Aus der Klinik für Kinder-Onkologie,-Hämatologie und Klinische Immunologie
der Heinrich-Heine-Universität Düsseldorf
Direktor: Prof. Dr. med. Arndt Borkhardt

Fever and neutropenia in paediatric oncology patients, a prospective cohort study from 2019-2021

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

Vorgelegt von
Marta Alústiza Zavala
2024

Als Inauguraldissertation gedruckt mit der Genehmigung der

Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

gez.:

Dekan: Prof. Dr. med. Nikolaj Klöcker

Erstgutachterin: PD Dr. med. Jennifer Neubert

Zweitgutacher/in: Prof. Dr. med. Colin R. MacKenzie

"I was taught that the way of progress was neither swift nor easy"

Marie Curie

Abstract

Background: Febrile neutropenia in paediatric oncology patients is a medical emergency that needs to be managed with precision and safety. Time to antibiotics (TTA) under one hour has been used to measure the quality of care and is a recommendation of the German guideline for the management of children with febrile neutropenia. However, data exploring the actual role of TTA in the patient's clinical outcome is scarce and show incongruent results. Furthermore, although a risk stratification of these patients has been discussed in the literature, there is no consensus on which available tools best predict patient outcomes.

Objective: This study aims to evaluate the association of TTA with the Infection-related length of stay (ILoS). Moreover, it explores the association of variables potentially useful for risk prediction with the patient's outcomes. Finally, it describes the microbial spectrum among the identified bloodstream infections (BSI). The results of this study will contribute to a better understanding of risk factors and optimal management strategies for this population.

Participants: Children (age <18 years) admitted with a febrile episode with a cancer diagnosis and undergoing intensive chemotherapy with no history of Hematopoietic stem cell transplantation (HSCT) at the Department of Pediatric Oncology, Hematology and Clinical Immunology, Heinrich-Heine University Hospital Düsseldorf.

Methods: Patients undergoing intensive chemotherapy in the Paediatric Oncology department were recruited between 2019 and 2021 and were included in the study after admission with a febrile episode and followed up until discharge. The admission data were collected through a newly implemented admission documentation system, and the remaining data from the regular ward documentation and laboratory and microbiology results. For the data analysis, after performing a univariate analysis for each variable, a multivariate Cox regression model was used to analyse the association of TTA with the ILoS. Moreover, a logistic regression model was used to evaluate the association of triage variables with having a bloodstream infection (BSI) and an adverse event (AE) during the hospital stay. Finally, summary statistics were performed to show the microbiology results of the BSI in the cohort. STATA 17 was used to perform all statistical analyses.

Results: 155 febrile episodes of 62 patients were included in this study between October 2019 and March 2021. The data showed no significant association of TTA ≥1 hour with the lLoS (HR=1.24 95% CI 0.85-1.81, p = 0.501). Triage bias was shown to have an impact on the results. The secondary analysis showed strong evidence of an association of CRP >5 mg/dl, leukocyte count <500/ mm^3 and platelet count < 50 10^3/ mm^3 with the likelihood of an adverse event (AE) or identifying a bloodstream infection (BSI) during the hospital stay. A positive SIRS Score was also associated with a higher AE risk but showed no association with BSI.

Conclusion:

In this study, a longer TTA was not associated with a longer lLoS. In addition, we identified the presence of residual confounding variables interfering with our results (*triage bias*). Therefore, the use of TTA as a measure of the quality of care alone should be approached with caution. More efficient measures should be promoted to improve the management of paediatric patients with FN. New tools for proper risk stratification of these patients are crucial and should be developed. In our study, the variables with the most robust evidence of association with a severe clinical outcome were: CRP >5 mg/dl, leukocyte count <500/ mm^3, and platelet count < 50 10^3/ mm^3.

Zusammenfassung

Hintergrund: Die febrile Neutropenie bei pädiatrischen onkologischen Patienten stellt einen potenziellen medizinischen Notfall dar und erfordert eine präzise und sichere Behandlung. Die Messung der Versorgungsqualität erfolgt unter anderem anhand der Zeit bis zur Einnahme von Antibiotika (TTA). Eine kurze TTA wird von der deutschen Leitlinie zur Versorgung von Kindern mit febriler Neutropenie empfohlen. Trotz der Empfehlung gibt es jedoch nur wenige Daten, die die tatsächliche Bedeutung von TTA für das klinische Outcome von Patienten untersuchen. Außerdem sind die verfügbaren Ergebnisse uneinheitlich. Eine Risikostratifizierung dieser Patienten wird in der Literatur diskutiert, jedoch herrscht keine Einigkeit darüber, welches der verfügbaren Instrumente den klinischen Verlauf am besten vorhersagt.

Zielsetzung: Das Ziel dieser Studie ist es, den Zusammenhang zwischen der Zeit bis zur ersten Gabe intravenöser Antibiotika (TTA) und der infektionsbedingten Aufenthaltsdauer (ILoS) zu untersuchen. Darüber hinaus werden die Zusammenhänge zwischen den potenziell nützlichen Variablen für die Risikovorhersage mit dem klinischen Outcome und dem mikrobiellen Spektrum der positiven Blutkulturen (BSI) beschrieben. Die Ergebnisse dieser Studie sollen dazu beitragen, das Verständnis der Risikofaktoren und des optimalen Managements von pädiatrischen onkologischen Patienten mit febriler Neutropenie zu verbessern.

Methoden:

Für diese Studie wurden Kinder und Jugendliche unter 18 Jahren mit hämato-onkologischen Grunderkrankungen, die sich einer intensiven Chemotherapie unterzogen und eine febrile Episode hatten, in die Studie aufgenommen. Patienten, die eine hämatopoetische Stammzelltransplantation (HSCT) erhalten hatten, wurden ausgeschlossen. Die Behandlung erfolgte in der Klinik für Kinder-Onkologie, Hämatologie und klinische Immunologie des Universitätsklinikums Düsseldorf. Die Aufnahmedaten wurden mithilfe eines neu eingeführten Aufnahmedokumentationssystems erhoben, während die übrigen Daten aus der regulären Stationsdokumentation und den Labor- und Mikrobiologie-Befunden stammten. Die Analyse des Zusammenhangs zwischen TTA und ILoS erfolgte mithilfe eines multivariaten Cox-Regressionsmodells. Darüber hinaus wurde ein logistisches Regressionsmodell verwendet, um die Assoziation von Triage-Variablen

mit Blutstrominfektionen (BSI) und unerwünschten Ereignissen während des Krankenhausaufenthalts (AE) zu bewerten. Zusammenfassende Statistiken wurden erstellt, um die mikrobiologischen Ergebnisse der Patienten mit BSI in der Kohorte darzustellen. Die gesamte statistische Analyse wurde mit STATA 17 durchgeführt.

Ergebnisse: In dieser Studie wurden 155 Fieber-Episoden bei 62 Patienten zwischen Oktober 2019 und März 2021 untersucht. Es konnte kein signifikanter Zusammenhang zwischen TTA ≥1 Stunde und der ILoS festgestellt werden (HR=1,24; 95%-KI 0,85-1,81; p=0,501). Es wurde jedoch ein Einfluss des Triage-Bias auf die Ergebnisse beobachtet. Eine sekundäre Analyse zeigte eine starke Evidenz für einen Zusammenhang zwischen einem CRP >5 mg/dl, einer Leukozytenzahl <500/mm^3 und einer Thrombozytenzahl <50.000/mm^3 mit einem erhöhten Risiko, während des Krankenhausaufenthalts ein unerwünschtes Ereignis (AE) zu erleiden oder eine Blutstrominfektion (BSI) zu entwickeln. Ein positiver SIRS-Score war ebenfalls mit einem höheren AE-Risiko assoziiert, zeigte jedoch keine Verbindung mit einer BSI.

Schlussfolgerung:

In dieser Studie war eine TTA≥ 1 Stunde nicht mit einer längeren ILoS assoziiert. Ein Triage-Bias hatte einen signifikanten Einfluss auf die erhobenen Daten. Die Verwendung von TTA als ein Qualitätskriterium bei Patienten mit Fieber und Neutropenie ist somit mit Vorsicht zu interpretieren. Ein besseres Tool für eine Risikostratifizierung dieser Patienten ist erstrebenswert, um die Patienten zu identifizierendie von einer TTA<1h profitieren. In dieser Studie zeigten die folgenden Variablen den stärksten Zusammenhang mit dem Auftreten eines schweren klinischen Ereignisses: CRP >5 mg/dl, Leukozytenzahl <500/ mm^3, und Thrombozytenzahl < 50 10^3/ mm^3.

Table of Contents

Abbreviation list/ Abkürzungsverzeichnis

AE = Adverse Event

BSI = Bloodstream infection

CNS = Coagulase negative Staphylococci

CRP = C reactive protein

ER = Emergency Room

FE = Febrile Episode

FN = Fever in Neutropenia

FUO = fever of unknown origin

GCS = Glasgow Coma Score

HR = Heart Rate

ILOS =Infection-related Length of Stay

MRGN = Multiresistant gram-negative bacteria

OOC = Oncology Outpatient Clinic

PCT = Procalcitonin

PICU = Paediatric Intensive Care Unit

qSOFA = quick Sequential Organ Failure Assessment

RR = Respiratory Rate

SIRS = Systemic Inflammatory Response Syndrome

Syst BP = Systolic Blood Pressure

TTA = Time to Antibiotics

WBC = White blood cell count

List of tables and figures/ Tabellen und Abbildungsverzeichnis

Tables

Figures

Introduction

Paediatric oncology patients have a high risk of infection due to an impaired immune response associated with their malignancy, chemotherapy-induced agranulocytosis (1), and the use of long-term central venous catheters (2). As a result, infections in this patient population may result in severe morbidity and mortality. Therefore, prompt identification and treatment of infections are crucial to mitigate their adverse outcomes.

In the context of infection, the most frequent presentation is a febrile episode, known as febrile neutropenia, when accompanied by agranulocytosis. Febrile neutropenia (FN) is the foremost and potentially lethal complication of cancer chemotherapy and is a significant contributor to mortality (3) when prompt intervention is lacking (4). Accordingly, in the last decades, clinicians have placed greater emphasis on the early initiation of broad-spectrum antibiotics for children presenting with febrile neutropenia, with a resultant reduction in mortality observed in this patient cohort (5,6).

On the other hand, recently, it has come to light that merely 10-30% (7) of cases involving febrile neutropenia are severe, with a lower proportion of bloodstream infections (BSI) and a substantial incidence of viral infections as the underlying cause of fever. In individuals with a low likelihood of severe infection, the implementation of broad-spectrum antibiotics, accompanied by prolonged hospitalization, results in increased morbidity and the potential for the emergence of antibiotic resistant bacteria.

In addition to the administration of broad-spectrum antibiotics, novel approaches have emerged in recent years aimed at enhancing the management of these patients. Notable examples include the utilization of time to antibiotics (TTA) as a measure for evaluating the quality of care, as well as the development of risk stratification tools, both of which have gathered significant attention within the field.

Time to antibiotics

Time to antibiotics (TTA) refers to the period between arrival at the hospital and starting intravenous antibiotics. A TTA < 60 min has been used to measure the quality of care; hence, centres have used resources to reduce the hospital TTA. For instance, European and American guidelines recommend a TTA below one hour in the treatment of FN in

adult patients with cancer (8) (9). In addition, although there is no target TTA specified in the international FN guidelines for paediatric oncology patients (3), the German paediatric guidelines recommend administering antibiotics within 60 minutes (10).

Although any attempt to draw attention to the importance of good and prompt management of these patients is likely to result in improved care, evidence on the association of TTA < 60 mins and patient's clinical outcome is scarce and inconsistent regarding paediatric oncology patients with FN. Understanding the role of TTA is critical for the optimisation and improvement in the management of these patients (11).

