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The Risk Factors and Outcomes of Neutropenic Colitis in Acute Lymphoblastic Leukemia During Chemotherapy

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Abstract

Objective: To evaluate the risk factors and outcomes of neutropenia colitis in acute lymphoblastic leukemia (ALL) during chemotherapy.
Methodology: This prospective observational study was conducted from June to December 2024 at the Pediatric Hematology and Oncology unit of Indus Hospital & Health Network, Karachi. Children aged 1–16 years with ALL on active chemotherapy presenting with neutropenia (ANC <1500/µL), fever, abdominal symptoms, or hypoalbuminemia and radiologic gut wall thickening were enrolled. Patients were assessed demographic and clinical characteristics, mortality and risk factors. Data were collected via structured proforma and analysis was done by SPSS version 26.
Results: Overall mean age of 64 patients 7.15 ± 1.19 years, and male predominance (67%). Out of all, 58% patients were classified as high-risk and 23% as standard-risk. Majority of patients (69%) occurred during the induction phase of chemotherapy, followed by delayed intensification (13%) and consolidation (10%) phases. Among 31% cases the blood cultures were positive, with E. coli being the most commonly isolated organism (25%). Overall mortality rate was 11%. Additionally, high-risk leukemia, signs of severe gastrointestinal involvement like blood in stool and increased gut wall thickness, and the presence of systemic infection, were observed to be predictor of mortality (p = >0.05).
Conclusion: The neutropenic colitis during chemotherapy in ALL carries a significant risk of the mortality. The cases with more aggressive disease, involvement of severe gastrointestinal conditions, or systemic infectious condition are at highest risk of adverse outcomes.
Keywords: Acute Lymphoblastic Leukemia, Neutropenic enterocolitis, Chemotherapy

Introduction

Pediatric oncology has witnessed remarkable advancements in recent years, leading to breakthrough outcomes in the management of various blood cancers affecting children.[1] Though by the early detection, perfect risk stratification, and the implementation of properly tailored protocols of treatment, the disease is related with a higher encouraging prognosis, revealed by substantial improvements in the rate of survival and long-term outcomes in these affected pediatric patients.[1] However, the intensive chemotherapy regimens utilized in pediatric oncology often come with a range of side effects that require careful management to ensure the best possible outcomes for patients.[2,3] The risk of gastrointestinal (GI) complications such as enteritis, typhlitis, and colitis has increased in acute lymphoblastic leukemia during chemotherapy over the past few years.[4,5] These adverse events are caused by inflammatory conditions in the small bowel, cecum, and large bowel and about 7% of children with blood cancer will experience CNS complications during treatment phases.[6,7] The risk factors that causes Neutropenic enterocolitis are corticosteroid exposure, prolonged periods of neutropenia, injudicious use of antibiotics, and repeated infection.[7] The underlined cause of these conditions is a combination of immunosuppression, mucosal injury, and bacterial invasion that leads to bowel wall edema, engorged blood vessels, and tissue necrosis.[8,9] NEC is a common cause of persistent fever in a neutropenic patients.[10] The mortality rate of these patients can reach as high as 50% to 100%.[11,12]

Neutropenic enterocolitis (NEC) is a gastrointestinal emergency that can be fatal in children with blood cancer.[13] The caecum & ascending colon are frequently involved site that is associated with bowel wall thickening and is usually observed in immunocompromised patients.[14] Patients can present with symptoms of abdominal pain , fever, neutropenia diarrhea ,lower gastrointestinal bleeding &abdominal distension but not

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all the features may be seen in the same patient with alteration in ultrasonography or computed tomography abdomen show gut wall thickness lead to in neutropenic colitis. Understanding the risk factors associated with this condition is crucial for early detection and management to improve patient outcomes. Failure to diagnose and not treat it promptly can lead to a lethal outcome.[15,16] In its initial stages, it was mostly observed in children with acute leukemia, but later, it was identified in other solid malignancies and non-neoplastic conditions like aplastic anemia and post-hematopoietic stem cell transplantation.[17,18]

