Original Article

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Time to Antibiotic Administration in Pediatric Oncology Patients Presenting to the Emergency Department with Fever and Neutropenia

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Author`s Contribution

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ABSTRACT

Objective: To evaluate the time to antibiotic administration (TTA) in febrile neutropenia patients, and their outcomes.

Methodology: The Descriptive cross-sectional cohort study was conducted at The Indus Hospital and Health Network in Karachi, from April 2021 to September 2021. All the children with fever and neutropenia secondary to malignancy or oncologic treatment and those who gave consent to being part of the study were included. Patient records was accessed through the Hospital Management Information System to identify pediatric oncology patients presenting to the ED with fever and neutropenia (antibiotic given on clinical assessment and then neutropenia confirmed on laboratory testing).

Results: A total of 357 patients were studied, their mean age was 7.40+4.13 years. Males were in majority 66.7%. Sever neutropenia was in 41.2% of the cases. Overalled of the patients and patients related barrier were most common. 71.40% cases given antibiotics within 60 minutes, while 28.60% were given after 60 minutes. Out of all 9.0% were discharged, 48.7% were followed in daycare, 29.4% were admitted in ward, 8.7% were admitted DHU, 4.2% were admitted in ICU and 2.2% cases were died. Outcomes of the patients were statistically insignificant according to time to antibiotic given after triage (p=>0.05), while ICU admission was significantly high among patients those were given antibiotic within 60 minutes (p=0.012).

Conclusion: The administration of antibiotics in pediatric oncology patients does not seem to have a significant impact on delaying the initiation. Current evidence suggests that such delays are minimal and do not have a significant impact on patient outcomes. Therefore, the use of antibiotics in pediatric oncology patients should continue to be based on clinical judgment and individual patient needs, rather than concerns about delaying initiation.

Key words: Febrile neutropenia, TTA, ICU admission, mortality.

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Introduction

Children with cancer who are receiving chemotherapy are highly vulnerable to illnesses caused by infections, which can lead to serious health complications or death due to a weakened immune system. This can be particularly problematic because the usual signs and symptoms of inflammation may be diminished, with fever being the only clear indication of a severe infection.[1] Rapid administration of broad spectrum antibiotics is necessary for children who experience a rise in body temperature during myelosuppressive chemotherapy or have a previous medical record of benign hematologic immunosuppression.[2] Without evident indications of illness, a delay in receiving treatment can result in the rapid advancement of infection and sepsis.[2] In immunocompromised oncology patients, the occurrence of neutropenic fever contributes to increased healthcare

expenses, morbidity, and mortality rates.[3] It has been revealed that extending the time frame beyond 60 minutes for administering antibiotics to pediatric oncology patients presenting with suspected neutropenic fever (NF) raises the likelihood of patient mortality, admission to the pediatric intensive care unit, the requirement for hemodynamic resuscitation, and overall length of Hospital stay.[3,4] The primary factors that make cancer patients more susceptible to immunodeficiency are the underlying disease itself and the associated treatment and care methods. Recently, the promptness of antibiotic administration, known as time to antibiotic administration (TTA), has emerged as a critical aspect of providing quality care for patients experiencing febrile neutropenia.[5]

Initiating antibiotic treatment promptly by clinicians can help minimize the associated morbidity and mortality linked to this condition.[5,6]Although the significance of administering antibiotics promptly has been acknowledged, there is no agreement on the specific time frame in which antimicrobial medications should be provided to patients with febrile neutropenia. Different institutions have set specific time targets, starting from the moment a patient arrives at the emergency department (ED), to ensure the timely administration of antibiotics.[2,7,8] Research has demonstrated that administering antibiotics to patients with febrile neutropenia within 60 minutes of their arrival in the emergency room (EAR) can significantly decrease mortality and morbidity rates.[9,10]

