

ORIGINAL ARTICLE

Outcomes in Stable Paediatric Patients With Cancer With Fever and Neutropenia According to Time to Antibiotic Administration: A Prospective Observational Study

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ABSTRACT

Aim: To evaluate whether an increase in the time to antibiotics (TTA) administration in the paediatric emergency department worsens the clinical outcomes of well-appearing paediatric cancer patients with febrile neutropenia (FN).

Methods: We performed a subanalysis of a prospective, observational study conducted in two hospitals between November 2019 and October 2021. Multivariate analysis was performed to identify independent risk factors for poor outcomes, defined as admission to the paediatric intensive care unit, sepsis or septic shock, acute organ dysfunction, long-term sequelae, or death.

Results: We included 192 episodes in 163 patients. A total of 110 episodes (57.3%) had a TTA ≤ 60 min (short TTA) and 82 (42.7%) had a TTA > 60 min (long TTA). Baseline characteristics were similar in both groups, except for previous FN episodes, which were more frequent in the short TTA group (64.5% vs. 8.5%, $p < 0.001$). Twelve episodes (6.3%) resulted in a poor outcome, although no deaths were reported. Poor outcomes were more common in patients with higher maximum temperature (odds ratio [OR]: 2.7; 95% CI: 1.1–6.6), and elevated CRP (OR: 1.01; 95% CI 1.003–1.02). In the multivariate analysis, no variable—including TTA—was identified as an independent risk factor for poor outcome.

Conclusions: Delayed antibiotic administration in clinically stable paediatric FN patients did not worsen outcomes, supporting the potential feasibility of a 'wait-and-observe focus' approach.

1 | Introduction

Febrile neutropenia (FN) presents a significant clinical challenge in paediatric oncology [1]. FN is associated with a high risk of severe bacterial infections; therefore, prompt empiric broad-spectrum antibiotic administration is considered the best therapeutic approach. Several guidelines regard time to antibiotic (TTA) administration as a quality-of-care indicator in the

paediatric emergency department (PED) [2], given its importance in reducing infection-related morbidity and mortality [3]. However, many febrile episodes are not caused by bacterial infections [4], and although TTA protocols are well established, recent perspectives advocate a more conservative approach in selected situations [3]. Lehrnbecher et al. [5] proposed that in clinically stable patients with FN without an identifiable focus, antibiotics can be delayed until the neutrophil counts are

Summary

- What is already known on this topic
 - In the current clinical context, serious bacterial infections and poor outcomes are relatively uncommon, particularly in patients with low-risk neutropenia.
 - Recent trends support a more conservative approach, delaying antibiotics in stable febrile neutropenia patients until neutrophil count results are available.
- What this paper adds
 - Increased time to antibiotic administration in clinically stable paediatric patients with febrile neutropenia may not necessarily worsen clinical outcomes, suggesting the possible feasibility of a ‘wait-and-observe focus’ approach.
 - No risk factors were identified as predictors of poor outcome; notably, time to antibiotic administration did not emerge as a significant factor.

available [5]. Nevertheless, it remains unclear whether this strategy may adversely affect prognosis.

The objective of this study was to evaluate whether increased TTA administration in the PED, by dividing patients into two groups (≤ 60 and > 60 min), worsens the clinical outcome of cancer patients with FN who had a normal Paediatric Assessment Triangle (PAT) on arrival [6].

2 | Materials and Methods

2.1 | Study Design, Setting and Population

We performed a secondary analysis of a large, two-centre, prospective cross-sectional registry conducted between November 2019 and October 2021 [7]. The study was endorsed by the Spanish Paediatric Emergency Research Group (SPERG).

Children were eligible if they were aged 2–18 years, had a cancer diagnosis, presented with FN, and had a stable PAT on arrival at the PED. Exclusion criteria were the presence of any focal infection, antibiotic treatment within the previous 48 h, or refusal to participate.

Patients were followed until recovery or poor outcome. The attending paediatricians adhered to local FN protocols. In both participating PEDs, empiric intravenous anti-pseudomonal β -lactams were recommended for all patients and administered as soon as possible, ideally within the first hour. Meropenem was reserved for patients with mucositis, and vancomycin was added if catheter-related or skin infection was suspected. Oncological patients with fever are prioritised and assessed in the PED within 15 min. Intravenous fluids were administered only when clinically indicated, after vital signs had been recorded [1].