Risk stratification tool

It is crucial to differentiate children with neutropenic fever into high and low-risk categories due to several reasons. Firstly, early identification of high-risk patients would enable prompt and comprehensive treatment and decrease mortality. Secondly, identifying low-risk patients would decrease morbidity by minimizing admissions and unnecessary use of broad-spectrum antibiotics. Furthermore, with regards to TTA, a risk stratification tool would facilitate the assessment of high-risk patients, where a more substantial effect is anticipated (12). Lastly, by accurately identifying low-risk patients, alternative measures such as oral antibiotic therapy could be explored with confidence to minimize hospital admissions (13).

Several indices have been developed for risk stratification in febrile neutropenic children, yet a consensus on their implementation remains elusive. For instance, the German guideline recommends identifying signs of sepsis rather than using a specific risk stratification tool. Instead, it refers to general paediatric sepsis management guidelines that utilize the SIRS score (Table 2) for early sepsis identification in children based on age- specific abnormal vital signs as detailed in Table 1. While quick SOFA (Table 3) has been adopted for adult patients, it lacks validation in the paediatric population, and its predictive value among immunocompromised children is largely unknown (13). Furthermore, the applicability of SIRS and qSOFA in the management of febrile neutropenia in children remains uncertain, as these tools were developed for use in immunocompetent populations. For instance, the criterion of leukopenia in the SIRS score cannot be reliably applied to children with neutropenia.

Table 1 Age-specific abnormal vital signs and laboratory variables

Age Group	Heart Rate, Beats/Min		Respiratory Rate Breaths/Min	Leukocyte Count, Leukocytes x10^3/mm	Systolic Blood Pressure, mm Hg
	Tachycardia	Bradycardia			
0 days to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1mo to 1yr	>180	<90	>34	>17.5 or <5	<100
2-5 yr	>140	NA	>22	>15.5 or <6	<94
6-12 yr	>130	NA	>18	>13.5 or <4.5	<105
13 to <18 yrs	>110	NA	>14	>11 or <4.5	<117

**NA, not applicable*

Note: Adapted from Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. 2005 (14).

Table 2 SIRS Criterion: ≥2 meets SIRS definition

Temperature >38.5°C or <36°C	**1pt**
Tachycardia or bradycardia	1pt
Tachypnea	1pt
Abnormal leukocyte count	1pt

Table 3 Quick SOFA Criterion: ≥ 2 meets qSOFA definition

Hypotension	1 pt
Decreased level of consciousness (GCS<15)	1 pt
Tachypnea	1 pt

In the case of adults, febrile neutropenia risk indeces are validated and recommended by European guidelines. Nevertheless, unfortunately, these are hardly applicable to children due to the relevant differences between adult and paediatric oncology patients. On the other hand, the international guideline on the assessment of children with neutropenic fever recommends incorporating an FN-specific risk stratification strategy, but there is no agreement on which method is most effective (15). Six different approaches have been outlined in this guideline; however, the authors stress that these should be validated locally before implementation.

Only two stratification strategies for the paediatric population with FN have been validated in Europe (16,17). Both methods included information about the underlying oncology disease and the febrile episodes within the index. Whereas the first score included information on the WBC and laboratory signs of infection (16), the second one included only WBC values for the episode-specific factors (17). None of the two scores validated in Europe considered information on the clinical status of the child presenting with the febrile episode, such as vital signs. Nevertheless, other international scores included clinical signs such as hypotension, fever, altered mental status or signs of mucositis within their risk index (3). The variety of variables used in these scores and the underlying data

scarcity highlight the need for more studies to explore risk stratification in pediatric patients presenting with neutropenic fever. No risk stratification strategy had been implemented in our centre at the time of the study

Microbiology Spectrum

The high risk of bacterial and fungal infections in the paediatric oncology population leads to increased antimicrobial prescribing (22) (23) similar to paediatric intensive care units. Prompt administration of broad-spectrum antibiotics in febrile neutropenic children has significantly reduced mortality. For example, in our paediatric hospital, broad-spectrum antibiotics are standardised for patients with FN, starting with monotherapy with Piperacillin-Tazobactam, then escalating to Teicoplanin first and Meropenem as a second escalation.

However, excess use of antimicrobials leads to an increase in antimicrobial resistance. Over the past years, multidrug-resistant organisms (MDROs) have become an increasingly common cause of infection in these patients (24–26). Moreover, excess use of antimicrobial therapy can lead to increased morbidity due to allergic reactions and organ toxicity (27,28). Implementing antibiotic stewardship and risk stratification tools would allow early discontinuation of antibiotics and the use of alternatives to intravenous antibiotics to reduce these risks. Paediatric oncology departments should regularly monitor and share local microbial resistance spectrum to enable the adaptation of local guidelines (10). It is noteworthy that in our paediatric oncology department, the most recent studies summarizing the microbial spectrum of children with febrile neutropenia were conducted in 1988 and 2000 (29).

Aim and objectives of the study

The study aims to provide valuable descriptive data on the presentation, prognosis and microbiological spectrum of paediatric oncology patients presenting with febrile neutropenia that should support clinicians and inform future guidelines. The primary objective is to analyse the association of Time to antibiotics (TTA) with the infection-related length of stay (ILoS). Moreover, it aims to perform a secondary analysis, to explore the association of potentially useful variables for risk prediction with the clinical outcome, and to summarise the microbial spectrum of bloodstream infections identified in the cohort.

Methods

Study design

We conducted a prospective cohort study of paediatric oncology patients admitted with fever during intensive chemotherapy at the Department of Pediatric Oncology, Hematology and Clinical Immunology in the Heinrich-Heine University Düsseldorf between October 2019 and March 2021.

Ethics

Ethical approval for this study was obtained from the Ethics Committee at the Medical Faculty of HHU-Düsseldorf *(Ethikkommission an der Med.Fakultät der HHU Düsseldorf, Studien-Nr: 2019-507)* in October 2019.

Informed Consent and Confidentiality

All study records were kept secure and confidential, with restricted access. Participant records were identified using participants' study numbers, and no participant-identifiable data was shared. Before their involvement, study participants informed consent was obtained from their legal guardians. For older children, the patient`s consent was also obtained (Appendix 2).

Sampling

The study included paediatric oncology patients under 18 years of age admitted to the paediatric oncology and haematology department with febrile neutropenia. Patients who did not present with neutropenia at admission but were at an elevated risk of developing neutropenia during their hospital stay due to exposure to intensive chemotherapy were also enrolled in the study. Patients who had undergone bone marrow transplantation or were receiving long-term therapy at the time of admission were excluded from the study. The study considered multiple febrile episodes in the same patient as independent.

Most patients were recruited in the study by the time of diagnosis of their malignancy. Others, however, were asked to participate during different visits or admissions in the hospital. Once they had given consent, they were included in the study by the time they were admitted with a fever.

Definitions

In this study, febrile neutropenia was defined as a neutrophil count of less than 500 cells/mm^3 upon admission or less than 1000 cells/mm^3 with an expected decline to below 500 cells/mm^3 within 48 hours after admission, in addition to an adjusted axillary temperature of 38.5°C or higher once, or 38.0°C or higher twice within a 12-hour period. In addition, high-intensity chemotherapy was defined as a treatment that posed a high risk of inducing deep and prolonged neutropenia.

Data Collection

We introduced a newly designed Admission Documentation Form for paediatric oncology patients with suspected infections (Appendix 1). Additionally, data were manually extracted from the regular ward documentation system and electronic medical records and entered directly into a relational database (Table 4). The principal investigator collected all variables. After the data collection, the primary investigator reviewed the data for inconsistent or missing values and corrected these where possible.

The data collection varied between admitting departments (emergency department and paediatric oncology department) because of the differences in the working systems and limited digitalisation. Patients admitted via the emergency department (ED) were directly admitted to the hospital computer system. Therefore, the time of arrival was directly digitally documented. Patients admitted via the oncology department were treated in the out-patient department and registered for admission later in the general registration office. Hence the registration time in the computer system did not correspond to the arrival time. We analysed the working system of the oncology outpatient clinic (OOC) and found that every patient received a whole blood count (WBC) upon arrival if they were not seen by the clinician directly. Therefore, the time of the WBC was used as a reference for arrival time in those patients. If a clinician saw the patient before the WBC was performed and documented the time of first contact, we used that time as the time of arrival.

Outcome Variables

A few patients received chemotherapy or other diagnostic and therapeutic procedures after being admitted with a fever during the same hospital stay. To avoid including these

extra admission days unrelated to an infection in our outcome variable, the end of the febrile episode was defined as the end of intravenous antibiotic therapy. Hence, ILoS was calculated as the time between admission and the end of intravenous antibiotic treatment. In addition, an adverse event was considered as either a bloodstream infection, the administration of a volume bolus or an admission to the paediatric intensive care unit (PICU).

Predictor Variables

Time to antibiotics (TTA) was calculated as the difference between the time of administration of antibiotics and arrival at the hospital.

Table 4 Covariates and Channels of Data Collection

1. Data collected via a newly implemented admission sheet
Presentation location
Time of arrival
Time of administration of antibiotics
Respiratory Rate
Heart Rate
Temperature
Systolic Blood Pressure
SpO2
Capillary refill time
SIRS Score at admission
qSOFA Score at admission
2. Data collected via the regular ward documentation system
Age
Sex
Underlying Malignancy
End of Antibiotic Therapy
Admission in PICU
Fluid bolus
Antibiotic Escalation
3. Data collected via laboratory findings
Leukocyte count at admission
Minimum Leukocytecount during the hospital stay
Thrombocyte count at admission
Haemoglobin at admission
PCT at admission
CRP at admission
Bloodstream infection (BSI)

Covariates

The study collected various covariates, as illustrated in Table 4. The SIRS and quick SOFA scores were calculated based on age and documented vital signs, excluding leukocyte count in the SIRS score for patients with leukopenia due to chemotherapy. Vital

signs variables were categorized as pathological or non-pathological based on the patient's age (Table 1).

Some continuous variables from the laboratory results were regrouped based on relevant cut-offs described in the literature: CRP was regrouped into three groups (<0.5 mg/dl, 0.5-5mg/dl, >5mg/dl) (30), PCT into two groups (<0.5 ng/ml, >0.5 ng/ml) (31), thrombocyte count into two groups (<50 $x10^3/mm^3$, > 50 $x10^3/mm^3$) and haemoglobin into two groups (< 10 g/dl, > 10 g/dl).

Leukocyte counts at admission and during the hospital stay were categorized into two groups: < 1 $x10^3/mm^3$ and > 1 $x10^3/mm^3$. The varaiable Severe Leukopenia was defined using a lower leukocyte count cutoff of < 0.5 $x10^3/mm^3$ and > 0.5 $x10^3/mm^3$.

Vital signs variables were regrouped into pathological or not based on the patient's age (Table 1). SIRS and quick SOFA scores were regrouped into positive or negative (Table 2-3). In the case of SIRS, considering that in the case of oncological patients, the number of leukocytes cannot be interpreted as the only sign of infection, it was not considered for the calculation of the score.

Analysis

The Data was collected in Microsoft Excel ™ and then imported to STATA/Se v17.0 for further analysis. All data were anonymised and checked for errors. First, summary statistics were used to describe the cohort and show all variables' crude association with the outcome by applying a univariate Cox regression model.

Primary Outcome

The influence of time to antibiotics (TTA) on the infection-related length of stay (ILoS) was calculated with a multivariate Cox regression model. Some variables were selected a priori, such as age and sex, and others were selected based on a previously designed conceptual framework (Appendix 4). The final multivariate model was determined considering collinearity and missing data. Finally, survival was graphically represented in a Kaplan-Meier curve.

Secondary Outcome

A secondary analysis using a logistic regression model adjusted for age and sex was conducted to analyse the association of a TTA ≥1 hour with SIRS, having an AE or BSI, and pathological vital and laboratory signs at admission.

