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Original Article

Clinical efficacy of Empirical (Piperacillin/tazobactam plus Amikacin) combined therapy of Febrile Neutropenia among Pediatric Patients with Cancer: A cohort Observational Study

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Abstract

Background: Febrile neutropenia (FN) is a life-threatening complication in pediatric oncology patients that requires prompt and effective empirical antibiotic treatment. Local data on the success of these regimens are essential for guiding clinical practice. This study assesses the effectiveness and safety of the local empirical combined therapy of Piperacillin/tazobactam plus Amikacin for FN in pediatric cancer patients.

Methods: A prospective observational cohort study was conducted on 68 FN episodes in 34 pediatric cancer patients between August 2022 and December 2023. The first-line regimen included intravenous Piperacillin/tazobactam and Amikacin, with Amikacin de-escalated after 72 hours of fever resolution. The primary outcome was the success rate of the first-line regimen, defined as fever resolution and clinical clearance without modification or switch. Safety was evaluated by monitoring creatinine levels.

Results: The overall success rate of the empirical regimen without modification was 63.2%, with a failure rate of 22%. The success rate increased to 77.9% when Vancomycin was added (14.7% of cases). Microbiologically documented infections (MDI) were mostly Gram-positive (62.5%), including MRSA isolates resistant to Piperacillin/tazobactam. No treatment-related mortality or significant nephrotoxicity was observed (mean creatinine difference: -0.0107, p=0.338). Additionally, the duration of neutropenia was strongly correlated with the length of hospital stay (r=0.7, p<0.00001).

Conclusion: The combined Piperacillin/tazobactam and Amikacin regimen shows a reasonable success rate and a good safety profile in the local setting, supporting its continued use as a first-line option. However, the high prevalence of Gram-positive MDI and the frequent need for Vancomycin addition highlight the importance of ongoing local resistance monitoring and maintaining a low threshold for early Vancomycin use in high-risk patients.

Keywords:

Febrile neutropenia
Piperacillin/tazobactam
Amikacin
Pediatric cancer

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1. INTRODUCTION

Survival in children with cancer has increased dramatically due to the introduction of more intensive chemotherapy, radiotherapy, and supportive care protocols(1). Febrile neutropenia events are common and serious complications of cancer therapy, accounting for 10-15% of patients with solid tumors, and between 70-80% of those with hematologic cancers(2).

Febrile neutropenia is considered a life-threatening event that needs urgent recognition and immediate intervention as soon as possible to improve the survival of patients with invasive infections(3, 4). Individuals with chemotherapy-related neutropenia have a higher risk of complications. They are at risk of most microbial infections, particularly bacterial infections(5).

The clinical practice guideline (CPG) for the management of febrile neutropenia recommends immediate initiation of empiric antibacterial therapy, ideally within 1 hour of presentation(6). Empirical administration of broad-spectrum antibiotics during neutropenia and within one hour has been shown to reduce mortality from bacterial infections and length of hospital stay(7, 8).

There are several guidelines on the management of patients with FN, including those from the Infectious Diseases Society of America (IDSA) and the European Society of Medical Oncology (ESMO)(9-11). According to the IDSA, FN is defined as 'a one-time oral temperature of greater than 38.3°C or a sustained temperature of greater than 38°C for ⩾ one hour in a patient who has an absolute neutrophil count of less than 500 cells/μL within a 48-h period'(11). The guidelines agree that all patients presenting with FN should be initiated on empiric antibiotics. To determine which therapy should be initiated, clinicians should consider assessing the patient's risk of infection; determining the local antimicrobial susceptibilities, the most common infecting organisms, and the potential sites of infection; ascertaining the need for therapy against Gram-positive or fungal pathogens; and assessing the patient's clinical stability, recent antibiotic use, and presence of antibiotic allergies(12).

The Infectious Disease Society of America (IDSA) recommends monotherapy with antipseudomonal beta-lactam agents such as cefepime, carbapenems, or piperacillin/tazobactam(11). Others suggest using combined aminoglycoside therapy as empirical antibacterial therapy. Many clinical trials report that there is no statistical difference between monotherapy and combined therapy with aminoglycosides for children with cancer (13-16). Vancomycin is not recommended for initial treatment and should be considered only if a catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability is suspected(17).