2.2 | Data Collection

The recorded variables included age, sex, cancer diagnosis, immunosuppressive treatment, trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, colony-stimulating factor treatment, duration and severity of fever, associated symptoms, physical examination findings, laboratory test results, TTA, and final diagnosis.

2.3 | Definition and Outcome Measures

The key definitions are presented in Table 1.

Patients undergoing active treatment for oncological diseases, as well as those with progressive or relapsed disease involving the bone marrow, were considered at an increased risk of developing neutropenia [9].

The main outcome variable was poor outcome, defined as admission to the paediatric intensive care unit (PICU), sepsis or septic shock, acute organ dysfunction, long-term sequelae, or death.

Sequelae were defined as organ or system dysfunction that interferes with normal life and requires long-term follow-up.

For the purposes of this study, if a patient experienced multiple episodes of FN but remained asymptomatic and untreated for at least 4 weeks between them, the subsequent episode was considered independent.

2.4 | Statistical Methods

Data normality was assessed by calculating skewness relative to standard error values. Normally distributed data were expressed as mean $\pm$ standard deviation and non-normally distributed data as median with interquartile range (IQR). Two-tailed t tests were used to compare mean values between groups for normally distributed data, and the Mann–Whitney U test was applied for non-normally distributed data. Categorical variables were expressed as percentages and compared using the χ^2 test. A p -value < 0.05 was considered statistically significant. Data were analysed using Stata version 17.0 (StataCorp).

Baseline risk factors analysed for poor outcome included age, sex, high-risk oncological disease, previous episodes of FN, maximum temperature, absolute neutrophil count (ANC), monocyte count, C-reactive protein, procalcitonin, and TTA. Logistic regression was performed for binary variables with a p -value < 0.2 in univariate analysis.

TTA was evaluated using the 60-min ‘golden hour’ cutoff to assess its clinical impact.

The article was drafted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research.

3 | Results

Between 2019 and 2021, the two institutions recorded a combined total of 209 FN episodes; of these, 192 (91.9%) were included. Seven patients were diagnosed with a focal infection and 10 declined to participate. The median age was 7.2 years (IQR 4.6–13.5). A total of 110 episodes (57.3%) had a TTA ≤ 60 min (short TTA) and 82 (42.7%) had a TTA > 60 min (long TTA). The median TTA was 35 min in the short TTA group (IQR 30–45) and 100 min in the long TTA group (IQR 65–120) ($p < 0.001$).

Table 2 presents the epidemiological and clinical data of the 192 episodes. Most episodes (88.5%) involved high-risk oncological patients, with a similar distribution across groups ($p > 0.05$).

Ongoing non-chemotherapy treatments at the time of PED presentation as well as fever characteristics are shown in Table 3, stratified by study group. Baseline characteristics were

comparable between groups, except for previous episodes of FN: 71 (64.5%) in the short TTA group and 7 (8.5%) in the long TTA group ($p < 0.001$). All patients met stable PAT criteria; therefore, vital signs were not compared between groups.

Blood test values by study group are presented in Table 4.

All episodes were treated with broad-spectrum antibiotics: piperacillin-tazobactam (55.2%), cefepime (40.6%), or meropenem (3.6%). In addition, vancomycin was administered in five (2.6%) episodes in combination with another antibiotic when there was clinical suspicion of central venous catheter infection.

Amongst the episodes with positive blood culture (18; 9.4%), pathogens included 15 coagulase-negative staphylococci and one isolate each of *Klebsiella pneumoniae*, *Escherichia coli*, and *Streptococcus viridans*. These are shown according to TTA in the PED in Figure 1.

TABLE 1 | Key definitions.

- Fever: a single temperature $> 38^{\circ}\text{C}$ or two consecutive measurements $> 37.5^{\circ}\text{C}$.
- High-risk oncologic diagnosis: acute lymphoblastic leukaemia and non-Hodgkin lymphoma in induction, reinduction or consolidation phase or relapse, and acute myeloid leukaemia in any phase.
- The PAT was used to assess the overall initial impression of the child. A stable PAT was defined as the absence of abnormalities in any of the 3 components assessed by this tool: appearance, work of breathing, and circulation to the skin, using specific and predefined physical, visual, and auditory findings. If any of these 3 components was abnormal, the patient was considered unstable [6]. Pallor was not considered an alteration of circulation to the skin if it was consistent with the patient's known baseline anaemia related to their oncological disease or treatment.
- Neutropenia: an ANC of < 500 cells/mm³ or an ANC expected to decrease to < 500 cells/mm³ over the following 48 h.
- Positive blood culture: the growth of a single pathogen. Blood cultures were obtained exclusively from a central venous catheter, using two different samples.
- Bacteraemia without a focus of infection: the isolation of a single pathogen in the blood of a well-appearing febrile child with a normal physical examination or with minor signs in the absence of an identifiable focus of infection. In cases where coagulase-negative staphylococci were isolated, classification as true bacteraemia or contamination was based on clinical judgement.
- Sepsis: suspected or confirmed infection identified as a Phoenix Sepsis Score^a of at least two points and septic shock defined as sepsis with a cardiovascular subscore of at least one point of the Phoenix Sepsis Score [8].