Nevertheless, certain studies fail to establish a correlation between time to antibiotic administration (TTA) and the outcome of patients. According to Fletcher et al., administering antibiotics between 60 and 120 minutes after a patient's presentation led to poorer outcomes compared to administering antibiotics within the initial 60 minutes of presentation.[11] Thus, the benefit of rapid antibiotic administration to high-risk patients likely outweighs any potential harm of administering a single dose of antibiotic prior to laboratory confirmation of neutropenia in patients on active chemotherapy. Our management goal is to provide the first dose of antibiotics within 60 minutes from patient triage. To our knowledge, there is limited published data regarding TTA in febrile neutropenia patients and their outcome. Frequent inpatient admissions due to febrile neutropenia and death due to infections impose a major hurdle in treatment of these patients. This study may highlight the importance of TTA in febrile neutropenia patients and associated barriers. The overarching goal is to define ways to decrease mortality and morbidity of neutropenic patients from infectious causes.

Methodology

This descriptive cross-sectional study was conducted at The Indus Hospital and Health Network in Karachi, Pakistan, during a period of six months from April 2021 to December 2021. A sample size of 357 cases was calculated by The World Health Organization (WHO) sample size calculator with level of significance (0.05) and power of error 80. All the children with fever and neutropenia secondary to malignancy or oncologic treatment (defined as a fever of 38.3°C (101°F) or higher and an absolute neutrophil count (ANC) of less than 500 cells/mm3 or an ANC that is expected to decrease to less than 500 cells/mm3 over the next 48 hours) and those who gave consent to being part of the study were included. All the patients with neutropenia due to causes other than malignancy or oncologic treatment, patients who have received antibiotics within the past 48 hours prior to presentation, and those who refuse or revoke participation were excluded. Non probability consecutive sampling technique was used. The study was commenced after attaining approval from the Institutional Review Board. Parents/Guardians of each patient was thoroughly briefed about the study and a verbal consent was obtained. In addition to the consent from their parents/guardians, an informed consent was obtained from children above 7 years of age. Physical examination of each patient was directed at the Pediatric Oncology Emergency Department (ED) of The Indus Hospital and Health Network (IHHN).

Clinical measures (The Common Terminology Criteria for Adverse Events, rendition 5.0) and laboratory examinations were documented. Patient records was accessed through the Hospital Management Information System to identify pediatric oncology patients presenting to the ED with fever and neutropenia (antibiotic given on clinical assessment and then neutropenia confirmed on laboratory testing). The following information were obtained for every participant: hematologic/oncologic diagnosis, absolute neutrophil count (ANC), patient triage time, time to antibiotic order by doctor, time to antibiotic administration (TTA), any barrier to TTA if given 60 minutes after triage, patient outcome 24 hours after TTA. Physician and nursing notes were reviewed to identify potential causes of delay in antibiotic administration. Standard IHHN laboratory reference values were used to interpret values as low or high. Data was analyzed using SPSS version 24.0. Mean ± SD were computed as

appropriate for all quantitative variables such as age, BMI, TTA and ANC based on the assumptions of normality. All categorical variables such as gender, outcomes, barriers and neutropenia categories were presented as frequency and percentages. Chi-squire test was applied as appropriate to assess association of gender, barriers, outcomes and initial diagnosis with different categories of neutropenia. A p-value <0.05 was considered statistically significant.

Results

A total of 357 patients were studied, their mean age was 7.40±4.13 years. Males were in majority 66.7% and females were 33.3%. Sever neutropenia was in 41.2% of the cases, followed by 16.2% had moderate neutropenia and 42.6% cases had mild neutropenia. Mean time triage was 8.26±3.29 minutes and mean time to antibiotic given after triage 61.93±25.55 minutes. Mean vitals are presented in table I

Table I: Demographic and clinical characteristics of the patients. (n=357)