Empiric antifungal coverage is considered in high-risk patients with persistent fever after 4 to 7 days of a broad-spectrum antibacterial regimen and suspicion of fungal infection(18).

This observational study assesses the efficacy of local empirical combined antibacterial therapy with piperacillin-tazobactam and Amikacin. To our knowledge, this is the first study from Libya.

2. MATERIAL AND METHOD

A prospective observational cohort study was conducted between August 2022 and December 2023 at the pediatric oncology department of the National Cancer Institute of Misurata, Libya, adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement Criteria(19). This study was approved by the Ethical Committee of the National Cancer Institute of Misurata, Libya (No. 03/2023). All episodes of febrile neutropenia in 34 included patients less than 16 years who have been treated for cancer, either hematological or solid tumor, are eligible for the study, including fever episodes (≥ 38.5 °C once or ≥ 38 °C at least twice occurring at least 1 hour apart), **figure 1**. An absolute neutrophil count (≤ 500 mm^3) and a total white blood cell count less than 1000 mm^3 were included. Oral antibiotic prophylaxis with trimethoprim/sulfamethoxazole was allowed for the patient as part of preventive measures. For specific criteria, an additional oral antibiotic prophylaxis was also allowed, such as fluconazole, voriconazole, and acyclovir, per protocol. The exclusion criteria include: 1- previously treated with intravenous antibiotics within 1 week of presentation, 2- allergic reaction to the study antibiotics, and 3- renal impairment with creatinine clearance less than 20ml/min.

All included patients underwent a thorough medical history and physical examination. Baseline laboratory investigations were requested, including blood cultures from either a central line (e.g., a central venous line or Port-a-Cath) or a peripheral line, before starting empirical antibiotics. Further blood cultures may be required for patients with persistent fever for 48 hours or new-onset fever after 24 hours of fever cessation, and for patients with isolated positive results until confirmation of sterile culture. Cultured blood by the standard technique of the Microbiology unit and isolated bacterial growth were tested for antibiotic sensitivity. Follow-up hematological analysis and electrolyte levels were repeated every other day, and liver function tests were performed twice per week.

The febrile episodes were classified according to previously published criteria into three main groups: 1- Clinically documented infection (CDI), 2- Microbiologically documented infection (MDI), and 3- Fever of unknown origin (FUO). Successful treatment is defined by resolution of fever, clinical clearance of symptoms, and negative blood cultures. In contrast, treatment failure includes: 1- persistence of fever and the need to upgrade antibiotics; 2- isolated microbiology results from blood cultures showing in vitro resistance; 3- readmission within a week post-discharge; and 4- death.

This study was used initially with intravenous piperacillin-tazobactam at a dose of (100mg/kg/dose q 8 hours) with a maximum dose of 4.5g/dose, and Amikacin 15mg/kg/dose q 24 hours. The local protocol for antibiotic use for early-responsive cases: Amikacin was stopped after 72 hours of fever cessation. Second-line treatment for treatment failure cases: Meropenem (40mg/kg/dose q 8 hours). For cases of persistent fever for 5 days (120 hours), antifungal treatment (Amphotericin B) was introduced. Vancomycin (20mg/kg/dose q 6-8 hours) was added for patients with unremitting fever after 48 hours.

Nephrotoxicity and hepatotoxicity were defined as a rise in serum creatinine, transaminases, bilirubin, or alkaline phosphatase by at least twice the upper limit of the normal range. The study data were analyzed using the Statistical Package for the Social Sciences for Windows version 27 (SPSS Inc., Chicago, IL, USA).