Abbreviations: ANC, absolute neutrophil count; PAT, paediatric assessment triangle.

^aPhoenix Sepsis score was calculated retrospectively.

TABLE 2 | Characteristics of the episodes included in the registry.

	Total ($n = 192$)	Short TTA ($n = 110$)	Long TTA ($n = 82$)	p
Sex (male), n (%)	85 (44.3)	46 (41.8)	39 (47.6)	0.52
Age in years, median (IQR)	7.2 (4.6–13.5)	7.1 (4.5–14.2)	7.3 (4.7–13.1)	0.48
Cancer diagnosis, n (%)				
Acute lymphoblastic leukaemia	84 (43.8)	60 (54.5)	24 (29.3)	< 0.001
Bone tumour	35 (18.2)	18 (16.4)	17 (20.7)	0.56
Central nervous system tumour	28 (14.6)	11 (10)	17 (20.7)	0.06
Non-Hodgkin's lymphoma	16 (8.3)	10 (9.1)	6 (7.3)	0.86
Hodgkin's lymphoma	6 (3.1)	3 (2.7)	3 (3.7)	1.00
Acute myeloid leukaemia	3 (1.5)	—	3 (3.7)	0.08
Other solid tumours ^a	20 (10.4)	8 (7.3)	12 (14.6)	0.16

Abbreviations: %, percentage; IQR, interquartile range; n , number.

^aOther solid tumours include sarcoma, neuroblastoma (abdominal), Wilms' tumour, hepatoblastoma, germ cell tumour and desmoplastic tumour.

TABLE 3 | Risk level of the oncological disease, non-chemotherapy treatment and fever characteristics of the study patients according to study group.

	Short TTA (<i>n</i> = 110)	Long TTA (<i>n</i> = 82)	<i>p</i>
High-risk oncological disease, <i>n</i> (%)	55 (50)	48 (58.5)	0.32
Previous episode of febrile neutropenia, <i>n</i> (%)	71 (64.5)	7 (8.5)	<0.001
Other immunosuppressive drugs ^a , <i>n</i> (%)	28 (25.5)	24 (29.3)	0.67
TMP-SMX prophylaxis, <i>n</i> (%)	107 (97.3)	80 (97.6)	1.0
Colony-stimulating factors, <i>n</i> (%)	37 (33.6)	36 (43.9)	0.19
Time from fever onset (hours), median (IQR)	2 (1–3)	2 (2–3)	0.83
Maximum temperature at home (°C), median (IQR)	38.1 (38–38.4)	38 (38–38.5)	0.91
Temperature on arrival at the emergency department (°C), median (IQR)	37.9 (37.6–38.2)	38 (37.9–38.3)	0.86

Abbreviations: %, percentage; IQR, interquartile range; *n*, number of patients; n.s., not significant; TMP-SMX, trimethoprim-sulfamethoxazole; TTA, time to antibiotics.

^aOther immunosuppressive drugs include corticosteroids, monoclonal antibodies, and purine analogue antimetabolites.

TABLE 4 | Values of blood tests in both study groups.

	Short TTA (<i>n</i> = 110)	Long TTA (<i>n</i> = 82)	<i>p</i>
Last blood test before PED			
ANC (cells/mm ³), median (IQR)	0 (0–500)	250 (0–1500)	0.01
Monocytes (cells/mm ³), median (IQR)	0 (0–100)	50 (0–150)	0.17
Blood test drawn at PED			
ANC (cells/mm ³), median (IQR)	0 (0–100)	0 (0–200)	0.14
CRP (mg/L), median (IQR)	29.5 (17.2–66.0)	40 (22.6–67.8)	0.24
PCT (ng/mL), median (IQR)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.40

Note: Bold indicates statistically significant differences.