Furthermore, to explore the association of the clinical presentation of the patients with their clinical outcome, an exploratory analysis of the association of SIRS, vital signs and laboratory results available at admission with having any adverse events and a bloodstream infection were performed using logistic regression model adjusted to sex and age. Finally, the microbiological spectrum of the BSI was described using summary statistics.

Sample size

The sample size for the study was determined by feasibility, considering the resources and constraints of the study. A post hoc power calculation was performed to confirm that the sample size was sufficient to detect meaningful differences in the variables under investigation with a reasonable level of statistical power.

Results

The cohort included 155 febrile episodes (FE) from 62 unique patients. Clinical characteristics of the patients and a univariable analysis of each variable's association with ILoS are summarised in Table 5.

Approximately half of all hospitalisations occurred in patients with acute lymphoblastic leukaemia (ALL). The most common admission location was the emergency department (ED), accounting for 67.1% of admissions. A bloodstream infection occurred in 12.9% of the febrile episodes, only three patients (1.9%) were admitted to PICU, and 37 patients (23.9%) experienced some adverse event (AE) during admission.

Out of the patients studied, 81 (54.4%) had leukocyte counts of less than 1000/mm^3 at the time of admission, and 77 (50.7%) had a leukocyte count of < 500/mm^3. Additionally, 11.8% of patients with higher leukocyte counts on admission developed neutropenia during their hospital stay.

Table 5 Categorical Variables - Descriptive and Univariable Analysis with ILoS

Variables		N(%)	P Y[1]	IR[2]	cRR (95%CI)	P value
TTA	<1h	60 (39.5)	5.22	11.49	1	0.006
(n=152)	≥1h	92 (60.5)	4.88	18.85	1.59 (1.13-2.22)	
Sex	Female	66 (42.6)	3.48	18.97	1	0.047
(n=155)	Male	89 (57.4)	6.80	13.09	0.71 (0.51-0.99)	
Age	≤ 6	98 (63.2)	7.13	13.74	1	0.536
(n=155)	7-12	32 (20.6)	1.78	17.98	1.21 (0.80-1.82)	
	>12	25 (16.1)	1.37	18.25	1.22 (0.78-1.91)	
Oncology	ALL	75 (48.4)	5.87	12.78	1	0.008
Diagnosis	AML	3 (1.9)	0.23	13.04	0.88 (0.27-2.79)	
(n=155)	Brain Tumor	20 (12.9)	0.66	30.3	2.97 (1.76-5.02)	
	Ewing Sarcoma	5 (3.2)	0.35	14.29	0.99 (0.40-2.48)	
	Nephroblastoma	5 (3.2)	0.27	18.52	1.44 (0.58-3.60)	
	Neuroblastoma	4 (2.6)	0.37	10.81	0.73 (0.26 – 1.99)	
	NH Lymphoma	13 (8.4)	0.95	13.68	0.95 (0.52-1.72)	
	Other S. Tumors[3]	27 (17.4)	1.23	21.95	1.80 (1.13-2.86)	
	Others	3 (1.9)	0.35	8.57	0.59 (0.19-1.91)	
Admission via	OOC	51 (32.9)	4.46	11.43	1	0.028
(n=155)	ER	104 (67.1)	5.82	17.87	1.47 (1.03-2.08)	
Initial antibiotics	Monotherapy	110 (71.1)	5.26	20.91	1	<0.001
scheme[3]	Dual Therapy	20 (12.9)	1.74	11.49	0.46 (0.28-0.75)	
(n=155)	Triple Therapy	18 (11.6)	2.71	6.64	0.27 (0.15-0.46)	
	Other combination	7 (4.5)	0.57	12.28	0.51 (0.23 – 1.09)	
BSI	No	135 (87.1)	7.25	18.62	1	<0.001
(n=155)	Yes	20 (12.9)	3.03	6.60	0.33 (0.19-0.56)	
PICU	No	152 (98.1)	9.88	15.38	1	0.109
(n=155)	Yes	3 (1.9)	0.40	7.50	0.44 (0.14-1.39)	
Fluid bolus	No	135 (87.1)	8.87	15.22	1	0.995
(n=155)	Yes	20 (12.9)	1.41	14.18	0.99 (0.62-1.60)	
Adverse Event	No	118 (76.1)	6.43	18.35	1	0.001
(n=155)	Yes	37 (23.9)	3.85	9.61	0.54 (0.37- 0.81)	
SIRS	Negative (<2)	79 (69.9)	4.53	17.44	1	0.029
(n= 113)	Positive (≥2)	34 (30.1)	3.28	10.37	0.63 (0.42 - 0.97)	
qSOFA	Negative (<2)	116 (99.1)	7.97	14.55	1	0.433

(n=117)	Positive (≥2)	1 (0.9)	0.11	9.09	0.51 (0.07-3.57)	
Respiratory Rate	Normal	31 (26.5)	1.62	19.14	1	0.192
(n=117)	High for age	86 (73.5)	6.5	13.31	0.75 (0.49-1.14)	
Heart Rate	Normal	31 (20.8)	2.72	8.0	1	0.099
(n=149)	High for Age	118 (79.2)	7.16	12.5	1.39 (0.93 - 2.08)	
Systolic BP	Normal	136 (88.3)	9.04	5.04	1	0.916
(n=154)	Low for age	18 (11.7)	1.15	15.65	0.97 (0.59 – 1.59)	
Temperature	≤38.5°C	107 (69)	6.44	16.61	1	0.104
(n=155)	>38.5°C	48 (30.9)	3.84	12.50	0.75 (0.53-1.07)	
Recap	≤2s	130 (92.9)	8.18	15.89	1	0.047
(n=140)	>2s	10 (7.1)	1.01	9.90	0.54 (0.28-1.04)	
CRP (mg/dl)	< 0.5 mg/dl	34 (22.4)	1.24	27.41	1	<0.001
(n=152)	0.5-5 mg/dl	94 (61.8)	6.21	15.14	0.46 (0.30-0.69)	
	>5 mg/dl	24 (15.8)	2.71	8.86	0.27 (0.15-0.47)	
PCT	≤ 0.5ng/ml	79 (73.8)	3.97	19.89	1	<0.001
(n=107)	>0.5ng/ml	28 (26.2)	3.12	8.97	0.42 (0.26-0.67)	
***Min* Leukocyte**	< 1x10^3/mm^3	91 (59.9)	7.28	12.50	1	<0.001
count	≥ 1x10^3/mm^3	61 (40.1)	2.73	22.34	1.91 (1.37-2.66)	
(n=152)						
Leukocyte count	< 1x10^3/mm^3	81 (54.4)	6.78	11.95	1	<0.001
at admission	≥ 1x10^3/mm^3	68 (45.6)	3.10	21.94	1.95 (1.40-2.72)	
(n=149)						
Severe	<0.5 x10^3/mm^3	77 (50.7)	6.52	11.81	1	<0.001
Leukopenia	≥0.5 x10^3/mm^3	75 (49.3)	3.49	21.49	1.89 (1.37-2.64)	
(n=152)						
Hb	≤10 g/dl	120 (78.4)	8.01	14.98	1	0.852
(n=153)	>10 g/dl	33 (21.6)	2.13	15.49	1.04 (0.70-1.53)	
Platelet-count	≤ 50 x10^3/mm^3	54 (35.3)	4.70	11.49	1	0.008
(n=153)	>50 x10^3/mm^3	99 (64.7)	5.44	18.20	1.57 (1.11-2.21)	

[1]P-Y **=** Person Years at risk per 100; [2]IR= Incidence Rate; ER: emergency Room, OOC: oncology outpatient clinic; [3] Initial Antibiotics Scheme based on the hospital SOP: 1° Piperacillin-Tazobactam, 2° Teicoplanin, 3° Meropenem.[3] Other solid tumors include: Synovial sarcoma, Osteosarcoma, BCOR positive sarcomas, Myelosarcoma, Rhabdomyosarcoma, Undifferentiated sarcoma, Mixed germ cell tumor, Epithelioid sarcoma.

Infection-related length of stay

The median length of stay was five days (IQR 3-9 days) with a maximum length of stay of 54 days. In a Cox-Regression analysis, the data showed no association between the ILoS and a delayed antibiotic administration (HR=1.47 95% CI 0.95-2.26, p = 0.076) after adjusting for age, sex, CRP, minimal leukocyte count, SIRS score and the presence of a BSI. The Kaplan-Meier curve in Figure 3 illustrates the survival estimate for patients based on the time to antibiotic administration, with no significant difference seen between those who received antibiotics within or beyond 1 hour of arrival at the hospital.

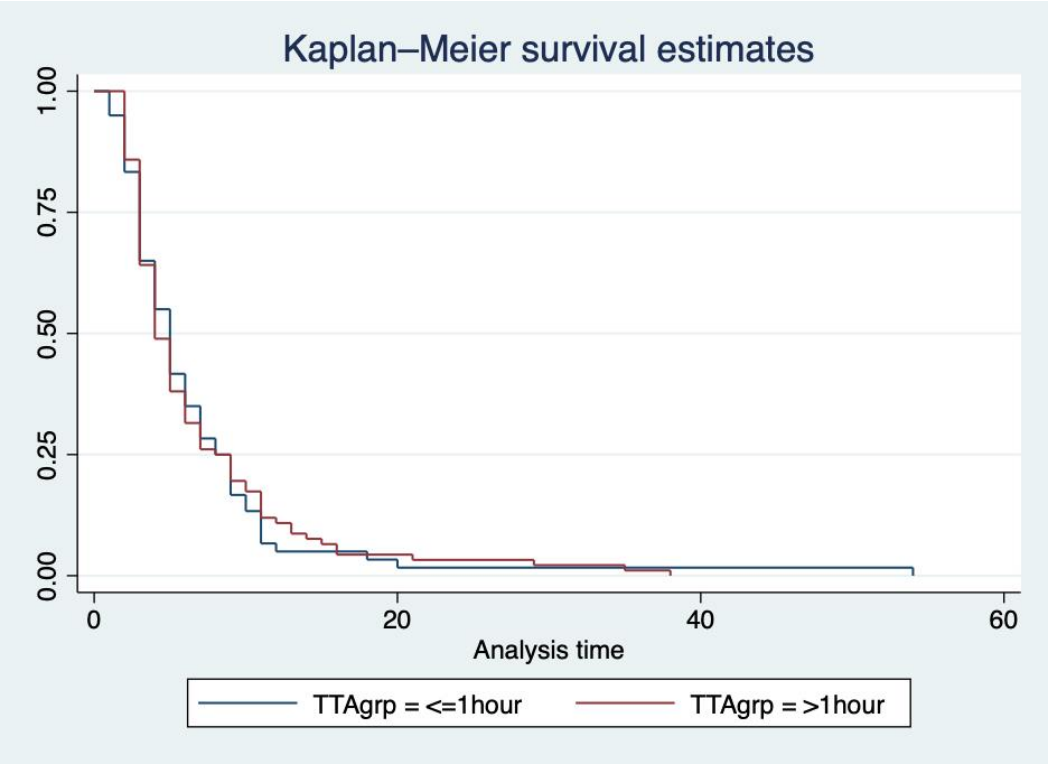


Figure 1 Kaplan-Meier Plot with Infection-related length of stay (ILoS) in days by TTA < 1 hour and ≥ 1 hour

Secondary Outcome

Association of TTA with Adverse Events and vital signs or laboratory values on admission

A TTA ≥ 1 hour is not associated with an increased risk of having an adverse event during the hospital stay (OR 0.45 95%CI 0.21-0.98, p-value 0.046). Table 6 shows the association of vital and laboratory signs available at the time of admission with a TTA ≥1h. In addition, a positive SIRS Score at admission is associated with a decreased risk of having a TTA ≥1h (OR 0.54, 95%CI 0.24-1.22); however, there is weak evidence supporting this finding (p-value 0.136).