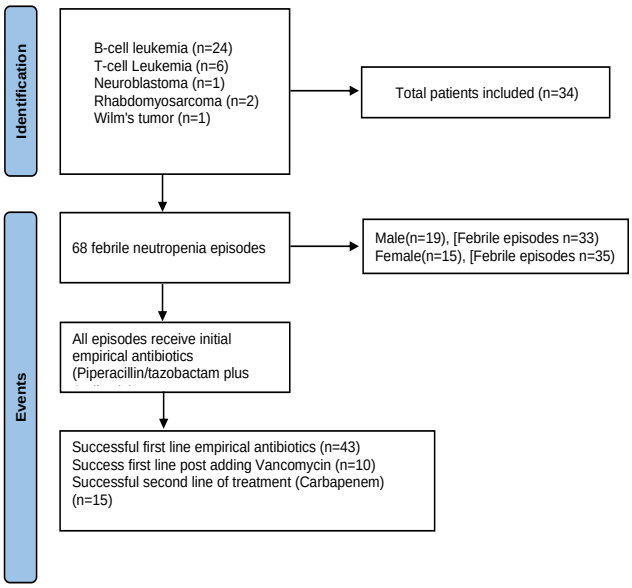

Figure1. Flow diagram of included patients and febrile episodes events.

3. RESULT

During the 16-month study period, a total of 68 febrile neutropenia episodes were documented in 34 patients admitted to the department who met the study criteria. **Table 1** shows the clinical characteristics of the patients and febrile episodes.

Out of the 68 episodes, 30(44.1%) were classified CDI, 30(44.1%) FUO, and 8(11.8%) episodes were MDI. The CDI represents the following: mucositis (11/30); herpetic lesions (3/11); pneumonia documented on (6/30) episodes; bronchiolitis (5/30); urinary tract infection (3/30); upper respiratory tract infection (4/30); and local abscess (1/30). Of the eight episodes of MDI, 5 (62.5%) were gram-positive micro-organisms (four were Staphylococcus aureus (MRSA), and one was Streptococcus alpha-hemolytic), two (25%) were gram-negative (Bacillus spp.), and one episode was PCR positive COVID-19. Regarding antibiotics, sensitivity results showed resistance to Piperacillin-tazobactam in two of four Staphylococcus aureus (MRSA) cultures.

The success rate of combined (Piperacillin-tazobactam + Amikacin) as empirical first-line antibiotic therapy was 63.2%, and the failure rate was 36.8%. The success rate increased to 77.9% for first-line treatment in cases combined with Vancomycin. Only 14.7% of cases require Vancomycin added therapy with first-line therapy, and failure of the first-line treatment requires a switch to whole therapy, accounting for 22%.

The success rates for MDI, CDI, and FUO were 75%, 73.3%, and 83.3%, respectively. The failure rate of the first-line treatment option was 22.1%. The cause of treatment failure includes persistent or relapsing fever after 48 hours.

No significant events were reported during this study, and no deaths occurred among the study group. The drug level of Amikacin was not available; however, no significant changes in creatinine monitoring during the treatment course. The mean difference between initial and discharge creatinine level is statistically insignificant (mean = -0.0107, $p = 0.338$).

The Chi-square ($\chi 2$) test is a statistical test of observed frequencies of length of hospital stay based on primary diagnosis of cancer ($\chi 2=90.945$, $P = 0.001$).

The Spearman correlation analysis reveals that most initial laboratory parameters and the duration of fever do not have a statistically significant monotonic relationship with the Duration of hospital admission (days). The duration of neutropenia shows a strong positive correlation ($r = 0.7$), indicating a monotonic relationship. This means that as the duration of neutropenia increases, the hospital stay tends to increase as well. Also, the duration of fever (days) has a moderate positive correlation ($r=0.507$). Notably, a near-

Table 1. Baseline patient's clinical characteristics of 68 febrile episodes for 34 patients.

