TTA in pediatric patients with FN [6] [8] [9]. Prolonged TTA is independently associated with the outcomes of increased mortality and length of stay (LOS) in conditions like bacterial meningitis [10], septic shock [11] and fever in solid organ transplant patients [12]. Bacteremia is present in approximately 20% of cases of febrile neutropenia in children, whereas no source of infection is identified in 30% to 40% of patients with febrile neutropenia, although 95% of patients respond and become afebrile following antibiotic therapy [13]. A number of studies had been done to see relationship between TTA and the outcomes in febrile neutropenic patients in children with cancer; but no study has been carried out in our country. The aim of this study was to assess the outcomes of different TTA in febrile neutropenic children with cancer, which help to decrease the mortality and morbidity of these patients.

2. Methodology

This observational study was conducted at the Department of Pediatrics Hematology and Oncology, Bangladesh Medical University (BMU), Dhaka, Bangladesh. The study was approved by the Institutional Review Board (IRB), BMU, Dhaka, Bangladesh. Total 40 children with cancer who developed febrile neutropenia were enrolled following selection criteria. Children with diagnosed cases of cancer, having new onset of fever by history or documented as >38.5˚C or 38.0˚C - 38.4˚C on two occasions 1 hour apart and absolute neutrophil count (ANC) < 500/mm^3 were included. Children with cancer had severe sepsis on initial presentation, or admission in the pediatric intensive care unit (PICU) at initial presentation or severe sepsis and received ≥40 ml/kg of fluid resuscitation and time to antibiotic (TTA) > 24 hours were excluded from the study. Patients with a time to antibiotic (TTA) greater than 24 hours are typically excluded from this study, because delayed antibiotic administration introduces significant confounding factors like—delayed recognition of infection, atypical presentation, or barriers to care; all of which can independently affect outcomes.

2.1. Operational Definition

Febrile neutropenia (FN): New onset of fever by history or documented as >38.5˚C or 38.0˚C - 38.4˚C on two occasions 1 hour apart with absolute neutrophil count (ANC) <500/mm^3 [14].

Time to antibiotic (TTA): The time (in minutes) required for the administra-

tion of the first dose of empiric antibiotics in children with FN [5].

Severe sepsis in febrile neutropenia: defined as FN and systolic hypotension (<5th percentile for age) on first blood pressure measurement [14].

2.2. Study Procedure

2.2.1. Patient Selection

After admission of children with cancer in the Department of Hematology and Oncology, BMU; the purpose of the study was explained to each patient's guardian (mother, father or legal guardian) and then gave the choice to accept or decline to participate in this study. If a patient guardian expressed interest in participating, then the children were assessed to ascertain whether the children met the inclusion criteria or not. Written consent was taken from patient's legal guardian prior to final selection.

2.2.2. Physical Evaluation

After obtaining consent, the patient demographic information and medical history were recorded. A details history of patient including diagnosis of cancer, previous antibiotic exposure was noted accordingly. Relevant physical examination was done to document height, weight and presence of fever.

2.2.3. Laboratory Evaluation

Ten (10) ml of blood samples were taken from each study patients to measure total count of white blood cells (WBC), differential count including absolute neutrophil count, hemoglobin (Hb) with erythrocyte sedimentation rate (ESR), platelet count, serum creatinine, serum albumin and blood culture with sensitivity. Urine samples were taken for routine microscopic examination and culture with sensitivity. X-ray chest (CXR) and abdominal ultrasonography were also done.

2.2.4. Data Collection

Data were collected from all study children as well as from their parents by interview, physical examination and evaluation of laboratory investigation reports. Demographic profile, primary disease, neutropenia, time to antibiotic (TTA) as <60 minutes, 60 - 120 minutes, 121 - 180 minutes and >180 minutes to 24 hours, etiologies and outcomes were recorded accordingly. All collected information was recorded in a data collection sheet.