Table 6 Association of TTA with vital signs and laboratory values on admission

Triage Information		TTA > 1 hour	OR	p-value*
SIRS (n=113)	< 2 (Neg)	47 (59.5)	1	0.136
	≥ 2 (Pos)	15 (44.1)	0.54 (0.24-1.22)	
RR (n= 117)	Normal	20 (64.5)	1	0.133
	High for Age	44 (51.2)	0.50 (0.20-1.25)	
HR (n=147)	Normal	17(54.8)	1	0.390
	High for Age	73 (62.9)	1.45 (0.62-3.38)	
Syst BP (n=152)	Normal	79 (59)	1	0.264
	Low for age	13 (72.2)	1.84 (0.61-5.54)	
Temperature (n=152)	≤ 38.5°C	66 (63.5)	1	0.228
	>38.5°C	26 (54.2)	0.65 (0.31-1.31)	
Capillary refill time (n=137)	≤ 2s	80 (63)	1	0.034
	> 2	3 (30)	0.24 (0.05-0.97)	
CRP (n=149)	<0.5 mg/dl	25 (75.5)	1	0.103
	0.5-5 mg/dl	55 (60.4)	0.54 (0.22-1.31)	
	>5 mg/dl	11 (45.8)	0.29 (0.09-0.92)	
PCT (n=105)	≤ 0.5 ng/ml	46 (59.1)	1	0.896
	>0.5 ng/ml	16 (59.3)	0.94 (0.37-2.41)	
Severe Leukopenia (n=149)	≤ 0.5 $x10^3/mm^3$	38 (50)	1	0.004
	> 0.5$x10^3/mm^3$	53 (72.6)	2.73 (1.37-5.49)	
Hb (n=150)	≤ 10 g/dl	69 (58.9)	1	0.561
	> 10 g/dl	22 (66.7)	1.28 (0.56-2.94)	
Platelets (n=150)	≤ 50 $x10^3/mm^3$	30 (55.6)	1	0.371
	>50 $x10^3/mm^3$	61 (63.5)	1.37 (0.68-2.73)	

Triage variables with Adverse Event and BSI

This study investigated the association of various triage variables with the outcome of adverse events (AEs) and the presence of a BSI alone in patients. The triage variables include SIRS score, respiratory rate (RR), heart rate (HR), systolic blood pressure (Syst BP), temperature, capillary refill time, C-reactive protein (CRP), procalcitonin (PCT), a leukocyte count < 500/mm^3 and the haemoglobin (Hb), and platelet-count.

In Table 7, the results show that patients who had a positive SIRS score (≥2) had a higher risk of AEs (41.2%) compared to those with a negative SIRS score (<2) (20.2%), with an odds ratio of 2.8 (95% CI 1.10-7.01) and a p-value of 0.03. Moreover, a CRP level >5mg/dl at admission was associated with a higher risk of having an AE during the hospital stay (OR 2.98, 95% CI 0.87 – 10.13: p = 0.049). In addition, a leukocyte count > 500mm^3 was associated with a reduced risk of experiencing an adverse event during the hospital stay (OR 0.43, 95% CI 0.19-0.96: p-value: 0.035). For respiratory rate, heart rate, systolic blood pressure, temperature, capillary refill time, and haemoglobin concentration, there was no significant association between the triage variable and the risk of AEs with a p-value > 0.05. However, patients who had a platelet count less than or equal to 50x10^3/mm3 had a higher risk of AEs (33.3%) compared to those with a platelet count greater than 50x103/mm3 (19.2%) (OR of 0.40 (95% CI 0.18-0.88), p of 0.023).

Table 7 Association of any Adverse Event (AE) with vital signs at admission

Triage Information		AE n (%)	OR (95%CI)	p-value*
SIRS (n=113)	< 2 (Neg)	16 (20.2)	1	0.030
	≥ 2 (Pos)	14 (41.2)	2.8 (1.10-7.01)	
RR (n= 117)	Normal	6 (19.3)	1	0.691
	High for Age	24 (27.9)	1.25 (0.41-3.74)	
HR (n=149)	Normal	9 (29)	1	0.422
	High for Age	28 (23.7)	0.67 (0.26-1.75)	
Syst BP (n=154)	Normal	31 (22.8)	1	0.463
	Low for age	6 (33.3)	1.51 (0.51-4.47)	
Temperature (n=155)	≤ 38.5°C	25 (23.4)	1	0.921
	>38.5°C	12 (25)	0.96 (0.42-2.16)	
Capillary refill time (n=140)	≤ 2s	30 (23.1)	1	0.638
	> 2s	3 (30)	1.43 (0.33-6.08)	
CRP (n=152)	<0.5 mg/dl	8 (23.5)	1	0.049
	0.5-5 mg/dl	19 (20.2)	0.81	
	>5 mg/dl	10 (41.7)	2.98 (0.87-10.13)	
PCT (n=107)	≤ 0.5 ng/ml	14 (17.7)	1	0.295
	>0.5 ng/ml	9 (32.1)	1.74 (0.62-4.88)	
WBC Admission (n=149)	< 1 $x10^3/mm^3$	24 (29.6)	1	0.079
	≥ 1$x10^3/mm^3$	12 (17.6)	0.49 (0.22-1.10)	
Severe Leukopenia (n=152)	≤ 0.5 $x10^3/mm^3$	24 (31.2)	1	0.035
	> 0.5$x10^3/mm^3$	13 (17.3)	0.43 (0.19-0.96)	
Hb (n=153)	≤10 g/dl	32 (26.7)	1	0.095
	>10 g/dl	5 (15.1)	0.42 (0.15-1.23)	
Platelets (n=153)	≤ 50 $x10^3/mm^3$	18 (33.3)	1	0.023
	>50 $x10^3/mm^3$	19 (19.2)	0.40 (0.18-0.88)	

**Likelihood Ratio test*

Regarding the association of the triage variables with BSI alone, the data in Table 8 shows that patients with a CRP value greater than 5 mg/dL had a significantly higher risk of a BSI (37.5%) compared to those with CRP values less than 0.5 mg/dL (5.9%), with an odds ratio (OR) of 12.89 (95% CI 2.30-72.07), $p < 0.001$.

Patients with severe leukopenia with a leukocyte count higher than 500/mm^3 had a significantly reduced risk of a BSI (6.7%), compared to those with WBC counts below than or equal to 500/mm^3 (19.5%) with an OR of 0.27 (95% CI 0.09-0.79), p 0.011. Patients with a platelet count less than or equal to 50x10^3/mm3 had a higher risk of a BSI (20.4%) compared to those with a platelet count greater than 50x10^3/mm^3 (9.1%), with an OR of 0.33 (95% CI 0.12-0.89) p-0.029. For the other variables, we found no significant association with the presence of a BSI.

Table 8 Association of a BSI with vital signs at admission

Triage Information		BSI n (%)	OR	p-value*
SIRS (n=113)	< 2 (Neg)	11 (13.9)	1	0.276
	≥ 2 (Pos)	8 (23.5)	1.81 (0.63-5.19)	
RR (n= 117)	Normal	3 (9.7)	1	0.425
	High for Age	16 (18.6)	1.73 (0.42-6.96)	
HR (n=149)	Normal	6 (19.3)	1	0.252
	High for Age	14 (11.9)	0.51 (0.17-1.56)	
Syst BP (n=154)	Normal	17 (12.5)	1	0.767
	Low for age	3 (16.7)	1.23 (0.32-4.8)	
Temperature (n=155)	≤ 38.5°C	12 (11.2)	1	0.477
	>38.5°C	8 (16.7)	1.44 (0.53-3.85)	
Capillary refill (n=140)	≤ 2s	14 (10.8)	1	0.099
	> 2s	3 (30)	3.97 (0.85-18.44)	
CRP (n=152)	<0.5 mg/dl	2 (5.9)	1	<0.001
	0.5-5 mg/dl	9 (9.6)	1.64 (0.33-8.17)	
	>5 mg/dl	9 (37.5)	12.89 (2.30-72.07)	
PCT (n=107)	≤0.5 ng/ml	5 (6.3)	1	0.068
	>0.5 ng/ml	6 (21.4)	3.45 (0.91-13.1)	
WBC Admission (n=149)	< 1 $x10^3/mm^3$	17 (21.0)	1	0.002
	≥ 1$x10^3/mm^3$	3 (4.4)	0.17 (0.05-0.60)	
Severe Neutropenia (n=152)	≤ 0.5 $x10^3/mm^3$	15 (19.5)	1	0.011
	> 0.5$x10^3/mm^3$	5 (6.7)	0.27 (0.09-0.79)	
Hb (n=153)	≤10 g/dl	18 (15)	1	0.130
	>10 g/dl	2 (6)	0.34 (0.07-1.60)	
Platelets (n=153)	≤ 50 $x10^3/mm^3$	11 (20.4)	1	0.029
	>50 $x10^3/mm^3$	9 (9.1)	0.33 (0.12-0.89)	

* Likelihood ratio test

The results indicate a correlation between some triage variables and patients' risk of adverse events (AEs) and bloodstream infections (BSIs). A positive Systemic Inflammatory Response Syndrome score (≥2) and CRP level (>5mg/dl) at admission were associated with a higher risk of AEs. Platelets count less than or equal to 50$x10^3/mm^3$

was also a significant predictor of AEs. Similarly, CRP levels greater than 5mg/dL, leukocyte count less than 500/mm^3, and platelet counts less than or equal to 50x10^3/mm^3 increased the risk of BSI. However, for other variables such as respiratory rate, heart rate, systolic blood pressure, temperature, capillary refill time, PCT, leukocyte count at admission, and haemoglobin, no significant association was found with the risk of adverse events or bloodstream infections.

Microbiology results

This table summarises the microbiology spectrum of bloodstream infections (BSIs) in the studied cohort. The table shows that a total of 20 cases of BSI were identified, with 4 of these cases (20%) showing resistance to some antibiotics. The most common microorganism identified was coagulase-negative staphylococci (CNS), accounting for 30% of the BSIs, 3 (33.3%) of which were methicillin-resistant (MR). Other microorganisms identified include *Escherichia coli* (20%), *Klebsiella pneumoniae*10%), *Pseudomonas aeruginosa*. (5%), streptococci (5%), and *Enterobacter cloacae* (5%). Additionally, there were four other cases (20%) of BSI caused by other microorganisms. Of the antibiotic-resistant Gram-negative bacteria, three were *Escherichia coli* (two 2MRGN and one 3MRGN), one *Klebsiella* (2MRGN), one *Enterobacter* (2MRGN), and one *Pseudomonas* (3MRGN) were resistant to relevant antibiotics.

Table 9 Microbiology spectrum of identified BSI

	Microorganism	N (%)	Resistance to 1st line antibiotics n (%)
Total		20	11(55)
Gram positive		9 (45)	3 (33.3)
	Coagulase-negative staphylococci	7 (30)	3 (42.8)[1]
	streptococci	1 (5)	0 (0)
	Other	1 (5)	0 (0)
Gram negative		11 (55)	6 (54.5)
	Escherichia coli	4 (20)	3 (75)[2,3]
	Klebsiella pneumoniae	2 (10)	1 (50)[2]
	Pseudomonas aeruginosa	1 (5)	1 (100)[3]
	Enterobacter cloacae	1 (5)	1 (100)[2]
	Others	3 (15)	0 (0)

[1]MRS, [2]2MRGN. [3]3MRGN

Power Calculation

The sample has 80% power to identify a 3-day difference in ILoS between patients receiving antibiotics within or beyond one hour. Our study does not have sufficient power to identify a one-day difference in ILOS. A one-day reduction in the length of stay is deemed as the minimum reduction in admission that is considered significant in terms of reducing morbidity by patients and their families.