Variable	Median (IQR), Frequency (%)
Age/year (34 patients)	5.5 (4-8)
Gender (34 patients)	
Male	19(55.9%)
Female	14(44.1%)
Weight (34 patients)	20.25 (16 – 26.5)
BMI (34 patients)	17.37 (16.5 – 18.5)
Diagnosis per episodes events	
Hematological	63 (92.6)
T-cell leukemia	14 (22.2)
B-cell leukemia	49 (77.7)
Solid tumor	5 (7.3)
Venous access	
Central access	33 (48.5)
Peripheral access	35 (51.5)
Antibiotic prophylaxis	
Yes	63 (92.6)
No	5 (7.2)
G-CSF administration	
Yes	6 (8.8)
No	62 (92.2)
ANC × 10^3 level at presentation	0.1 (0.2 -0.3)
ANC level at discharge	1.12 (0.6-1.2)
Classification of fever	
CDI	30 (44.1)
MDI	8 (11.8)
FUO	30 (44.1)

significant correlation for WBC (r = - 0.234, p=0.056) and ANC (rho = -0.237, p=0.054). They suggest a weak, negative trend: patients with slightly higher initial WBC and ANC counts tend to have a slightly shorter hospital stay, though this trend is not statistically robust at the 0.05 level. The platelet level at admission shows a weak negative correlation with the length of hospital stay (r = -0.262, p = 0.034) (**Table 3**).

A paired-samples T-test is used to determine whether there is a statistically significant difference between the means of the initial and discharge laboratory results. The total white blood cell (WBC) cunts and absolute neutrophil count (ANC) show positive mean difference results increased from initial to discharge with a p-value < 0.0001. The lymphocyte and monocyte percentages have no statistical difference between admission and discharge values (**Table 4**).

4. DISCUSSION

This study is the first from Libya to evaluate the efficacy of a local empirical combined antibacterial regimen of piperacillin-tazobactam and Amikacin for febrile neutropenia (FN) in pediatric oncology patients. The primary finding is a high overall success rate of 63.2% for the empirical regimen that does not require modification. This success rate supports the continued use of this combination as a viable first-line option in the local setting, particularly given the absence of treatment-related mortality in this cohort.

The observed success rate aligns favorably with global data. Furno et al conducted a meta-analysis of empirical monotherapy versus combination therapy in FN among adult patients, reporting overall response rates ranging from 60% to 80%(20). Afterward, several clinical trials specify the pediatric age group, confirming successful initiation of combined therapy, as with monotherapy empirical treatments. Our study found 63.2% success without modification, 14.7% with modification, and 22% failure of the first-line therapy protocol. Zengin et al.(13) reported a success rate of 45.9% for empirical combined therapy without modification, 35.1% with modification, and 18.9% with protocol failure, respectively.

The local protocol, which includes the rapid de-escalation of Amikacin after 72 hours of starting therapy, balances the need for broad-spectrum coverage against the risk of aminoglycoside-related toxicity, a strategy supported by the statistically insignificant change of the mean difference in creatinine levels between admission and discharge laboratory observed in this study, p =0.338. In the Zengin et al. clinical trial, one patient experienced nephrotoxicity due to Amikacin, whereas in the Hamidah et al. study, no nephrotoxicity was reported.

The microbial profile of microbiologically documented infections (MDI) shows a clear dominance of Gram-positive organisms (62.5%), including four cases of Staphylococcus aureus (MRSA). This prevalence of Gram-positive bacteria aligns with a prior local study(21). It supports the empirical use of an anti-Gram-positive agent, even though Vancomycin was not part of the initial treatment. The fact that two of the four MRSA isolates were resistant to piperacillin-tazobactam highlights a notable challenge. The high rate of Vancomycin use (29.4% of episodes) indicates that clinicians often suspected or encountered Gram-positive infections requiring targeted coverage, underscoring the importance of a low threshold for adding Vancomycin, especially in patients with persistent fever beyond 48 hours, as outlined in the local protocol.

Table 2. Treatment outcomes of 68 febrile episodes.