2.3. Outcome Measures

Outcomes of the study was labelled as composite adverse events (AE) outcome and good outcome:

- Composite adverse events (AE) outcome: in hospital mortality, need admission in pediatric intensive care unit (PICU) within 24 hours and children received resuscitation fluid > 40 ml/kg within 24 hours.
- Good outcome: discharge from hospital in stable condition.

2.4. Data Analysis

After collection, all data were cross-checked and verified. Statistical analysis was done by a computer-based software Statistical Package for Social Sciences (SPSS) version 26. The quantitative data were expressed using the mean and standard deviation (SD), whereas qualitative data were indicated using frequencies and percentages. The data was analyzed using the Fisher Exact test and the Unpaired t-test according to applicability. A p-value of less than 0.05 was considered as statistically significant.

3. Results and Observations

A total of 40 children with cancer and febrile neutropenia (ANC < 500/mm^3) were included in this study and followed up. Mean age of the study children was 64.23 ± 14.60 months (range 15 - 144 months). Among them 62.5% were male and 37.5% were female child. A male to female ratio was 1.6:1. Mean weight of the study children was 17.33 ± 7.68 Kg (range 4 - 45 kg), mean height was 102.6 ± 22.06 cm (range 55 - 152 cm) and mean body surface area (BSA) was 0.718 - 0.264 m^2.

Analyzing the primary neoplastic disease of the study children revealed that, 70% children had acute lymphoblastic leukemia (ALL), 10% had Lymphoma, 7.5% had Wilm's tumor and 5% had acute myeloblastic leukemia (AML). Rest of the children (7.5%) was suffering from other cancer (heptoblastoma, ewing's sarcoma) (Figure 1).

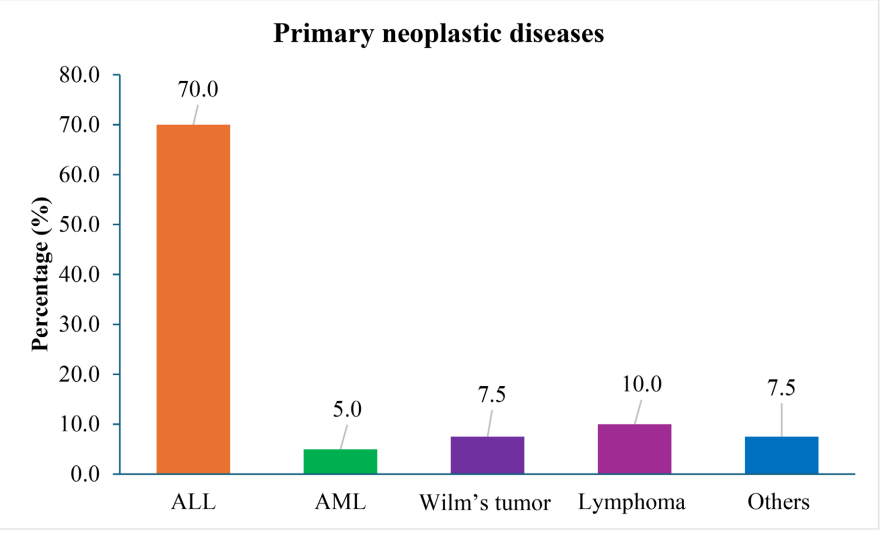

Figure 1. Primary neoplastic diseases among the study children (N = 40).

Among the study children; mean hemoglobin (Hb) level was 8.95 ± 2.45 gm/dl and ESR was 37.51 ± 16.37 mm in 1st hr. Mean total WBC count (TC) was 1096.2 ± 173.3/mm^3. Mean neutrophil count was 144.74 ± 43.03/mm^3 which ranges from 10 to 500/mm^3. Mean serum creatinine level was 0.596 ± 0.170 mg/dl and mean

serum albumin level was 36.15 ± 5.27 gm/dl (Table 1).