Discussion

Managing febrile neutropenia in paediatric oncology patients is a critical medical emergency that requires careful and safe treatment. A TTA under one hour is often used to measure the quality of care and is recommended in the German guidelines for managing children with febrile neutropenia. However, there is limited and inconsistent data on the actual impact of TTA on patient outcomes. Therefore, this study aimed to investigate the relationship between TTA and length of hospital stay as an indicator of the clinical severity of illness.

The hazard ratio in the crude analysis measures the likelihood of being discharged from the hospital. Initially, the crude analysis suggested that administering antibiotics after one hour may have a potentially beneficial effect (HR 1.59 95% CI 0.95-2.26, p-value = 0.006). However, after adjusting for several variables, such as age, sex, the presence of a bloodstream infection, C-reactive protein concentration, leukocyte count, and SIRS score, the association was no longer statistically significant. Nevertheless, the data still revealed a positive correlation between a TTA of one hour or more and an increased length of stay in the hospital (HR=1.47 95% CI 0.95-2.26, p = 0.076).

Our analysis suggests that this finding may be due to considerable residual confounding factors, wherein unmeasured variables may influence both the timing of antibiotic administration and the clinical outcome. This phenomenon has been previously described as *triage bias* in the literature (11). For example, when presented with a patient in a more severe clinical state, a clinician is more likely to administer antibiotics earlier than when the patient presents in good general condition. Although we adjusted for clinical severity using the SIRS score in our model, this may be insufficient. The clinician's assessment provides additional unmeasurable information beyond the SIRS score that can affect their approach. Additionally, other factors, such as delays in seeking care, could potentially influence the data, a factor that was unmeasured in this study.

The aim of the secondary analysis in this study was to investigate the relationship between time to antibiotic administration (TTA) and vital signs and laboratory findings to gain a better understanding of the residual confounding variables observed in the primary

analysis. Our results suggest that patients with a SIRS score ≥2, abnormal respiratory rate, fever, capillary refill time >2 sec, elevated C-reactive protein (CRP) or procalcitonin (PCT) concentration, and low leukocyte count (<500/mm3) were more likely to receive antibiotics within the first hour of admission. However, we only observed strong evidence of association with the variables capillary refill time and a leukocyte count <500/mm3 (p-value <0.05). It is important to note that these findings should be interpreted with caution due to limited statistical power. Nevertheless, the results suggest that patients with more severe symptoms are more likely to receive antibiotics sooner upon admission.

In conclusion, our data show that residuals confounders, the so-called *triage bias*, is a persistent issue whenever measuring time-to-antibiotic administration, and presently, there are no suitable measures to control for it. In our view, while this situation prevails, the use of time-to-antibiotic administration as a metric for assessing safety and quality must be interpreted with caution. Thus, it is imperative to focus on implementing more objective measures to enhance the management of neutropenic fever (32).

Risk stratification

In the last decades, the management of neutropenic fever has primarily focused on enhancing patient safety using broad-spectrum antibiotics. This strategy has been successful in reducing deaths related to neutropenic fever. However, with the emergence of antibiotic resistance and a greater emphasis on minimising patient morbidity, there is a need to re-evaluate current management strategies (33). The goal should be to balance patient safety with reducing the harm associated with prolonged antibiotic therapies and hospital stays.

A key strategy in balancing patient safety and morbidity in the management of neutropenic fever is the ability to accurately risk-stratify patients. This includes distinguishing between those with high-risk and low-risk neutropenic fever, which can guide appropriate management decisions and ultimately improve patient outcomes. Unfortunately, despite the availability of various proposed risk stratification methods outlined in the International Guidelines for Neutropenic Fever in Pediatrics (3), none have been extensively validated or widely adopted in clinical practice. Therefore, creating,

validating, and integrating risk-stratification tools are essential for appropriately managing patients with neutropenic fever.
While this study did not focus on developing or validating such tools, it sought to examine the potential utility of certain triage variables in identifying severe infection among patients with neutropenic fever.

In our study, we found that elevated CRP >5 mg/dl, low leukocyte count <500/ mm^3, and platelet count <50 103/ mm^3 upon admission were strongly correlated with adverse events (AE) or bloodstream infections (BSI) occurring alone during hospitalization. Furthermore, a positive SIRS score was associated with an increased risk of AE but not BSI alone. The quick SOFA score could not be evaluated in our cohort due to insufficient data. In our study, some clinicians used SIRS as a criterion for administering fluid bolus therapy to patients. Therefore, these findings should be interpreted cautiously; further research is necessary for validation. We found no compelling evidence for an association between other clinical and vital signs on admission and the outcome in our cohort. However, we acknowledge that limited number of participants in our study may have reduced the ability to detect associations with other variables. As a result, other variables should not be disregarded in future studies. Moreover, other laboratory tests, such as IL10 (34) or IL8 (35), may be considered potential tools for identifying severe infection in this population.

In a recent study, Delabrre and colleagues (2021) introduced a clinical decision rule called DISCERN-FN to identify pediatric patients with neutropenic fever who are at low risk of severe infection. This rule utilizes variables such as age, chills in the last 24 hours, temperature, CRP and PCT concentrations, leukocyte and platelet counts, and exposure to chemotherapy for solid tumors to help clinicians identify low-risk patients (36). Our findings are consistent with this study, particularly regarding the association between CRP, platelet and leukocyte counts, and the risk of severe infection. Therefore, we believe that newly developed clinical decision rules like DISCERN-FN have significant potential, and we encourage further development and validation of these or similar risk stratification tools by the scientific community.

Trends in Microbiology Findings

In the context of microbiological results, it is worth comparing our findings with previous studies conducted at our center in 1980 and 2000 (29). Our study observed a slight

predominance of gram-negative bacterial infections (55%) compared to gram-positive infections (45%), which differs from previous studies reporting proportions of 17% and 80%, respectively. This findings of increasing gram-negative bloodstream infections in the studied population has been reported in the literature, albeit at a lower proportion of 34% (37).

Furthermore, it is worth noting that the prevalence of coagulase-negative staphylococci infections in our study was 30%, which is consistent with the incidence observed in 1980 (33%) and lower than that in 2000 (42%). Similarly, the proportion of streptococcal infections identified in our study was 5%, which is comparable to the rates reported in the studies conducted in 1980 (7%) and 2000 (6%).

In our study, *E. coli* was the most frequently identified gram-negative organism. The proportion of *E. coli* infections has increased over time, from 6% in 1980 to 12% in 2000 and 20% in our study. We also observed an increase in the proportion of *Klebsiella pneumoniae* (1% in 1980, 0% in 2000, and 10% in 2019/20) and *Enterobacter cloaca* (1% in 1980, 0% in 2000, and 5% in 2019/20) infections.

Our analysis of antibiotic resistance revealed a positive correlation between the increase in gram-negative bacteria and the prevalence of 2MRGN and 3MRGN bacteria. In addition, we found that 42.8% of coagulase-negative staphylococci (CoNS) were resistant to methicillin. This percentage is lower in comparison to the documented methicillin resistance rates reported in the literature for CoNS. The 1988 and 2000 studies did not report on MRSA or VRE resistance, nor did they investigate resistance in gram-negative bacteria. In our study, 55% of bloodstream infections exhibited relevant resistance to antibiotics, with 33.3% of gram-positive strains and 36.3% of all gram-negative infections demonstrating such resistance. Notably, the overall proportion of multidrug-resistant bacteria in gram-negative bacteria within our cohort (55%) was higher than the figures reported in previous descriptive studies on this patient population, which ranged from 11% to 20% (38).

In summary, our study observed a shift in the microbiological spectrum of bacterial infections in patients with neutropenic fever, with an increased proportion of gram-negative bacteria. The most frequently identified gram-negative organism was *E. coli*,

which has increased over time. We also observed an increase in the proportion of *Klebsiella pneumoniae* and *Enterobacter cloacae* infections. Notably, we identified a case of *Pseudomonas aeruginosa* infection, which was not present in previous studies from our center. While the isolation of *Pseudomonas aeruginosa* in these patients is commonly reported in the literature (40), this was not found in previous observational studies in our service. We also observed a relevant increase in the proportion of multidrug-resistant gram-negative bacteria, consistent with trends described in other studies in this patient population (41). These findings highlight the need for continued surveillance and vigilance in the management of bacterial infections in patients with neutropenic fever.

Strengths and Limitations of the Study

This study shows the limited impact of TTA on the clinical outcome of paediatric patients with febrile neutropenia and explores relevant triage information that can predict the clinical development of patients. Our results help clarify an unwieldy clinical encounter and bring attention to the most crucial issues in febrile neutropenia. These findings should inform guidelines and guide clinical researchers aiming to develop or validate specific risk stratification tools.

However, there are significant limitations in the study. Firstly, the study has adequate power for the primary outcome but limited power for the secondary analysis results. Furthermore, the study's single-centre design may affect the generalizability of the findings.

Overall, this study provides valuable insights into the association between the studied variables and the outcome of interest. Still, the findings should be interpreted cautiously, and further studies must confirm the results.

Conclusions and Recommendations

In our study, we observed that a TTA over 1 hour did not significantly impact the clinical outcome of paediatric patients with neutropenic fever. Although prompt assessment and management of these patients is always encouraged, our findings suggest that the implementation of this measure may not be an effective use of resources. Therefore, clinical guidelines should recommend such measures with caution, as they may divert

resources away from more effective strategies for optimizing the management of patients with neutropenic fever.

The complex medical needs and fragile health status of patients with severe illnesses necessitate that healthcare providers have access to more sophisticated and precise resources to guide clinical decision-making. The development of clinical decision rules, such as newly developed risk stratification tools, is critical in enabling clinicians to better manage these patients. Collaboration among clinical researchers is essential to ensure the safe implementation of such tools. Rapid and safe implementation of these decision-making resources can significantly reduce morbidity and mortality in these vulnerable patient populations.

Finally, our microbiological findings indicate a trend towards an increased incidence of gram-negative infections and an elevated level of multidrug resistance. These results underscore the importance of regularly monitoring bacterial strains and antibiotic susceptibility patterns and the need for optimised use of broad-spectrum antibiotics.