Variable	N = 68	P value
Duration of fever [days, median(range)]	1(1-5)	*P = 0.058*
Duration of neutropenia [days, median (IQR)]	5 (4-7)	*P = 0.099*
Duration of hospitalization [days, median (IQR)]	5 (5-10)	*P =0.001**
Modification of treatment		
+ Vancomycin [n (%)]	20 (29.4)	
Carbapenem- Second line [n (%)]	13 (19)	
Antifungal treatment [n (%)]	3 (4.4)	
Successful first-line treatment [n (%)]		
Without modification	43 (63.2)	
Vancomycin	10(14.7)	
Combined	53(77.9)	
Failure of first-line treatment [n (%)]	15 (22)	
Successful second-line treatment	10 (14.7)	

* Significant p value ≤ 0.05

Table 3. The correlation analysis between the length of hospital admission and study characteristics elucidates

	Variable	n	Correlation Coefficient (r)	P value
Correlation against Length of hospital admission (days)	Total WBC	67	-0.234	0.056
	ANC	67	-0.237	0.054
	Platelet	66	-0.262	0.034*
	Hemoglobin	66	-0.019	0.881
	Lymphocyte	64	-0.003	0.211
	Monocyte	64	-0.158	0.211
	CRP	67	-0.239	0.051
	Duration of neutropenia(days)	66	0.7	<0.00001*
	Duration of fever(days)	67	0.507	<0.00001*
	Laboratory results at admission: WBC (white blood cell), ANC (absolute neutrophil count), and CRP (C-reactive protein). (*) statistically significant			

Table 4. The mean difference between the initial and discharge laboratory results

Variables	Mean difference 2.09	SD	SE	95% Confidence Interval		t	df	P value
				Lower	Upper			
WBC	912.2	1.7	0.206	1.68	2.5	10.16	67	<0.0001*
ANC	-6.20	1212.04	146.98	618.8	1205.6	6.206	67	<0.0001*
Lymphocyte%	1.296	26.9	3.56	-13.33	0.935	-1.74	56	0.087
Monocyte%	0.46	15.9	2.125	-2.96	5.55	.610	55	0.544
Hemoglobin g/l	-35.9	1.81	0.22	.0186	0.904	2.08	66	0.041*
CRP	-0.0107	50.04	9.29	-54.93	-16.86	-3.86	28	0.001*
Creatinine	-0.0107	.09	0.01	-.033	0.012	-0.96	65	0.338
WBC (white blood cell), ANC (absolute neutrophil count), and CRP (C-reactive protein). (*) statistically significant								

The statistical analysis provides valuable insights into prognostic factors. The strong positive correlation between neutropenia duration and hospital stay ($r = 0.7$, $P < 0.00001$) is a well-established finding in FN management (22, 23). Similarly, the moderate correlation with fever duration ($r = 0.507$, $P < 0.00001$) underscores that the severity and duration of the underlying myelosuppression are the primary drivers of clinical response, rather than initial laboratory parameters. The significant association between the primary cancer diagnosis and the length of stay further

suggests that underlying disease characteristics and treatment intensity influence FN outcomes.

This study has limitations that warrant consideration. First, its single-center, observational design limits the generalizability of the findings. The lack of Amikacin drug level monitoring is a significant methodological limitation, as it prevents a definitive assessment of therapeutic drug exposure and the true incidence of subclinical nephrotoxicity, despite the reassuring creatinine data.

This study, the first report from Libya, demonstrates that the local empirical combined regimen of Piperacillin/tazobactam and Amikacin is a viable and safe first-line treatment option for febrile neutropenia in pediatric oncology patients. The rapid de-escalation of Amikacin appears to be a safe strategy.

However, the findings highlight a critical challenge in local microbial epidemiology: the predominance of Gram-positive organisms in MDI and the identification of Piperacillin/tazobactam-resistant MRSA isolates. This microbial profile, coupled with the high rate of Vancomycin use, suggests that the current first-line regimen may not fully cover the local pathogen spectrum.

In conclusion, while the current regimen is effective and safe, continuous surveillance of local resistance patterns is mandatory. We recommend that clinicians maintain a low threshold for early Vancomycin addition in high-risk patients or those with signs suggestive of Gram-positive infection, and consider future comparative studies to determine the optimal empirical regimen for this patient population.

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Conflict of interest

The authors declared no conflicts of interest.

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Ethical statement

This study was approved by the Ethical Committee of the National Cancer Institute of Misurata, Libya (No. 03/2023) and conducted in accordance with the Declaration of Helsinki.

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