



Research Article

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Time to First Dose of Antibiotics in Children with Cancer and Febrile Neutropenia. A Report from a Peruvian Hospital

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Abstract

The Febrile Neutropenia (FN) in children with cancer may be the only indication of a serious underlying infection, which can lead to sepsis and be fatal; it is recommend start antibiotics as soon as possible. We realized a retrospective analysis of all patients under 14 years of age with cancer, who attended the Pediatric Emergency of Rebagliati Hospital (Lima-Peru), between July 2016 and February 2017, due to fever, neutropenia and history to received chemotherapy in the last 15 days. Of 36079 emergency attentions, 31 were episodes of FN. The median of time from arrival to emergency to the first dose of antibiotic or Time To Antibiotics (TTA) was 206 minutes (Interquartile range [IQR], 137-390). Patients with leukemia had a lower TTA than patients with solid tumors ($p = 0.037$). The TTA after 120 minutes was not associated with longer hospital stay, transfer to the PICU or mortality. In the cases evaluated, the TTA exceeded the international standards. Patients with solid tumors have higher TTA than patients with leukemia. It is necessary to create a multidisciplinary program to improve this time.

Keywords: Antibiotics; Children; Febrile neutropenia; Neoplasms; pediatric emergency

Abbreviations: TTA: Time From Arrival at The Emergency Room to First Dose of Antibiotics, or Time to Antibiotics.

Introduction

Cancer in the pediatric population has increased in recent years, each year more than 200 000 children are diagnosed with cancer worldwide [1], in the Americas region, more than 27 000 cases of cancer are diagnosed in children under 14 years, and an estimated 10 000 deaths are due to this disease [2]. In Peru, according to the Ministry of Health (MINSa), there are 1600 new cases per year of childhood cancer [3]. The treatment of cancer in pediatrics has three main components: surgery, radiotherapy and chemotherapy [4], which together had improved the 5-year survival less than 30% to more than 80% in the high-income

countries.¹ However, like all treatment, chemotherapy has adverse effects on patients, the most important, neutropenia. This state of neutropenia causes oncology patients to be more vulnerable to severe infections, which can lead to sepsis and be fatal [5]. Fever during neutropenia induced by chemotherapy may be the only indication of a serious underlying infection, since the signs and symptoms of inflammation are usually attenuated [6]. Clinical practice guidelines, such as the Consensus of the Latin American Society of Pediatric Infectious Disease [7], emphasize the prompt institution of broad spectrum empirical antibiotic treatment, at the onset of fever, since it has been shown to be determinant for patient survival, because the progression of the infection can be rapid and cannot be reliably distinguished from fever due to other causes [8]. In Peru, no information has yet been published on this topic, so this study seeks to know the time to start treatment with antibiotics, in pediatric cancer patients, who come to the emergency department with Febrile Neutropenia (FN), and its impact on mortality, in a

referral hospital such as the Edgardo Rebagliati Martins National Hospital (HNERM).

Materials and methods

Study Design

Retrospective study. We analyzed the data obtained from the pediatric clinical records of the HNERM, in Lima-Peru.

Population

Pediatric oncology patients treated for FN, in the pediatric emergency service of the Edgardo Rebagliati Martins Hospital, between July 2016 and February 2017.

Selection Criteria

We included all cases of patients under 14 years of age, with any confirmed oncological diagnosis, who had received treatment with chemotherapy in the last 15 days before the episode of FN that attended the Pediatric Emergency. FN was defined by an absolute neutrophil count of <500 cells/mm³ or <1000 cells/mm³ if predicted to fall to <500 cells/mm³ in the next 24-48 hours, and at least one episode of fever ($T > 38^{\circ}\text{C}$, taken by any method) [9]. We excluded cases where medical records were not available for review or were incomplete, cancer patients in palliative treatment or children with hematopoietic stem cells transplants.

Variables

Epidemiological information was included (sex, age, diagnosis). The following times were determined: (1) From the last day treatment of chemotherapy until the onset of fever, (2) From the onset of fever until they reached the Pediatric Emergency, (3) Since the patient arrived at the Emergency until received the first dose of antibiotics or Time to Antibiotics (TTA). The TTA was evaluated in subcategories of time if there was re-evaluation (time from and admission to emergency until the result of the blood count, from the result of the blood count to the re-evaluation, from the re-evaluation to the first dose of antibiotics). Data of hospital stay, admission to The Pediatric Intensive Care Unit (PICU) and mortality were recorded.