Variables			Statistics	
Age (mean ±SD)			7.40±4.13 years	
Weight (mean ±SD)			19.22±10.85 kg	
Heart rate			141.0±21.15 /m	
Respiratory rate			26.77±5.44 /m	
Temperature			100.87±1.20 F	
O2			103.14±67.60%	
Mean time triage			8.26±3.29 minutes	
Mean time to antibiotic given after triage			61.93±25.55 minutes	
Gender	Female		119	33.3%
	Male		238	66.7%
Severity of neutropenia		Severe	147	41.2%
		Moderate	58	16.2%
		Mild	152	42.6%
Barrier (in case of delay in antibiotic administration i.e more than 60 min from triage (n=102)	Patients overload	Yes	25	24.5%
		No	77	75.5%
	Staff related delay	Yes	87	85.3%
		No	15	14.7%
	Doctor related delayed	Yes	95	93.1%
		No	7	6.9%
	Patient-related delay	Yes	74	72.5%
		No	28	27.5%

In accordance to the barrier (in case of delay in antibiotic administration i.e. more than 60 min from triage) the 24.5% cases delayed due to overload of patients, 85.3% cases were delayed by staff, 93.1% were doctor related delayed and 72.5% were delayed by patients out of 102 delayed cases. Table II

Table II: Outcome of the patients (n=357)

Variables		N(%)	
Discharged	Yes	32	9.0%
	No	325	91.0%
Follow in daycare	Yes	174	48.7%
	No	183	51.3%
Admitted in ward	Yes	105	29.4%
	No	252	70.6%
Admitted in DHU	Yes	31	8.7%
	No	326	91.3%
Admitted in ICU	Yes	15	4.2%
	No	342	95.8%
Expired	Yes	8	2.2%
	No	349	97.8%

In accordance to time to antibiotic given after triage, the 71.40% cases given antibiotics within 60 minutes, while 28.60% were given after 60 minutes. Figure 1

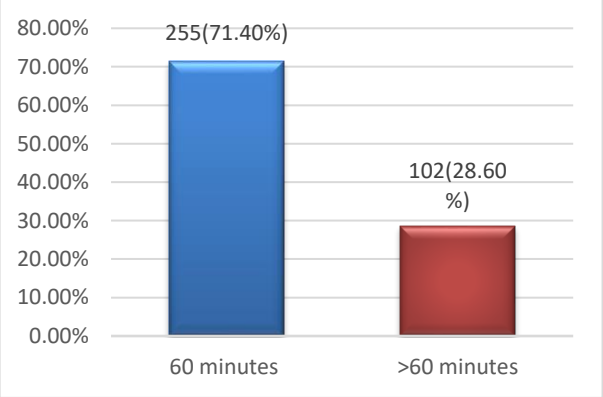

Figure 1. Time to antibiotic given after triage. (n=357)

Out of all 9.0% were discharged, 48.7% were followed in daycare, 29.4% were admitted in ward, 8.7% were admitted DHU, 4.2% were admitted in ICU and 2.2% cases were died. Table II

Outcomes of the patients were statistically insignificant according to time to antibiotic given after triage (p=>0.05), while ICU admission was significantly high among patients those were given antibiotic within 60 minutes (p=0.012). Table III

Discussion

Febrile neutropenia (FN) is a medical emergency that occurs in patients with cancer, particularly those who receive chemotherapy. The prompt administration of antibiotics is crucial in the management of FN patients to reduce the risk of complications and mortality. The time to antibiotic administration (TTA) is a critical factor that affects the outcomes of FN patients. A delay in initiating antibiotic therapy can result in an increased risk of septic shock, organ dysfunction, and death. Current study has been conducted to evaluate the time to antibiotic

administration (TTA) in febrile neutropenia patients, and their outcomes. In this study outcomes of the patients were statistically insignificant according to time to antibiotic given after triage (p=>0.05), while ICU admission was significantly high among patients those were given antibiotic within 60 minutes (p=0.012).