Table 1. Hematological and biochemical parameters of the study children (N = 40).

Parameters	Range (minimum - maximum)	Mean ± SD
Hb (gm/dl)	5.90 - 14.60	8.95 ± 2.45
ESR (mm in1st hr)	15.0 - 78.0	37.51 ± 16.37
TC (/mm^3)	110.0 - 6960.0	1096.2 ± 173.3
Neutrophil (/mm^3)	10 - 500	144.74 ± 43.03
Creatinine (mg/dl)	0.26 - 1.0	0.596 ± 0.170
Albumin (gm/dl)	24.0 - 48.0	36.15 ± 5.27

SD = Standard deviation.

Urine cultures showed no growth in 90% (36/40) of the study children. However, 7.5% children urine had growth of E. coli and 2.5% had growth of Acinetobacter (Table 2). While blood culture and sensitivity (CS) tests of the study children showed that, most of the children (97.5%) had no growth of organisms. Only 1 child (2.5%) had growth of Klebsiella in blood culture (Table 2).

Table 2. Blood culture and sensitivity tests findings of the study children (N = 40).

Variables	Frequency (n)	Percentage (%)
	Urine CS	
Acinetobacter	1	2.5
E. Coli	3	7.5
No growth	36	90.0
	Blood CS	
Klebsiella	1	2.5
No growth	39	97.5

X-ray chest (CXR) reports of the study children showed; 85.0% of the children had normal chest X-ray, whereas 12.5% had pneumonitis and 2.5% had pleural effusion (Figure 2).

We evaluated the empirical antibiotic therapy among the study children. More than one third [29 (72.5%)] of the study children got dual antibiotic therapy in the form of carbapenem and vancomycin/clindamycin. While, 6 (15%) of the children got monotherapy (carbapenem) and another 5 (12.5%) children had received triple antibiotic therapy in the form of carbapenem, vancomycin/clindamycin and metronidazole (Figure 3).

Regarding time to antibiotic (TTA) of the study children. It was observed that, TTA of 67.5% children was < 60 minutes, whereas 60 - 120 minutes in 15% children, 121 - 180 minutes in 12.5% children and >180 minutes in 5% children (Table 3).

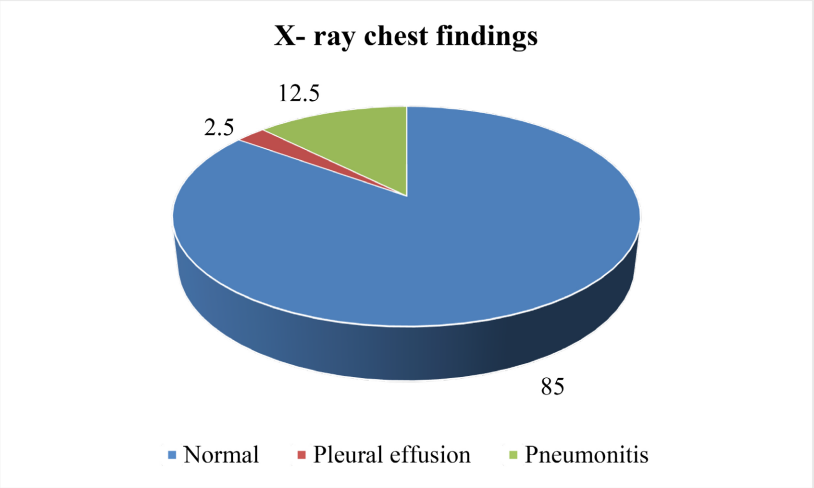

Figure 2. X-ray chest findings of the study children (N = 40).