Statistical Analysis

The descriptive data was analyzed as median (Interquartile Range [IQR]) for continuous variables and frequency with percentages for categorical variables. The TTA was reported as a continuous variable and then as a dichotomous variable with episodes divided into the following groups according to the administration of the first dose of antibiotics: ≤ 120 minutes vs. >120 minutes. The other subcategories of time and hospital stay were analyzed as continuous variables. For the comparisons between 2 groups, the Fisher exact test was used for the categorical variables and the U-Mann-Whitney test was used for the medians. The final model included only significant factors ($p < 0.05$).

Statistical analyzes were performed using Stata version 14 (Stata Corp, College Station, TX).

Ethical Aspects

The protocol of this study was approved by the Ethics Committee of HNERM. The confidentiality of the data obtained from the medical records was maintained.

Results

General Description of The Population

Between July 2016 and February 2017, the Pediatric Emergency Service of HNERM performed 36079 attentions, of which 181 were attentions to pediatric patients with cancer, of these, only 31 were episodes of FN, the others 150 attentions corresponded to children with cancer with other diagnoses, such as neutropenia without fever, or fever without neutropenia, dehydration, pathological fractures, respiratory infections or palliative patients. The 31 episodes of NF corresponded to 23 patients. The median age of the 23 patients was 7 years (IQR, 4-9 years), 61% were women, and 56% were diagnosed with leukemia (Table 1).

Characteristics	N = 23
Age, median (range)	7 years (0.5 - 13)
Sex:	
Male (%)	9 (39)
Female (%)	14 (61)
Diagnosis:	
Leukemia (%)	13 (56)
Bone and soft tissue sarcomas (%)	5 (22)
Brain tumors (%)	2 (9)
Liver tumors (%)	2 (9)
Retinoblastoma (%)	1 (4)

Table 1: Characteristics of patients who attended emergency due to Febrile Neutropenia.

Time from the onset of the fever to the start of antibiotic treatment

In the 31 episodes of FN, it was determined that the median time between the last day of chemotherapy and the onset of fever was 7 days (IQR, 4-8 days). The median time between the onsets of fever until the patient arrived at the emergency service was 16 hours (IQR, 6-25 hours). The emergency physician evaluated the 100% of the patients, within 10 minutes of their arrival at the hospital. After the initial medical evaluation, 35% of the cases had an indication for antibiotic treatment, while in 65% of the cases; a blood count was requested for subsequent reassessment.

The median time from arrival at the emergency room to first dose of antibiotics or to antibiotics (TTA), in general, including both those who had only one medical evaluation and those who were reassessed, was 206 minutes (IQR, 137-390), as observed in Figure 1.

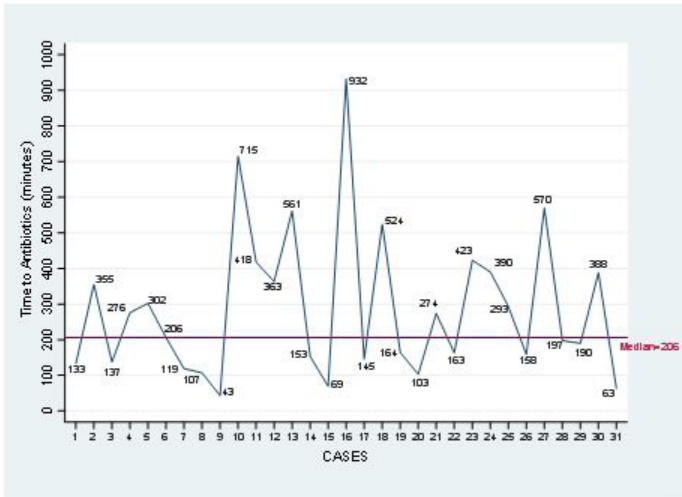


Figure 1: Time from arrival at the emergency room to first dose of antibiotics or time to antibiotics (minutes), from 31 cases. The median of time was 206 minutes, the time shorter was 43 minutes and the longer was 932 minutes.