Table III: Outcome according to time to antibiotic given after triage. (n=357)

Variables		Time to antibiotic given after triage: 60 minutes	Time to antibiotic given after triage: >60 minutes	Total	p-value
Discharge	Yes	22	10	32	0.725
		6.2%	2.8%	9.0%	
	No	233	92	325	
		65.3%	25.8%	91.0%	
Admit in ward	Yes	81	24	105	0.123
		22.7%	6.7%	29.4%	
	No	174	78	252	
		48.7%	21.8%	70.6%	
Admit in DHU	Yes	25	6	31	0.235
		7.0%	1.7%	8.7%	
	No	230	96	326	
		64.4%	26.9%	91.3%	
Admit in ICU	Yes	15	0	15	0.012
		4.2%	0.0%	4.2%	
	No	240	102	342	
		67.2%	28.6%	95.8%	
Expired	Yes	8	0	8	0.070
		2.2%	0.0%	2.2%	
	No	247	102	349	
		69.2%	28.6%	97.8%	

In the comparison of this study Abrate AM et al[13] observed that they did not find a link between a delay in TTA and hospital mortality or ICU admission, the prompt initiation of empirical antibiotic therapy remains a critical risk factor in the prognosis of patients with FN. On the other hand, Murray K et al[14] reported that the patients who receive their first dose of antibiotics within 60 minutes tend to have better outcomes. The data reveals that more than 50% of patients received their first dose of antibiotics within this timeframe after the intervention, compared to only 17% before. Furthermore, following the intervention, there were no cases of ICU admissions or deaths, and the average length of hospital stay improved significantly by 26.68%, with an average length of stay of 5.8 days compared to 7.91 days pre-intervention.[13]

In the study by Todurkar N et al[15] also reported that the approximately 66% of the patients successfully met the target TTA of 60 minutes or less. However, there was a noticeable delay in TTA for patients who were seen during daytime hours or on weekends when compared to those who arrived in the evening or at night or on weekdays. In this study according to the barrier (in case of delay in antibiotic administration i.e more than 60 min from triage (n=102)) the 24.5% cases delayed due to overload of patients, 85.3% cases were delayed by staff, 93.1% were doctor related delayed and 72.5% were delayed by patients. In accordance to time to antibiotic given after triage, the 71.40% cases given antibiotics within 60 minutes, while 28.60% were given after 60 minutes. Several studies have investigated the TTA in FN patients and its association with patient outcomes. One such study found that providing antibiotics within an hour has been shown to reduce hospital stays, mortality rates, and admissions to the intensive care unit (ICU).[15] Similarly, another study demonstrated that administering antibiotics within 60 minutes was linked to an 82.1% decrease in relative risk of mortality compared to administering antibiotics after 60 minutes.[16] These findings highlight the importance of prompt antibiotic administration in FN patients. Despite these findings, some studies have failed to demonstrate a clear association between delayed TTA and poor patient outcomes. For instance, a recent study found that delaying antibiotic administration for more than 90 minutes did not affect patient outcomes in FN patients.[17] However, this study had some limitations, including a small sample size and the inclusion of patients who were not at high risk of complications. Furthermore, in a study by Alsadoon A et al[18] demonstrated that the delayed administration of antibiotics (more than 3 hours) was linked to a 3.85 times higher mortality rate in the pediatric intensive care unit (PICU) among children with septic shock compared to those who received antibiotics within 3 hours, after adjusting for factors such as severity of illness, age, comorbidities, and volume resuscitation.[18] Therefore, it is important to consider these factors when evaluating the impact of TTA on patient outcomes. The study may suffer from a small sample size, which can limit the generalizability of the findings. There may be other factors that affect the outcome of febrile neutropenia patients besides TTA, such as comorbidities, cancer type, and severity of the neutropenia. Failure to account for these factors can lead to biased results.

Conclusion

The administration of antibiotics in pediatric oncology patients does not seem to have a significant impact on delaying the initiation. While antibiotics are commonly used to prevent and treat infections in these patients, concerns have been raised regarding potential delays initiation due to antibiotic use. However, current evidence suggests that such delays are minimal and do not have a

significant impact on patient outcomes. Therefore, the use of antibiotics in pediatric oncology patients should continue to be based on clinical judgment and individual patient needs, rather than concerns about delaying initiation. However, it is important to monitor patients closely for any signs of antibiotic resistance or adverse reactions to antibiotics, and to use these medications judiciously to prevent the development of antibiotic-resistant infections.

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