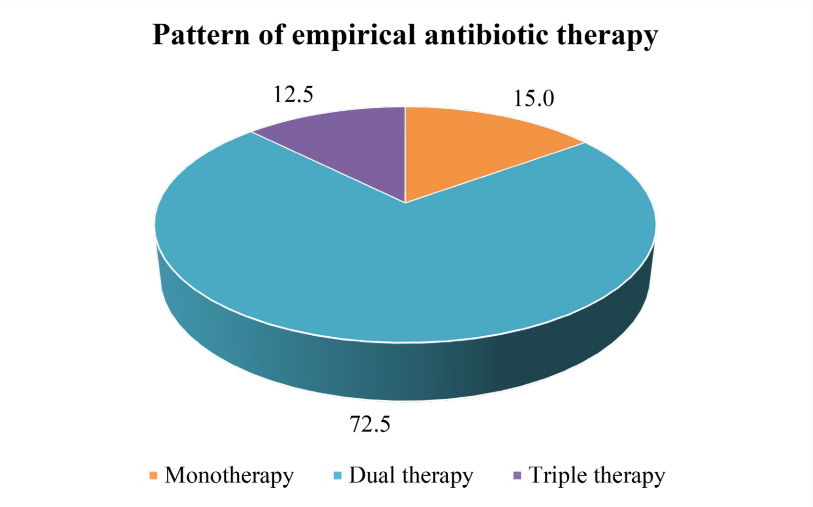

Figure 3. Pattern of empirical antibiotic therapy among the study children (N = 40).

Table 3. Time to antibiotic (TTA) of the study children (N = 40).

TTA	Frequency (n)	Percentage (%)
<60 minutes	27	67.5
60 - 120 minutes	6	15.0
121 - 180 minutes	5	12.5
>180 minutes up to 24 hours	2	5.0

In this study composite adverse events (AE) outcome like—in hospital mortality, transfer to pediatric intensive care unit (PICU) and children received resuscitation fluid > 40 ml/kg within 24 hours, occurred in only 15% study children; whereas good outcome (discharge from hospital in stable condition) observed in 85% children. Mortality rate was 7.5%, whereas 1 (2.5%) child transferred to the PICU within 24 hours after presentation and 2 (5%) children received resuscita-

tion fluid >40 ml/kg within 24 hours (Table 4).

Table 4. Outcomes of the study (N = 40).

Outcomes	Frequency (n)	Percentage (%)
In-hospital mortality	3	7.5
Admission to the PICU within 24 hours	1	2.5
Receive >40 ml/kg of fluid resuscitation within 24 hours	2	5.0
Good outcome (discharge from hospital in stable condition)	34	85.0

Regarding association between outcomes with different types of cancer; underlying diagnosis of cancer were ALL, AML, Wilm's tumor, lymphoma and others include ewing's sarcoma/ hepatoblastoma. There were no significant association found between outcomes and different types of cancer ($p > 0.05$) (Table 5).

Table 5. Association between outcome and type of cancer (N = 40).

Types of cancer	Outcomes		p value*
	Good (n = 34)	Composite adverse events (n = 6)	
ALL	25 (62.5%)	3 (7.5%)	0.498^{ns}
AML	1 (2.5%)	1 (2.5%)	0.684^{ns}
Wilm's tumor	2 (5.0%)	1 (2.5%)	0.933^{ns}
Lymphoma	4 (10.0%)	0.0%	0.882^{ns}
Others	2 (5.0%)	1 (2.5%)	0.933^{ns}

*p value measured by Fisher Exact test, ns = not significant.

Table 6. Association between outcomes and hematological and biochemical parameters of the study children (N = 40).

Variables	Outcome		p-value*
	Good (n = 34) Mean ± SD	Composite adverse events (n = 6) Mean ± SD	
Hb%	9.78 ± 2.59	8.79 ± 2.43	0.389^{ns}
ESR (mm)	38.33 ± 8.31	36.67 ± 11.72	0.743^{ns}
TC (/mm^3)	1234.12 ± 227.4	1061.67 ± 154.67	0.084^{ns}
Neutrophil (/mm)	165.15 ± 50.88	161.67 ± 11.67	0.869^{ns}
S. creatinine (mg/dl)	0.60 ± 0.16	0.59 ± 0.22	0.895^{ns}
S. albumin (mg/dl)	36.0 ± 5.22	36.33 ± 5.89	0.889^{ns}

*p-value performed by Unpaired t-test, ns = not significant.