Appendix

Appendix 1: Admission Sheet

Klinik für Kinder-Onkologie, -Hämatologie und Klin. Immunologie
Direktor der Klinik Univ.-Prof. Dr. A. Borkhardt

Patientenaufkleber/Name

Diagnose:

Aufnahmegrund / Symptome:

Größe:_____ Gewicht:_____
KOF:__

Erfolgte Diagnostik: (Nicht erfolgte Maßnahmen streichen)
Blutbild, CRP, PCT, Leberwerte, Nierenwerte, Elektrolyte, BGA, Gerinnung, Blutkulturen

Rö-Thorax Sono-Abdomen
Rachenabstrich: Virologie (Resp. Viren)
(bei allen Patienten mit Fieber)

Sonstiges:

Med Zusatzinformation:
Besiedlung mit MRE (MRSA,MRGN, VRE...)___
Allergien: _____

bestehend seit (Tag/Uhrzeit):
Ankunft Krankenhaus:_____Uhr

Klinische Warnzeichen für eine beginnende Sepsis:
* Altersnorm siehe Rückseite

RR:____mm/Hg **MAD:**	**Beeinträchtigte Vigilanz** **nein** **ja GCS :**
AF:____/min	**HF:____/min**
Temperatur:___°C	SaO2: ____ (<94% Raumluft) ja nein

→**Verdacht auf Sepsis:** **nein** **(Verordnung 1)**
ja* **(Verordnung 2)**

*Volumengabe, Hintergrund informieren. Hinweis septischer Schock benötigt darüberhinaus ein weiter eskaliertes Konzept

<u>Klinischer Untersuchungsbefund:</u>

Sonstige Auffälligkeiten:

Allgemeinzustand	
Bewusstsein (GCS)	
Hautkolorit	
Petechien/Purpura	
Rekapillierungszeichen (>2s)	
Mundschleimhaut / Rachen	
Ohren	
Leber	
Milz	
Cor	
Pulmo	
Lymphknoten	
Anal-Genital	

VERORDNUNG 1:

Flüssigkeit: _____ml Paed 2-Lösung /24h (enthält u.a: 18mmol KCl, 70mmol NaCl je 1 L)

Antibiotika (s.SOP Fieber im Zelltief). Start der antibiotischen Therapie um**:** _____ Uhr

Piperacillin/Tazobactam (100mg/kg 3xtgl; max 4,5 g ED)

VERORDNUNG 2:

Flüssigkeitsbolus: (20ml/kg Jonosteril 1/1 oder NaCl 0,9% über 20 min), **Uhrzeit:**

*bei septischen Schock 20ml/kg Jonosteril 1/1 innerhalb von 5 Min (bis - 60ml/kg Jonosteril 1/1 in 15min)

Flüssigkeit: _____ml Paed 2-Lösung /24h (enthält u.a: 18mmol KCl, 70mmol NaCl je 1 L)

Antibiotika (s.SOP Fieber im Zelltief) **, Gabe innerhalb von 30 min,** Start der antibiotischen Therapie um**:** _____ Uhr

Piperacillin/Tazobactam (100mg/kg 3xtgl; max 4,5 g ED)
Teicoplanin (3 x 10 mg/kg im Abstand von 12 Stunden, dann10 mg/kg/Tag ;max. 400 mg/Gabe)
Meronem (3 x 20 mg/kg/Tag; max 3 x 1 g)

Überwachung (bitte ankreuzen):

RR/AF/HF alle ____min (bei V.a. Sepsis alle 30 min) / _____pro Sicht
Bilanz alle 8 Std
Monitor SaO2 + HF
erneute klinische Untersuchung nach 60 min

Schmerztherapie/Antipyretika/Antiemetika:

Medikamente p.o:

Sonstige Verordnungen (Blutentnahme…):

Rachenabstrich: Virologie (Resp. Viren) ***Bitte bei allen Patienten mit Fieber ankreuzen***

Bestellte Blutprodukte: _____EK; _____ TK

Name in Druckschrift, Unterschrift /Datum:_____

Richtwerte Vital- und Laborparameter im Kindes- und Jugendalter mit Bezug zur SIRS-/Sepsis- Definition

Altersgruppe	Definition	Hypotension (RR Syst)	Bradykardie (bpm)	Tachykardie (bpm)	Tachypnoe (rpm)
Säugling	*29 d bis < 1 Jahr*	< 65 mmHg	<90	>180	>50
Kleinkinder	*1 bis <6 Jahre*	< 65 mmHg	N.D.	>140	>40
Schulkinder	*6 bis 12 Jahre*	< 83 mmHg	N.D.	>130	>20
Jugendliche	*12 bis < 18 Jahre*	< 90 mmHg	N.D.	>110	>20

Kriterien und Definition für SIRS

SIRS	*Unauffällig*	*Auffällig*
Herzfrequenz	0	1
Atemfrequenz	0	1
Temperatur (>38,5 oder <36ºC)	0	1
Leukozytose/ Leukopenie*	0	1

*Diese Parameter entfallen bei Onkologischen Patienten im Zelltief.

Kriterien und Definition für qSOFA*

qSOFA	*Unauffällig*	*Auffällig*
Atemfrequenz	0	1
RR Systolisch	0	1
Vigilanz (GCS)	0	1

*qSOFA: quick Sequential Organ Failure Assesment.

10/19

Neubert/Alustiza

Appendix 2: Information Sheet and Consent Form

Zentrum für Kinder- und Jugendmedizin
Klinik für Pädiatrische Hämatologie, Onkologie und Klinische Immunologie
Direktor: Universitätsprofessor Dr. A. Borkhardt
Moorenstr.5, D-40225 Düsseldorf

Elterninformation und Einverständniserklärung zur Teilnahme an der Studie zu Infektionen bei Kindern mit Fieber und onkologischer Grunderkrankung. Eine prospektive Datenerhebung von 2019 – 2021.

Liebe Eltern,

wir möchten Sie um Ihre Einwilligung zur Teilnahme Ihres Kindes an der obengenannten Studie bitten. Im Folgenden möchten wir Ihnen nähere Informationen dazu geben, damit Sie Ihre Entscheidung über die Teilnahme treffen können. Bitte lesen Sie die Patienteninformation sorgfältig durch. Ihre Ärztin /Arzt wird mit Ihnen auch direkt über die Studie sprechen. Bitte fragen Sie Ihren Arzt, wenn Sie etwas nicht verstanden haben.

Die Behandlung einer Krebserkrankung (onkologischen Erkrankung) bedeutet eine lange und intensive Therapie. Die onkologische Grunderkrankung und die intensive Chemotherapie können das körpereigene Abwehrsystem (Immunsystem) beeinträchtigen. Dadurch ist der Körper anfälliger für Infektionen. Diese Infektionen können von verschiedenen Erregern verursacht werden. Das sind Bakterien, Viren oder Pilze.

Zur sicheren Verabreichung der Chemotherapie gegen den Krebs, hat ihr Kind einen zentralen Venenkatheter vom Typ Broviac oder Port

bekommen. Dieser Katheter stellt einen zusätzlichen Risikofaktor für BlutstromInfektionen dar.

Granulozyten sind Teil der Leukozyten (= weiße Blutkörperchen), die zuständig für den Kampf gegen Infektionen im Körper sind. Die intensive Therapie gegen die Grunderkrankung senkt die Anzahl dieser Blutzellen und dadurch steigt das Risiko für schwerwiegende Infektionen. Besonders wenn die Granulozyten unter 500/µl liegen (das sogenannte Zelltief), besteht ein hohes Risiko für Infektionen.

Fieber ist häufig das erste Zeichen einer Infektion. Aufgrund der obengenannten Risikofaktoren müssen Kinder mit Zeichen einer Infektion zügig eine antibiotische Therapie erhalten. Die zeitnahe Vorstellung der Kinder und die zügige und zielgerichtete Antibiotikatherapie hat die Prognose von Kindern mit onkologischen Erkrankungen erheblich verbessert. Da Erreger, Resistenzen gegen bestimmte Antibiotika entwickeln können, ist es wichtig diese Resistenzmerkmale zu erfassen, damit eine effektive Antibiotikatherapie ausgewählt wird.

Das Ziel dieser Studie ist es, die klinische und Labordaten, die erhoben werden, wenn onkologische Patienten sich mit Fieber in der Klinik vorstellen, systematisch zusammenzuführen. Dabei werden Daten zur klinischen Untersuchung, Laborwerte, Antibiotikatherapie und Daten zu den Erregern und deren Resistenzmerkmalen analysiert. Diese Datenerhebung dient der Qualitätskontrolle. Die behandelnden Ärzte können daraus neue Erkenntnisse gewinnen und zukünftig diese in die Behandlung einfließen lassen. Die Daten werden im Rahmen der Routine erhoben. Es wird kein zusätzliches Blut abgenommen und es werden keine zusätzlichen Untersuchungen veranlasst.

Wenn Sie damit einverstanden sind an der Studie teilzunehmen, werden die Daten verschlüsselt in einer Datenbank eingegeben und ausgewertet.

Die Mitwirkung an der Studie kann jederzeit ohne Nennung von Gründen und ohne persönliche Nachteile beendet werden.

Patienteninformation für Jugendliche (12-17 J) über die Studie zu Infektionen bei Kindern mit Fieber und onkologischer Grunderkrankung. Eine prospektive Datenerhebung von 2019 – 2021.

Lieber Patient,

wir möchten Dich um deine Einwilligung zur Teilnahme an der obengenannten Studie bitten. Im Folgenden möchten wir dir nähere Informationen dazu geben, damit Du deine Entscheidung über die Teilnahme treffen kannst. Bitte lies die Patienteninformation sorgfältig durch. Deine Ärztin/Arzt wird mit dir auch direkt über die Studie sprechen. Bitte frag deinen Arzt, wenn Du etwas nicht verstanden hast.

Die Behandlung einer Krebserkrankung (onkologischen Erkrankung) bedeutet eine lange und intensive Therapie. Die onkologische Grunderkrankung und die intensive Chemotherapie können das körpereigene Abwehrsystem (Immunsystem) beeinträchtigen. Dadurch ist der Körper anfälliger für Infektionen. Diese Infektionen können von verschiedenen Erregern verursacht werden. Das sind Bakterien, Viren oder Pilze.

Zur sicheren Verabreichung der Chemotherapie gegen den Krebs, hast Du einen zentralen Venenkatheter vom Typ Broviac oder Port bekommen. Dieser Katheter stellt einen zusätzlichen Risikofaktor für BlutstromInfektionen dar.

Granulozyten sind Teil der Leukozyten (=weißen Blutkörperchen), die zuständig für den Kampf gegen Infektionen im Körper sind. Die intensive Therapie gegen die Grunderkrankung senkt die Anzahl dieser Blutzellen und dadurch steigt das Risiko für schwerwiegende Infektionen. Besonders wenn die Granulozyten unter 500/µl liegen (das sogenannte Zelltief), besteht ein hohes Risiko für Infektionen.

Fieber ist häufig das erste Zeichen einer Infektion. Aufgrund der obengenannten Risikofaktoren müssen Kinder mit Zeichen einer Infektion zügig eine antibiotische Therapie erhalten. Die zeitnahe

Vorstellung und die zügige und zielgerichtete Antibiotikatherapie hat die Prognose von Kindern mir onkologischen Erkrankungen erheblich verbessert. Da Erreger Resistenzen gegen bestimmte Antibiotika entwickeln können, ist es wichtig diese Resistenzmerkmale zu erfassen, damit eine effektive Antibiotikatherapie ausgewählt wird.

Das Ziel dieser Studie ist es, die klinische und Labordaten, die erhoben werden, wenn onkologische Patienten sich mit Fieber in der Klinik vorstellen, systematisch zusammenzuführen. Dabei werden Daten zur klinischen Untersuchung, Laborwerte, Antibiotikatherapie und Daten zu den Erregern und deren Resistenzmerkmalen analysiert. Diese Datenerhebung dient der Qualitätskontrolle. Die behandelnden Ärzte können daraus neue Erkenntnisse gewinnen und zukünftig diese in die Behandlung einfließen lassen. Die Daten werden im Rahmen der Routine erhoben. Es wird kein zusätzliches Blut abgenommen und es werden keine zusätzlichen Untersuchungen veranlasst.

Wenn Du damit einverstanden bist an der Studie teilzunehmen, werden die Daten verschlüsselt in einer Datenbank eingegeben und ausgewertet.

Die Mitwirkung an der Studie kann jederzeit ohne Nennung von Gründen und ohne persönliche Nachteile beendet werden.

Patienteninformation für Kinder <12 J über die Studie zu Infektionen bei Kindern mit Fieber bei onkologischer Grunderkrankung. Eine prospektive Datenerhebung von 2019 – 2021.

Liebe/r_____,

wir möchten Dich fragen, ob du bereit bist an der obengenannten Studie teilzunehmen. Im Folgenden möchten wir dir nähere Informationen dazu geben, damit Du deine Entscheidung über die Teilnahme treffen kannst. Nimm dir bitte Zeit, diese Informationen gut durchzulesen und frage Deinen Arzt oder Deine Eltern, wenn Du etwas nicht verstehst.

Aufgrund deiner Erkrankung kommst Du regelmäßig ins Krankenhaus für Untersuchungen und um deine Medikamente zu erhalten. Einige dieser Medikamente (z.B. Chemotherapie) können dein Abwehrsystem beeinträchtigen. Das heißt, dass du anfälliger für Infektionen bist.