For those cases in which antibiotic was given was after the initial medical evaluation (without reassessment), the median of TTA was 119 minutes (IQR, 69-158), while for those who were reevaluated, the median of TTA 359 minutes (IQR, 211-499), being statistically significant (Mann-Whitney $p = 0.0012$). For the cases that were reevaluated, the subprocesses were verified (Table 2).

	N (%)	Median (minutes)	IQR (minutes)
TTA global	31 (100%)	206	137 - 390
TTA without reassessment	11 (35%)	119	69 - 158
TTA with reassessment	20 (65%)	359	211 - 499
Subprocesses in the cases of reassessment:			
- Time from the initial evaluation to the result of the blood count		104	70 - 121
- Time from laboratory result to reevaluation		179	113.5 - 263
- Time from re-evaluation to the first dose of antibiotic		110	60 - 141

Table 2: Time from arrival at the emergency room to first dose of antibiotics or time to antibiotics (TTA), according to the presence of reassessment.

The TTA was significantly higher in patients with solid tumors unlike patients with leukemias (median = 388 vs 171 minutes, U. Mann-Whitney, $p = 0.0374$) Figure 2.

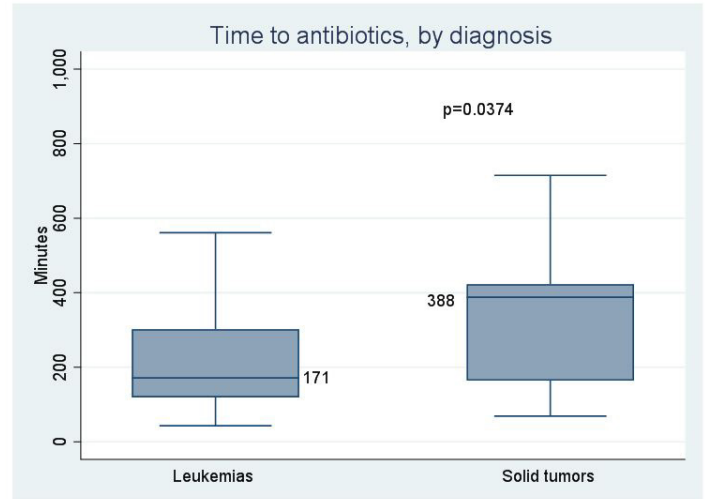


Figure 2: Time from arrival at the emergency room to first dose of antibiotics or time to antibiotics (minutes), according to diagnosis. The patients with leukemias had less time to antibiotics (171 minutes) than patients with solid tumors (388 minutes).

Association Between Time to Antibiotics and Clinical Outcomes

In the 31 episodes analyzed, the TTA greater than 120 minutes did not have a statistically significant relationship with the days of hospital stay, transfer to the PICU or mortality (Table 3).

	≤ 120 minutes (n=6)	> 120 minutes (n=25)	p-Value
Days of hospital stay, median (IQR)	16 (8-20)	7 (4-11)	0.1453*
Transfer to UCIP, n (%)	0 (0%)	2 (8%)	0.645**
Death, n (%)	1 (16.6%)	0 (0%)	0.194**
* Value calculated by the U. Mann-Whitney test; ** Value calculated by Fisher's exact test			

Table 3: Clinical outcomes by Time from arrival at the emergency room to first dose of antibiotics or time to antibiotics (TTA).

We also evaluated whether the diagnosis and time from the onset of fever until the patient arrived at the emergency, were related to the clinical outcomes, not finding any statistical significance, except in the days of hospital stay where patients with leukemia had a longer stay than patients with solid tumors (10.5, IQR 5.7-19 days vs. 4, IQR 5-7.5 days, $p = 0.0244$).

Discussion

The oncology patient's care is multidisciplinary, and requires the joint work of both the health personnel and the family that supports the patient. This is reflected in the management of the pediatric patient, who depends on their relatives to attend their appointments, comply with the treatment or go to the emergency when is necessary [10], being of vital importance in the case of the FN, since these children have up to 1.6 times more risk of dying from sepsis than children with other diseases [11]. Neutropenia is the most serious toxicity of chemotherapy, depends on the type and dose of chemotherapy, the degree and duration of the neutropenia determine the risk of infection [12], and generally presents its nadir between 7 and 14 days after treatment, in our case we observed that the median time of onset of the fever was 7 days (IQR, 4-8). On the other hand, the Pediatric Oncology services always emphasize to their patients and relatives, the need to go to the Emergency as soon as the patient has fever, however, we see with regret in this study, that the median time since the family member perceived the fever and took the child to emergency, it was 16 hours, only 25% of patients arrived at the emergency within the first 6 hours after the fever started, this time is longer than reported in El Salvador [13], where it was 12.5 hours, as observed in a Chilean study [14], which reported a median of 2 hours.