No statistically significant association was observed between outcomes of the

study children and laboratory parameters; Hb% (p = 0.389), ESR (p = 0.743), total WBC count (TC, p = 0.084), neutrophil count (p = 0.869), serum creatinine (p = 0.895) and serum albumin (p = 0.889) (Table 6).

In this study, statistically significant association was observed between UTI, bacteremia, respiratory tract infection (RTI) and early TTA with outcomes of the study (p < 0.05). But no statistically significant association was observed between outcomes of the study and pattern of antibiotic therapy like—monotherapy (meropenem, p = 1.000), dual therapy (meropenem + vancomycin/clindamycin, p = 0.399) and triple therapy (meropenem + vancomycin/clindamycin + metronidazole, p = 0.315) (Table 7).

Table 7. Association between outcomes and different clinical variables (Urine C/S, Blood C/S, Chest X-ray, TTA and Pattern of antibiotic therapy) (N = 40).

Variables	Outcomes		p value*
	Good	Composite adverse events	
Urine CS	n =36	n = 4	
UTI	1 (2.25%)	3 (7.5%)	<0.001[s]
No growth	35 (87.5%)	1 (2.25%)	
Blood CS	n = 39	n = 1	
Klebsiella	0	1 (2.25%)	0.002[s]
No growth	39 (97.5%)	0	
Chest X-ray	n = 34	n = 6	
Normal	33 (82.5%)	1 (2.25%)	<0.001[s]
RTI	1 (2.25%)	5 (12.25%)	
TTA	n = 34	n = 6	
Early (<60 minutes)	26 (65.0%)	1 (2.5%)	0.015[s]
Delayed (60 minutes - 24 hours)	8 (20.0%)	5 (12.5%)	
Pattern of antibiotic therapy	n = 34	n = 6	
Mono therapy	5 (14.71%)	1 (16.67%)	1.000[ns]
Dual therapy	26 (76.47)	3 (50.0%)	0.399[ns]
Triple therapy	3 (8.82%)	2 (33.33%)	0.315[ns]

*p value obtained by Fisher Exact test, s = Significant, ns = Not significant.

Table 8 shows the association between outcomes and different TTA. Statistically significant association was observed in case of TTA < 60 minutes (p = 0.015); whereas, no significant association was observed between outcomes of the study children and TTA in 60 - 120 minutes (p = 0.456), 121 - 180 minutes (p = 0.315) and TTA > 180 minutes to 24 hours (p = 0.684) (Table 8).

Table 8. Association between outcomes and different TTA (N = 40).

TTA	Outcomes		p-value*
	Good (n = 34)	Composite adverse events (n = 6)	
<60 minutes	26 (76.47)	1 (16.67%)	0.015^{s}
60-120 minutes	4 (11.76%)	2 (33.33%)	0.456^{ns}
121-180 minutes	3 (8.82%)	2 (33.33%)	0.315^{ns}
>180 minutes to 24 hours	1 (2.94%)	1 (16.67%)	0.684^{ns}

* Fisher Exact test was done, s = Significant, ns = Not significant.

4. Discussion

Febrile neutropenia (FN) is still a common consequence of chemotherapy for cancer patients, despite recent improvements in infection prevention. The prompt administration of empirical parenteral antibiotics is a mainstay in the initial treatment of FN [15].