Granulozyten zählen zu den weißen Blutkörperchen (Leukozyten). Das sind wichtige Abwehrzellen gegen Viren, Pilze und Bakterien. Durch die Chemotherapie kommt es häufig zu einem Abfall der Granulozytenzahl.

Fieber ist oft das erste Zeichen, das man bei einer Infektion entwickelt. Deswegen werden deine Eltern dich bei Fieber direkt ins Krankenhaus bringen. Im Krankenhaus, wirst du untersucht, es wird Blut abgenommen und meistens wird dann auch ein Antibiotikum verabreicht. Wir möchten die Ergebnisse der Blutuntersuchungen, die im Rahmen der Infektionen abgenommen werden, auswerten. Die Daten werden im Rahmen der Routine erhoben. Es wird kein zusätzliches Blut abgenommen und es werden keine zusätzlichen Untersuchungen veranlasst. Die behandelnden Ärzte können daraus neue Erkenntnisse gewinnen.

Wenn Du damit einverstanden bist an der Studie teilzunehmen, werden die erhobenen Daten verschlüsselt (mit einem Code) in einer Datenbank eingegeben und ausgewertet.

Die Mitwirkung an der Studie kann jederzeit ohne Nennung von Gründen und ohne persönliche Nachteile beendet werden.

Einverständniserklärung

Die Einwilligung verbleibt in den Unterlagen der meldenden Klinik
Sie erhalten eine Kopie

Name der Patientin/ des Patienten: .....

Geburtsdatum: .....

Wohnanschrift – Straße: .....

PLZ und Ort: .....

Telefon- Nummer: .....

Sorgeberechtigte: .....

Als Patient/ Sorgeberechtigte/r wurde ich mündlich durch unseren behandelnden Arzt über die Studie zur "Infektionen bei Kindern mit Fieber und onkologischer Grunderkrankung. Eine prospektive Datenerhebung von 2019 – 2021 " aufgeklärt. Ziel der Studie ist es, klinische und Labordaten, die erhoben werden, wenn onkologische Patienten sich mit Fieber in der Klinik vorstellen, systematisch zusammenzuführen, damit die behandelnden Ärzte daraus neue Erkenntnisse gewinnen können und zukünftig diese in die Behandlung einfließen lassen.
Ich habe den Inhalt der Aufklärung verstanden und mit meinem Kind in einer seinem Entwicklungsstand angemessenen Weise besprochen.

Mit meiner Unterschrift bestätige ich nach erfolgter Aufklärung und unter Kenntnis meines Widerrufsrechtes mein Einverständnis zur Auswertung der erhobenen Daten. Ich bin damit einverstanden, dass die Daten in pseudonymisierter Form für wissenschaftliche Zwecke genutzt/publiziert werden können.

Es ist mir bekannt, dass die Mitwirkung an der Studie jederzeit ohne Nennung von Gründen und ohne persönliche Nachteile beendet werden kann.

.....	.....
Ort, Datum	Unterschrift eines Sorgeberechtigten
.....	.....
Ort, Datum	Unterschrift des Patienten/ der Patientin
.....	.....
Ort, Datum	Unterschrift des aufklärenden Arztes

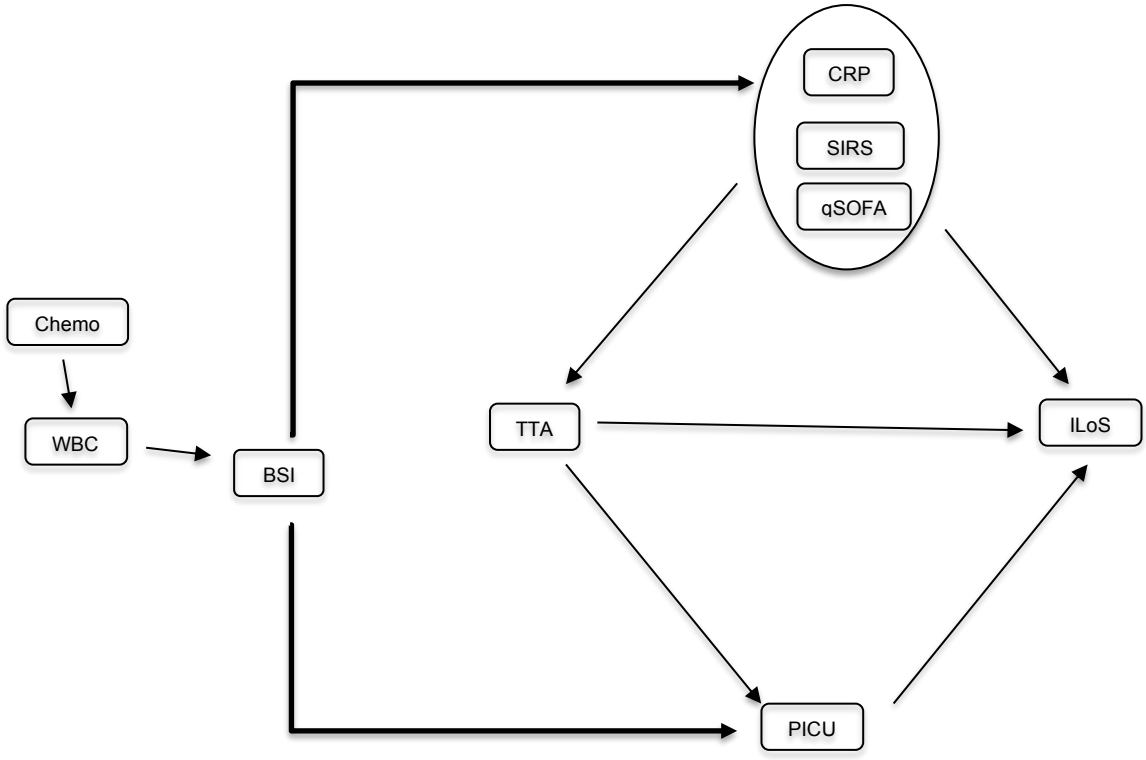
Appendix 3: Cohort Variables

Variable	Description	Coding	Available Data (n = 155)	Regrouped
IdPat	Code for the PATIENT	1-60		
idFE	ID Febrile Episode	1-155		
Code	Code for the Admission		155	
Admission_NA1	ID admitted via Emergency Department	1= Emergency 0 = Oncology		
Sex_ M1	Sex of the patient	1= Female 0= Male		
Age	Age of the patient by admission with Febrile Episode	continuous Min 0.2-Max 17.8		age2
Birthdate	Date of birth of the child	DD/MM/YY		
PrimDisease	Underlying malignancy		155	
iLOS*	Infection-related length of stay	Continuous Min: 1 Max: 54	155	
TTA	Time to Antibiotics (h)	Continuous Unit: hours		TTAgrp
TTA_Decimals	Time to Antibiotics (decimals)	Continuous Unit: numeric Min: 0 Max: 8.7	152	TTAgrp
BP_SYST	Systolic BP by admission	Continuous: Min: 84 Max: 144	154	
BP_DYAST	Diastolic BP by admission	Continuous Min: 35 Max: 98	154	

MAD	Mittlerer srterieller BlutDruck by admission	Continuous Min: 55.6 Max: 108	154	
AF	Atemfrequenz by admission	Continuous Min: 12 Max: 64	117	
HF	Herzfrequenz by admission	Continuous Min: 70 Max: 207	149	
Temperature	T° by admission	Continuous Min: 36.8 Max: 40	155	
SpO2	Oxygen Saturation by admission	Continuous Min: 92 Max: 100	141	
GCS	Glasgow Coma Scale by admission	1-15 Min: 14 Max: 15	143	
Recap_01	Capillary refill time by admission	0= ≤2sec 1= >2sec	140	
SIRS	SIRS-Score	0-4 Min: 0 Max: 3	113	SIRS_Code
qSOFA	qSOFA Score	0-4 Min: 0 Max: 2	117	qSOFA_Code
Leuk_Min	Minimal WBC during admission	Continuous Min: 0.09 Max: 9.9	152	WBC CRPgrp
CRP_Admission	CRP by admission	Continuous Min: 0.01 Max: 22.74	152	CRPgrp
BcuContinuous	Any positive Bloodculture during admission	0= Negative 1= Positive	155	
Chemo Bestrahlungim	Whether the patient received	0= no 1= yes	155	

Aufenthalt_	any additional therapy (Chemo) during the admission			
VolumenBolus_JA1	Whether the child received a fluid bolus during the admission	0= no 1= yes	155	
Intensiv_Ja1	Whether the child was admitted to PICU during admission	0= no 1= yes	155	
TTAgrp	Time to antibiotics group in > or <= 1 hour	0= <1 h 1 = ≥1h	152	
age2	Age regrouped	0= ≤6 1= 6-12 2= >12		
SIRS_Code	SIRS regrouped Positive is defined as ≥2	0= Negative 1=Positive		
qSOFA_Code	qSOFA regrouped Positive is defined as ≥2	0= Negative 1= Positive		
WBC	Zelltied Ja/Nein defines as < $1x10^3$ Leuk	0= <1 1= ≥1		
CRPgrp[1]	CRP regrouped.	0= <0.5 mg/dl 1= 0.5-5mg/dl 2= >5 mg/dl		

Appendix 4: Conceptual Frameworks



References

1. Lehrnbecher T, Koehl U, Wittekindt B, Bochennek K, Tramsen L, Klingebiel T, et al. Changes in host defence induced by malignancies and antineoplastic treatment: implication for immunotherapeutic strategies. Lancet Oncol [Internet]. 2008 Mar 1 [cited 2022 Dec 15];9(3):269–78. Available from: http://www.thelancet.com/article/S1470204508700718/fulltext
2. Cecinati V, Brescia L, Tagliaferri L, Giordano P, Esposito S. Catheter-related infections in pediatric patients with cancer. Eur J Clin Microbiol Infect Dis [Internet]. 2012 Nov [cited 2022 Dec 15];31(11):2869–77. Available from: https://pubmed.ncbi.nlm.nih.gov/22661169/
3. Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. J Clin Oncol [Internet]. 2017 Jun 20 [cited 2022 Dec 15];35(18):2082–94. Available from: https://pubmed.ncbi.nlm.nih.gov/28459614/
4. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med [Internet]. 1966 [cited 2022 Dec 15];64(2):328–40. Available from: https://pubmed.ncbi.nlm.nih.gov/5216294/
5. Phillips RS, Sutton AJ, Riley RD, Chisholm JC, Picton S V., Stewart LA. Predicting infectious complications in neutropenic children and young people with cancer (IPD protocol). Syst Rev [Internet]. 2012 Feb 9 [cited 2023 May 7];1(1):1–11. Available from: https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-1-8
6. Hann I, Viscoli C, Paesmans M, Gaya H, Glauser M. A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). Br J Haematol [Internet]. 1997 [cited 2023 May 7];99(3):580–8. Available from: https://pubmed.ncbi.nlm.nih.gov/9401070/