Several guidelines [6,9,15,16], suggest to give antibiotic treatment promptly to oncologic patients with FN, multiple investigations mention that it should be initiated within the first 60 minutes of arrival at the hospital, as this has a positive impact on the evolution and survival [17-19]. Even in the study conducted by Rosa et al, in adult patients with cancer who attended emergency due to FN, they showed that each increase of 1 hour in the time of administration of antibiotic increased the mortality within the 28 days by 18% [20]. In our study we observed that although 100% of the cases of FN were evaluated by a physician within the first 10 minutes of arrival to the Emergency, the TTA was 206 minutes (IQR, 137-390), if we compare it with other Latin American studies, we see that it is very similar to that reported in El Salvador [13], whose median TTA was 210 minutes, and also in Chile [14], where the median TTA was 200 minutes. Regarding the type of cancer, we had a greater number of patients with hematological neoplasms, and we determined that those had a TTA significantly lower than the patients with solid tumors (171 vs. 388 minutes, $p = 0.0374$), these results are similar to those published in other studies [12], and it may be because patients with hematologic malignancies when they present to the emergency are generally clinically more unstable than patients with solid neoplasms.

It is interesting to note that countries with higher economic income had a prolonged TTA at one time. Fletcher et al. [17], conducted an investigation at the Children's Medical Center of Dallas, between 2001 and 2009, and determined that the median

TTA for oncology patients who attended in Emergency by FN was 145 minutes. On the other hand, success stories have been published, based on the implementation of multidisciplinary programs in order to reduce the TTA, for example, Volpe et al. [21], decreased the TTA from 112 to 59 minutes, demonstrating together with others studies [18,22-25], that multidisciplinary intervention programs reduce the TTA and therefore improve the quality of care and patient survival. Part of the actions that the studies did before developing the intervention programs, was to analyze the sub processes, as in the case of Salstrom et al. [18], which determined that the time from when the laboratory results were held until it was reevaluated to indicate the antibiotic was 63 minutes and the time from when the antibiotic was indicated until the first dose was given was 34 minutes; in our study these times were higher, 179 minutes and 110 minutes, respectively. These data indicate that in order to better the TTA the support of all the health personnel and their respective dependencies (emergency, laboratory, and pharmacy) is needed.

The impact of the TTA on clinical outcomes has been well established, Fletcher, et al. [17], research showed that the TTA after 60 minutes was associated with greater adverse events such as mortality and admission to the PICU (61-120 vs. ≤ 60 minutes, OR 1.81, 95% CI 1.01-3.26). The study by Salstrom, et al. [18], determined that the TTA within 60 minutes of arrival at the hospital significantly reduced the need for PICU ($p = 0.003$). However, other studies such as that of Ko, et al. [26], in Korea, where the TTA was 140 minutes (IQR, 111-180 min), showed no significant association with complications or mortality, the same was observed in the study de De la Maza, et al. [14], where a TTA > 60 minutes, was not related to an increase in the number of fever days, more transfers to the PICU or an increase in mortality. In our study we determined that there was no statistically significant relationship between the TTA was greater than 120 minutes and the days of hospital stay, transfer to PICU or mortality, this probably due to the limited number of cases.

Among the strengths of this study is to be the first to analyze the TTA in a pediatric population with cancer and FN in Peru. On the other hand, the limitations of this research are to be a retrospective study and to have a small sample, which may affect its external validation and generalization of its results.

Conclusion

In the evaluated cases the TTA for pediatric oncology patients who attend emergency due to FN, exceeds the international standards, and the patients with solid tumors have TTA longer than patients with leukemia. This study provides basic information to encourage the creation of multidisciplinary teams (emergency, oncology, nursing, laboratory, pharmacy, etc.) to improve the TTA. It is also important to emphasize the role played by family members

in the care of these patients, and the importance of coming early in the case of fever in children with cancer. Finally, it is necessary to carry out more extensive studies on this topic in our country.

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