In this present study, a total of 40 children with cancer and febrile neutropenia (ANC < 500/mm^3) were included and followed up. Majority 28 (70.0%) patients belonged to age ≤ 7 years. Regarding the primary diagnosis majority 28 (70.0%) study children had ALL, followed by lymphoma, wilm's tumor, AML and others. TTA was recorded as <60 minutes, 60 - 120 minutes, 121 - 180 minutes and > 180 minutes to 24 hours. TTA < 60 minutes was found in 27 study children (67.5%), 60 - 120 minutes in 6 children (15.0%), 121 - 180 minutes in 5 (12.55) and >180 minutes to 24 hours in 2 (5.0%) children. Early TTA (<60 minutes) was found in 27 (67.5%) children and delayed TTA was found in 13 (32.5%) children. Outcome of the children was recorded as composite adverse event (AE) outcome-in-hospital mortality, PICU admission or fluid resuscitation ≥ 40 ml/kg within 24 hours of presentation and good outcome (discharge from hospital in stable condition). In this study, composite adverse events outcome occurred in only 15% study children whereas good outcome observed in 85% children. Mortality rate was 7.5%, where as 2.5% children transferred to PICU within 24 hours after presentation and 5% children received fluid resuscitation > 40 ml/kg within 24 hours. Our study findings demonstrated that children with early antibiotic therapy (<60 minutes) have better outcome than those with delayed TTA (>60 minutes to 24 hours) antibiotic therapy. Previous research involving distinct populations have confirmed the impact of early antibiotic administration on clinical outcomes [4]. 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 [5]. Prolonged TTA is independently associated with the outcomes of increased mortality and length of hospital stay [16]. Proulx N *et al.,* in their study showed that, there was an independent incremental association between delays in administrating antibiotics and mortality from adult acute bacterial meningitis [16]. Rivers E *et al.,* in their study observed that early goal-directed antibiotic ther-

apy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock [11]. In a similar study by Hamandi B *et al.* found that, there was a significant association between increasing TTA (24 hours increments) and increased hospital mortality rates in solid-organ transplant patients [12]. It was reported that TTA is independently associated with improved outcomes in febrile neutropenia in children with cancer [4]. Another study showed that early application of antibiotics as well as good clinical care are able to improve clinical outcomes from empirical antibiotic treatment in FN patients with hematological malignances [17]. Similarly, our study shows a reduction in the mortality risk and adverse events from early TTA. Therefore, in a specific population of high-risk neutropenic patients in whom the correct implementation of antimicrobial strategy is of paramount importance.

Beyond that, we further evaluated the intervals varying from <60 minutes, 60 - 120 minutes, 121 - 180 minutes and >180 minutes to 24 hours to identify the most appropriate time period for TTA. In our study, we found <60 minutes TTA was significant ($p = 0.015$) than other time intervals. In a study by Gaieski *et al.* showed a relative risk reduction of mortality by 70% for non-neutropenic intensive care patients with severe sepsis and septic shock treated with an appropriate antibiotic within 1 hour of triage compared with those with TTA > 1 hour ($p = 0.02$) [18]. One related study tried to determine whether TTA is a predictor of mortality in adult cancer patients with FN [19]. In that study, TTA was independently associated with all-cause 28-day mortality in the context of FN after cytotoxic chemotherapy; each hour of delay in TTA raised the risk for death by 18% [19]. Fletcher *et al.* in their study observed that TTA ≤ 60 minutes, when compared with a TTA of 61 minutes to 120 minutes, was associated with a lower incidence of a composite end point that included in-hospital mortality, intensive care unit admission and fluid resuscitation >40 ml/kg within 24 h of presentation in pediatric FN patients [4]. These study results support our study result which identified TTA < 60 minutes for most beneficiary in terms of good outcome for febrile neutropenic children with cancer. Achieving a time to antibiotic (TTA) of less than 60 minutes for patients with febrile neutropenia (FN) often requires the implementation of specific quality improvement initiatives within hospitals. This target is challenging due to delays in triage, diagnosis, order entry and medication administration. To overcome these barriers, hospitals may need to adopt: dedicated febrile neutropenia (FN) triage, protocolized order settings and rapid access to antibiotics.