Abbreviations: %, percentage; ANC, absolute neutrophil count; CRP, C-reactive protein; IQR, interquartile range; *n*, number of patients; PCT, procalcitonin; PED, paediatric emergency department; TTA, time to antibiotics.

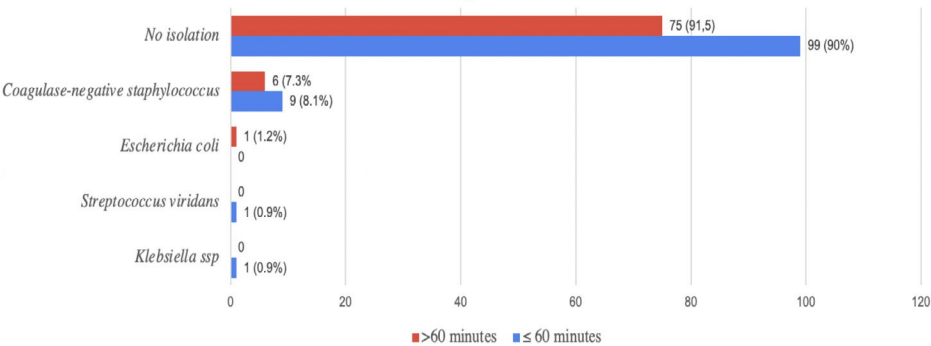


FIGURE 1 | Isolated microorganisms in both study groups.

The final diagnoses were FN in 160 (83.3%) episodes, bacteraemia in 13 (6.8%), sepsis/septic shock in 5 (2.6%), upper tract infection in 5 (2.6%), typhlitis in 3 (1.6%), catheter-related bloodstream infection in 3 (1.6%) catheter-associated infections, urinary tract infection in 2 (1.0%), and pneumonia in 1 (0.5%).

A total of 12 episodes (6.3%) were associated with a poor outcome: 8 children (66.7%) developed sepsis, 2 (25.0%) of whom fulfilled criteria for septic shock, and 5 (41.7%) required PICU admission, including both shock cases. Regarding long-term sequelae, 1 patient (8.3%) required intermittent oxygen therapy after the episode. No deaths were reported. Table 5 shows

TABLE 5 | Differences between patients with and without poor outcomes.

	Patients with poor outcome (<i>n</i> = 12)	Patients without poor outcome (<i>n</i> = 180)	<i>p</i>
Age (years), median (IQR)	11.3 (6.9–15.1)	7.2 (4.3–13.5)	0.07
Sex (male), <i>n</i> (%)	6 (50)	94 (52.2)	1.0
High-risk oncological disease, <i>n</i> (%)	8 (66.7)	95 (52.7)	0.40
Previous episode of febrile neutropenia, <i>n</i> (%)	3 (25)	22 (12.2)	0.19
Maximum temperature (°C), median (IQR)	38.4 (38.2–39)	38 (38–38.4)	0.81
ANC (cells/mm ³), median (IQR)	0 (0–257.5)	0 (0–192.5)	0.67
Monocytes (cells/mm ³), median (IQR)	400 (300–500)	250 (62.5–485)	0.27
CRP (mg/L), median (IRQ)	60 (22.3–95.8)	32.2 (19.8–65.5)	0.17
PCT (ng/mL), median (IRQ)	0.2 (0.1–0.3)	0.2 (0.12–0.3)	0.53
TTA (minutes), median (IRQ)	50 (33.7–60)	60 (40–100)	0.08
TTA ≤ 60 min, <i>n</i> (%)	10 (83.3)	100 (55.6)	0.07

Abbreviations: %, percentage; CRP, C-reactive protein; IQR, interquartile range; *n*, number of patients; PCT, procalcitonin; TTA, time to antibiotics.

the differences between patients with and without a poor outcome.

Table 6 presents the results of the bivariable and multivariate analyses for risk factors associated with poor outcome.

4 | Discussion

The results of this study in children with cancer and FN indicate that when the PAT is stable, prognosis does not worsen if antibiotic treatment is delayed beyond the first hour after arrival at the PED, in contrast to unstable patients for whom immediate therapy is essential. In the long TTA group, antibiotics were administered later than in the short TTA group, yet this was not associated with an increase in poor outcomes.