7. Duncan C, Chisholm JC, Freeman S, Riley U, Sharland M, Pritchard-Jones K. A prospective study of admissions for febrile neutropenia in secondary paediatric units in South East England. Pediatr Blood Cancer [Internet]. 2007 Oct 15 [cited 2023 May 7];49(5):678–81. Available from: https://pubmed.ncbi.nlm.nih.gov/17066460/
8. Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, et al. Management of febrile neutropaenia: ESMO clinical practice guidelines. Annals of Oncology [Internet]. 2016 Sep 1 [cited 2022 Dec 15];27:v111–8. Available from: http://www.annalsofoncology.org/article/S0923753419316436/fulltext
9. Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical practice guideline update. Journal of Clinical Oncology. 2018 May 10;36(14):1443–53.
10. Simon A, DGPI, GPOH. Diagnostik und Therapie bei Kindern mit onkologischer Grunderkrankung , Fieber und Granulozytopenie (mit febriler Neutropenie) außerhalb der allogenen Stammzelltransplantation [Internet]. AWMF S2K Leitlinie. 2016. p. 1–27. Available from: http://www.awmf.org/leitlinien/ awmf-regelwerk.html
11. Koenig C, Schneider C, Morgan JE, Ammann RA, Sung L, Phillips B. Association of time to antibiotics and clinical outcomes in patients with fever and neutropenia during chemotherapy for cancer: a systematic review. Support Care Cancer [Internet]. 2020 Mar 1 [cited 2022 Feb 17];28(3):1369–83. Available from: https://pubmed.ncbi.nlm.nih.gov/31264188/
12. Fletcher M, Hodgkiss H, Zhang S, Browning R, Hadden C, Hoffman T, et al. Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer. Pediatr Blood Cancer [Internet]. 2013 Aug [cited 2022 Dec 15];60(8):1299–306. Available from: https://pubmed.ncbi.nlm.nih.gov/23417978/
13. Avilés-Robles MJ, Reyes-López A, Otero-Mendoza FJ, Valencia-Garin AU, Peñaloza-González JG, Rosales-Uribe RE, et al. Safety and efficacy of step-down to oral outpatient treatment versus inpatient antimicrobial treatment in

pediatric cancer patients with febrile neutropenia: A noninferiority multicenter randomized clinical trial. Pediatr Blood Cancer [Internet]. 2020 Jun 1 [cited 2022 Dec 16];67(6). Available from: https://pubmed.ncbi.nlm.nih.gov/32196898/

14. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics*. 2005;
15. Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. J Clin Oncol [Internet]. 2017 Jun 20 [cited 2023 May 7];35(18):2082–94. Available from: https://pubmed.ncbi.nlm.nih.gov/28459614/
16. Ammann RA, Bodmer N, Hirt A, Niggli FK, Nadal D, Simon A, et al. Predicting adverse events in children with fever and chemotherapy-induced neutropenia: the prospective multicenter SPOG 2003 FN study. J Clin Oncol [Internet]. 2010 Apr 20 [cited 2022 Dec 16];28(12):2008–14. Available from: https://pubmed.ncbi.nlm.nih.gov/20231680/
17. Ammann RA, Hirt A, Lüthy AR, Aebi C. Identification of children presenting with fever in chemotherapy-induced neutropenia at low risk for severe bacterial infection. Med Pediatr Oncol [Internet]. 2003 Nov 1 [cited 2022 Dec 16];41(5):436–43. Available from: https://pubmed.ncbi.nlm.nih.gov/14515382/
18. Rackoff WR, Gonin R, Robinson C, Kreissman SG, Breitfeld PB. Predicting the risk of bacteremia in childen with fever and neutropenia. J Clin Oncol [Internet]. 1996 [cited 2022 Dec 16];14(3):919–24. Available from: https://pubmed.ncbi.nlm.nih.gov/8622040/
19. Alexander SW, Wade KC, Hibberd PL, Parsons SK. Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. J Pediatr Hematol Oncol [Internet]. 2002 [cited 2022 Dec 16];24(1):38–42. Available from: https://pubmed.ncbi.nlm.nih.gov/11902738/
20. Rondinelli PIP, Ribeiro KDCB, de Camargo B. A proposed score for predicting severe infection complications in children with chemotherapy-induced febrile neutropenia. J Pediatr Hematol Oncol [Internet]. 2006 Oct [cited 2022 Dec

16];28(10):665–70. Available from: https://pubmed.ncbi.nlm.nih.gov/17023827/

21. Santolaya ME, Alvarez AM, Becker A, Cofré J, Enríquez N, O'Ryan M, et al. Prospective, multicenter evaluation of risk factors associated with invasive bacterial infection in children with cancer, neutropenia, and fever. J Clin Oncol [Internet]. 2001 Jul 15 [cited 2022 Dec 16];19(14):3415–21. Available from: https://pubmed.ncbi.nlm.nih.gov/11454890/
22. Scheler M, Lehrnbecher T, Groll AH, Volland R, Laws HJ, Ammann RA, et al. Management of children with fever and neutropenia: results of a survey in 51 pediatric cancer centers in Germany, Austria, and Switzerland. Infection [Internet]. 2020 Aug 1 [cited 2023 Jan 2];48(4):607–18. Available from: https://link.springer.com/article/10.1007/s15010-020-01462-z
23. Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H, Calle GM, et al. The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. Journal of Antimicrobial Chemotherapy [Internet]. 2016 Apr 1 [cited 2023 Jan 2];71(4):1106–17. Available from: https://academic.oup.com/jac/article/71/4/1106/2363769
24. Sifri CD, Ison MG. Highly resistant bacteria and donor-derived infections: treading in uncharted territory. Transpl Infect Dis [Internet]. 2012 Jun [cited 2023 Jan 4];14(3):223–8. Available from: https://pubmed.ncbi.nlm.nih.gov/22676635/
25. Bock AM, Cao Q, Ferrieri P, Young JAH, Weisdorf DJ. Bacteremia in Blood or Marrow Transplantation Patients: Clinical Risk Factors for Infection and Emerging Antibiotic Resistance. Biology of Blood and Marrow Transplantation. 2013 Jan;19(1):102–8.
26. Theodoropoulos N, Ison MG. Current issues in transplant infectious diseases. Curr Infect Dis Rep [Internet]. 2013 Dec [cited 2023 Jan 4];15(6):453–4. Available from: https://pubmed.ncbi.nlm.nih.gov/24142771/
27. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. The Lancet [Internet]. 2019 Jan 12 [cited 2023 Jan 2];393(10167):183–98. Available from: http://www.thelancet.com/article/S0140673618322189/fulltext

28. Herberger S, Oberkircher N, Wenzel GI, Hecker D, Wagenpfeil G, Furtwängler R, et al. Prospektives Audit des Gentamicin Drug Monitorings in einem Kinderkrebszentrum. Klin Padiatr [Internet]. 2021 May 1 [cited 2023 Jan 2];233(3):123–6. Available from: http://www.thieme-connect.de/products/ejournals/html/10.1055/a-1352-5053
29. Laws HJ, Schneider DT, Janssen G, Wessalowski R, Dilloo D, Meisel R, et al. TRENDS IN INFECTIONS IN CHILDREN WITH MALIGNANT DISEASE IN 2000: Comparison of Data of 1980/81. http://dx.doi.org/101080/08880010701391788 [Internet]. 2009 Jun [cited 2023 Jan 30];24(5):343–54. Available from: https://www.tandfonline.com/doi/abs/10.1080/08880010701391788
30. Secmeer G, Devrim I, Kara A, Ceyhan M, Cengiz B, Kutluk T, et al. Role of procalcitonin and CRP in differentiating a stable from a deteriorating clinical course in pediatric febrile neutropenia. J Pediatr Hematol Oncol [Internet]. 2007 Feb [cited 2023 Feb 2];29(2):107–11. Available from: https://pubmed.ncbi.nlm.nih.gov/17279007/
31. Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K. The role of procalcitonin in febrile neutropenic patients: review of the literature. Infection [Internet]. 2008 Oct [cited 2023 Jan 13];36(5):396–407. Available from: https://pubmed.ncbi.nlm.nih.gov/18759057/
32. Koenig C, Schneider C, Morgan JE, Ammann RA, Sung L, Phillips B. Interventions aiming to reduce time to antibiotics (TTA) in patients with fever and neutropenia during chemotherapy for cancer (FN), a systematic review. Supportive Care in Cancer [Internet]. 2020 May 1 [cited 2023 Feb 2];28(5):2369–80. Available from: https://link.springer.com/article/10.1007/s00520-019-05056-w
33. Lehrnbecher T. Treatment of fever in neutropenia in pediatric oncology patients. Curr Opin Pediatr [Internet]. 2019 Feb 1 [cited 2023 Feb 2];31(1):35–40. Available from: https://pubmed.ncbi.nlm.nih.gov/30461508/
34. Doerflinger M, Haeusler GM, Li-Wai-Suen CSN, Clark JE, Slavin M, Babl FE, et al. Procalcitonin and Interleukin-10 May Assist in Early Prediction of Bacteraemia in Children With Cancer and Febrile Neutropenia. Front Immunol

[Internet]. 2021 May 20 [cited 2023 Jan 2];12. Available from: https://pubmed.ncbi.nlm.nih.gov/34093531/

35. Miedema KGE, Tissing WJE, Abbink FCH, Ball LM, Michiels EMC, van Vliet MJ, et al. Risk-adapted approach for fever and neutropenia in paediatric cancer patients--a national multicentre study. Eur J Cancer [Internet]. 2016 Jan 1 [cited 2023 Jan 2];53:16–24. Available from: https://pubmed.ncbi.nlm.nih.gov/26700076/
36. Delebarre M, Gonzales F, Behal H, Tiphaine A, Sudour-Bonnange H, Lutun A, et al. Decision-tree derivation and external validation of a new clinical decision rule (DISCERN-FN) to predict the risk of severe infection during febrile neutropenia in children treated for cancer. Lancet Child Adolesc Health [Internet]. 2022 Apr 1 [cited 2023 Apr 10];6(4):260–8. Available from: https://pubmed.ncbi.nlm.nih.gov/34871572/
37. Klastersky J, Ameye L, Maertens J, Georgala A, Muanza F, Aoun M, et al. Bacteraemia in febrile neutropenic cancer patients. Int J Antimicrob Agents [Internet]. 2007 Nov [cited 2023 Feb 2];30 Suppl 1(SUPPL. 1):51–9. Available from: https://pubmed.ncbi.nlm.nih.gov/17689933/
38. Macesic N, Morrissey CO, Cheng AC, Spencer A, Peleg AY. Changing microbial epidemiology in hematopoietic stem cell transplant recipients: increasing resistance over a 9-year period. Transpl Infect Dis [Internet]. 2014 Dec 1 [cited 2023 Jan 30];16(6):887–96. Available from: https://pubmed.ncbi.nlm.nih.gov/25298044/
39. Nouér SA, Nucci M, Anaissie E. Tackling antibiotic resistance in febrile neutropenia: current challenges with and recommendations for managing infections with resistant Gram-negative organisms. Expert Rev Hematol [Internet]. 2015 Sep 3 [cited 2023 Jan 30];8(5):647–58. Available from: https://pubmed.ncbi.nlm.nih.gov/26115679/
40. Siddaiahgari S, Manikyam A, Anand Kumar K, Rauthan A, Ayyar R. Spectrum of systemic bacterial infections during febrile neutropenia in pediatric oncology patients in tertiary care pediatric center. Indian J Cancer [Internet]. 2014 Oct 1 [cited 2023 Apr 10];51(4):403–5. Available from: https://pubmed.ncbi.nlm.nih.gov/26842136/

41. Alali M, David MZ, Danziger-Isakov LA, Elmuti L, Bhagat PH, Bartlett AH. Pediatric Febrile Neutropenia: Change in Etiology of Bacteremia, Empiric Choice of Therapy and Clinical Outcomes. J Pediatr Hematol Oncol [Internet]. 2020 Aug 1 [cited 2023 Apr 10];42(6):E445–51. Available from: https://pubmed.ncbi.nlm.nih.gov/32404688/

Acknowledgements

I would like to extend my gratitude to my mentor Jennifer Neubert for her guidance and support throughout this project. Her trust in me to conduct the study and encouragement during challenging times is greatly appreciated. I would also like to express my appreciation for Malte Kohns for the valuable contributions to this project by bringing his expertise in epidemiology and his willingness to collaborate through meetings in Düsseldorf, online, and in London. Additionally, I would like to acknowledge Hans-Juergen Laws for highlighting the significance of this project's theme and Colin MacKenzie for his support.

Lastly, I am grateful to my partner for his assistance navigating excel, willingness to delve into the medical field, and patience while dedicating time to this project during our leisure hours.