Identifying the expected risk factors for poor outcome of FN with cancer in children, we evaluated different hematological, biochemical parameters and also X-ray chest (CXR), blood and urine culture with sensitivity reports. Mean hemoglobin (Hb) level was 8.95 ± 2.45 gm/dl, mean ESR was 37.51 ± 16.37 mm in 1st hour, mean total count of WBC (TC) was 1096.2 ± 173.3/mm^3, mean absolute neutrophil count was 144.74 ± 43.03/mm^3, mean serum creatinine level was 0.596 ± 0.170 mg/dl and mean serum albumin level was 36.15 ± 5.27 gm/dl. In urine

culture, only 4 children (10.0%) showed growth of organisms in urine. Among them 3 children (7.5%) had growth of E. Coli and one had growth of Acinetobacter. In blood culture, only one child (2.5%) showed growth of klebsiella. CXR reports of 34 (85.0%) children had normal findings whereas 5 children (12.5%) had features of pneumonitis and one child (2.5%) had pleural effusion. We found presence of UTI, bacteremia, respiratory tract infection (RTI) and early TTA were significantly associated with outcomes of the study children ($p < 0.05$). Fletcher *et al.* in their study showed that bacteremia, the diagnosis of acute myeloblastic leukemia (AML), decreasing total WBC count, and increasing initial creatinine were associated with the composite adverse event (AE) outcome [4]. Another related study showed that the risk factors for poor FN outcomes were associated with prolonged duration of neutropenia over 9 days, slow neutrophil recovery and respiratory infection [17]. Additionally, patients with multi-bacterial infection, as well as further absolute neutrophil count (ANC) decrease after fever, had a poor prognosis. One previous study documented that diagnosis of leukemia and bacteremia were significantly correlated hospital mortality and/or ICU admission [19]. In our study, no significant association was observed between outcome of the study children and underlying disease, hematological parameters like Hb%, TC or absolute neutrophil count and biochemical parameters like serum creatinine or serum albumin, which may be due to small sample size.

Empirical therapies with antimicrobials were always used in patients with FN, even without clear microbiological evidence [20]. Although rapid and accurate antibiotic regimens in the first line could ensure better outcome in FN patients; increasing incidence of antibiotic resistances and changes of pathogen epidemiology require improved treatment strategies in FN patients, especially for the initial empirical approach. Previous study showed that initial monotherapy with drugs recommended by the guidelines indicated better outcome in FN patients [17]. In our study we did not find any statistically significant association between different pattern of antibiotic therapies like—monotherapy; meropenem, dual therapy; meropenem + vancomycin/clindamycin and triple therapy; meropenem + vancomycin/clindamycin + metronidazole. In this context, related studies in FN patients with cancer did not find any significant association between different modes of antibiotic therapy and outcome of the patients [4] [18] [19].

5. Conclusion

The current study concludes that children with early TTA (antibiotic therapy < 60 minutes) have better outcome than those with delayed TTA (antibiotic therapy 60 minutes to 24 hours). To identify the most appropriate time period for TTA, we found <60 minutes TTA is significant than other time intervals. This study showed that composite adverse events outcome occurred in only 15% study children whereas good outcome was observed in 85% children. Presence of UTI, bacteremia, RTI and early TTA were significantly associated with outcomes of FN in children with cancer.

Limitations of the Study

It was a single center study with a relatively small sample size. Moreover, the exclusion of patients with TTA > 24 hours and those with severe sepsis on initial presentation may indeed limit the generalizability of the study findings. Although, these exclusions remove a subset of patients who are often at higher risk of poor outcomes and may present with atypical or delayed care pathways.

Recommendation

The study suggests that early TTA has better outcome than those with delayed TTA. To know the exact or effective antibiotic therapy and also the appropriate TTA in FN children with cancer, a large-scale multicenter study will likely to be needed.

Conflicts of Interest

All authors declared that they have no conflict of interest.

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