According to the updated systematic review and meta-analysis by Phillips et al. [10], several validated clinical decision rules (CDRs)—including SPOG 2003/2015, PICNICC, Klaassen, and EsVan/EsVan2—have been developed to stratify risk in children with FN and identify those at low risk for serious complications. These models use clinical and laboratory parameters to select low-risk candidates for outpatient or less intensive care. However, their performance and external validity vary across settings, and local validation or recalibration is recommended before routine implementation. In our cohort, all episodes were initially managed as high risk with prompt parenteral therapy. Although a CDR was not applied prospectively, these models provide a pragmatic framework for future piloting of low-risk pathways in our PED.

Although oncological risk classification did not differ between groups, we observed a higher proportion of acute lymphoblastic leukaemia in the early antibiotic group. This finding is consistent with previous studies reporting that patients with acute lymphoblastic leukaemia were more likely to receive antibiotics

TABLE 6 | Bivariable and multivariate analysis to identify independent risk factors for poor outcome.

Risk factors for poor outcome	OR	CI 95%	<i>p</i>
Bivariable analysis			
Age (years)	1.1	0.9–1.3	0.21
Sex (male)	1.0	0.3–3.0	0.95
High-risk oncological disease	1.8	0.5–6.3	0.35
Previous episode of febrile neutropenia	2.4	0.6–9.0	0.2
Maximum temperature (°C)	3.2	1.0–9.7	0.04
ANC (cells/mm ³)	1.00	0.99–1.01	0.28
Monocytes (cells/mm ³)	1.00	0.998–1.003	0.31
CRP (mg/L)	1.10	1.03–1.22	0.01
PCT (ng/mL)	1.2	0.9–1.5	0.35
TTA ^a (minutes)	1.1	0.8–1.6	0.9
Multivariate analysis			
Maximum temperature (°C)	2.1	0.8–5.8	0.13
CRP (mg/L)	1.09	1.00–1.21	0.07
TTA (minutes)	1.8	0.4–8.7	0.45

Abbreviations: ANC, absolute neutrophil count; CI, confidence interval; CRP, C-reactive protein; PCT, procalcitonin; TTA, time to antibiotics.

^aThis variable was included in the multivariate analysis for theoretical reasons.

within 60 min [11]. In our cohort, the prevalence of high-risk oncological diseases predisposing to neutropenia was comparable between groups, suggesting that differences in underlying

disease severity did not explain variations in TTA. Instead, other contextual or organisational factors may have influenced the timeliness of antibiotic administration.

The only differentiating baseline characteristic between the short and long TTA groups was the higher frequency of previous FN episodes amongst patients who received antibiotics within 60 min, possibly reflecting heightened clinical vigilance. The literature indicates that recurrent FN episodes are associated with increased mortality, invasive bacterial infections (IBIs), and haemodynamic instability [4]. Scheler et al. [12] similarly reported that previous FN episodes were associated with faster interventions, consistent with our findings.

Contrary to previous studies [13–17], some commonly proposed risk factors, such as higher temperature at presentation, low ANC, low monocyte count, or elevated inflammatory biomarkers including CRP and PCT, were not independently associated with worse outcomes. Although high fever has been consistently linked to bacteraemia and sepsis in neutropenic children [13–15], most patients in our cohort presented with low-grade fever, and this variable did not show prognostic value. Likewise, although elevated CRP has been associated with an increased risk of invasive bacterial infection [17], it did not discriminate outcomes in our population, which may reflect the overall clinical stability of the cohort. Neutropenia was severe in most episodes, but neither ANC nor monocyte count was useful for predicting complications. These findings are in line with studies suggesting that haematological parameters should not be used in isolation to determine risk, as their predictive capacity depends heavily on the broader clinical context [14–18].

In this regard, it is important to acknowledge the fundamental differences between neutropenic and non-neutropenic pathways. Neutropenic patients require immediate broad-spectrum empiric therapy due to their high risk of rapid progression to severe infection and sepsis, often necessitating longer treatment until neutrophil recovery, although recent evidence supports earlier de-escalation [19]. By contrast, non-neutropenic patients allow for more conservative and targeted antimicrobial strategies, with stewardship principles more readily applied. This distinction has major implications for antimicrobial exposure, resistance, and stewardship, and should be considered when interpreting our findings [19].

It should also be emphasized that our findings are specific to paediatric patients evaluated in the PED and may not be generalizable to hospitalised patients. Inpatients often differ markedly in terms of the intensity of clinical monitoring, underlying disease severity, and risk of nosocomial infection. Moreover, fever onset is detected earlier due to continuous monitoring, making delayed antibiotic administration less justifiable in this context. Therefore, caution is warranted when extrapolating to inpatients.

Importantly, TTA was not identified as a significant determinant of poor outcome in our analysis, even when included in the multivariate model. Although early antibiotic administration remains a cornerstone of FN management, our findings suggest that, in clinically stable patients, short delays in TTA may not

increase risk, supporting the consideration of individualised decision-making rather than rigidly time-based benchmarks.

In our study, the incidence of microbiologically confirmed bacteraemia was low, approximately 10%, with coagulase-negative staphylococci as the most common pathogen. This is consistent with previous reports indicating that paediatric patients with FN lack microbiologically defined infections in nearly 80% of cases [4]. Molecular studies have identified pathogens, particularly respiratory viruses, in many FN episodes, highlighting their potential significance. Other causes include fungal infections, drug reactions, transfusions, or mucositis [4].

Traditionally, the prompt administration of broad-spectrum antibiotics has been emphasized, and rapid action remains crucial in unstable patients. However, in stable situations, such as those observed in our cohort, a more conservative ‘wait-and-observe focus’ approach may be feasible without increasing adverse outcomes [20]. Although all patients in our study ultimately received intravenous antibiotics, the absence of worse outcomes with delayed administration in clinically stable patients raises the possibility that selected low-risk cases might safely avoid immediate empiric therapy.

Nonetheless, we acknowledge that current clinical practise favours prompt empiric antibiotic administration followed by ongoing risk reassessment, and that delaying antibiotics could be dangerous in the small subset of patients with unrecognised bacterial infections. Additionally, the interval between fever onset at home and presentation to the PED may act as an informal observation period, potentially contributing to the safety of delayed antibiotic initiation in stable patients. Future studies should further explore this pre-hospital interval to clarify its influence on outcomes.

Our analysis showed no significant differences in outcomes between early and late antibiotics administration groups, with both experiencing a similar $\approx 10\%$ rate of poor outcomes. These findings are consistent with previously published studies [12, 21, 22]. Scheler et al. [1] reported that variations in the initial management of FN, including TTA and antibiotic selection, did not significantly affect overall patient outcomes. Esbenschade et al. [21] studied febrile paediatric cancer patients without severe neutropenia, using a risk prediction model (EsVan) to guide antibiotic administration; they found that delaying antibiotics in low-risk patients did not increase adverse outcomes. The FN working group of the German Societies for Paediatric Oncology and Haematology and Paediatric Infectious Diseases has also discussed best practises for the timing of antibacterial therapy, acknowledging methodological limitations and biases in supporting studies [22]. Together, these findings suggest that structured evaluation in PED is essential, and that many FN episodes in clinically stable patients may not require immediate antibiotics [12, 21, 23, 24].

The concordance of our findings with previous studies highlights the need for tailored treatment protocols that prioritise patient stability over rigid timeframes. Ongoing refinement of FN management strategies, incorporating risk prediction models and individualised patient assessments, will be crucial in enhancing patient care and outcomes [5].

5 | Limitations

This study has several limitations. First, it was not specifically designed to address the impact of TTA, as it represents a secondary analysis of a registry that included only patients older than 2 years—an inclusion criterion of the original study. Additionally, platelet counts were not collected, as they were not considered relevant to the registry's primary objective, despite their known association with poor outcomes. Second, TTA was determined by the clinical judgement of the attending physician rather than predefined criteria, introducing potential variability. Third, the number of poor outcomes in our cohort was low, limiting the statistical power and warranting caution when interpreting the findings. Furthermore, no formal sample size or power calculation was performed, and the wide confidence intervals in our analyses suggest that the study may have been underpowered to detect clinically meaningful differences related to TTA. Finally, although most patients in our cohort had high-risk oncological diagnoses, the generalizability of our findings to low-risk FN populations remains uncertain. The low event rate precluded subgroup analysis. Further research is needed to clarify the impact of TTA across different risk groups to inform individualised treatment strategies.

6 | Conclusions

In summary, longer TTA in stable paediatric FN patients may not compromise clinical outcomes, supporting the feasibility of a 'wait-and-observe focus' approach. Such an approach could help reduce unnecessary antibiotic exposure, limit the development of antibiotic resistance, and optimise resource use in PEDs.

Ethics Statement

This study's ethical approval was provided by the Hospital Infantil Universitario Niño Jesús's ethics committee, Madrid, Spain (number: R-0003/19).

Consent

Informed consent was obtained from the older children, parents, or guardians of all patients.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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