Over the past few decades, several studies have demonstrated favourable outcomes with the use of bowel rest and antibiotic therapy as initial management strategies, often avoiding the need for surgical intervention. However, the role of surgery in the treatment of NEC continues to be a topic of debate, with conflicting evidence regarding its impact on patient outcomes. Despite growing interest in the management of NEC, there is a notable gap in the literature concerning its incidence, risk factors, treatment approaches, and outcomes in low- and middle-income countries. Existing data are limited, and most retrospective studies report a highly variable incidence ranging between 1.7% and 16.2%. Given the scarcity of region-specific research, especially in paediatric oncology populations where immunosuppression may further complicate the clinical course, there is a critical need for more comprehensive studies in these settings. To address this gap, we conducted this study to analyze the prevalence, risk factors, treatment modalities, and outcomes of NEC among paediatric oncology patients, to provide essential understanding that could guide clinical decision-making, improve management strategies, and ultimately enhance patient outcomes in resource-limited settings.

Methodology

This prospective observational study was conducted in the inpatient department of the Pediatric Hematology and Oncology unit at the Indus Hospital & Health Network (IHHN), a tertiary care center in Karachi, Pakistan. The study period extended from June 2024 to December 2024. Ethical approval was obtained from the Institutional Review Board of IHHN (IRB approval number: IHHN IRB 2024_01_012), and written informed consent was taken from the parents or legal guardians of all participating patients. Children aged 1 to 16 years diagnosed with acute lymphoblastic leukemia and receiving active chemotherapy were included if they presented with clinical and laboratory features suggestive of neutropenic enterocolitis (NEC), including neutropenia (absolute neutrophil count <1500 cells/μL), fever, abdominal pain, abdominal distension, diarrhea, blood in stool, hypoalbuminemia, and increased bowel wall thickness on abdominal ultrasonography and/or CT scan were included. Conversely all the children aged less than 1 year or older than 16 years, had hematologic malignancies other than acute lymphoblastic leukemia like acute myeloid leukemia or chronic myeloid leukemia, relapsed disease or were receiving palliative care, children with pre-existing gastrointestinal disorders, history of recent abdominal surgery and children with metastatic disease who were planned for palliative intent were excluded. A sample size of 63 patients was calculated using OpenEpi online software, based on a reported prevalence of NEC of 6.3%, with a precision of 6%, a 95% confidence interval, and 80% power. A non-probability consecutive sampling technique was employed. Study was conducted after obtaining informed consent from the parents or legal guardians of each child, following proper counseling regarding the purpose of the study. Participation of the patients was entirely voluntary, and confidentiality of all patient data was maintained. All the patients were evaluated for NC based on clinical signs and symptoms, laboratory parameters, and imaging findings. Assessment of the risk factors was done by recording demographic data, leukemia subtype, chemotherapy phase, duration and severity of neutropenia, and based on serum albumin levels and anthropometric measurements. Patients were also assessed for duration of hospitalization, requirement for intensive care support, development of complications, response to medical treatment, and mortality. Data were systematically collected using a pre-designed proforma and analysis was done using SPSS version 26.

Results

The result shows that 64 participants with neutropenic colitis were included in the study, with a mean age of 7.15 ± 1.19 years and male predominance. Abdominal distension and tenderness were the most frequent clinical findings, while visceromegaly was moderately common and blood in stool or ascites were rare. Mean

Table I. Clinical and study related variables of the patients.		
Characteristics	%	Total Number
Gender		
Male	67%	43
Female	33%	21
Sign and symptoms		
Abdominal Distension	31%	20
Abdominal Tenderness	27%	17
Visceromegal	24%	15
Blood in Stool	9%	06
Ascites	9%	06
Others	24%	15
Type of Leukemia		
B ALL HR	58%	37
B ALL SR	23%	15
T ALL	19%	12
Treatment		
Surgical Treatment	2%	1
Conservative Treatment	98%	62
Phases Of Cancer Treatment		
Induction	69%	43
Consolidation	10%	06
Interim Maintenance	9%	05
Delayed Intensification	13%	08
Maintenance	2%	01
Chemotherapeutical drug		
Dexa	27%	14
Pred	58%	30
Outcomes		
Expired	11%	07
Recover	89%	57
Blood Cultures		
Positive Blood Cultures	31%	18
Negative Blood Cultures	64%	37
Not done	5%	09
Organism Name		
Acinetobacter species	2%	01
E-coli	25%	16
Staphylococcus Aureus	3%	02
Candida	2%	01
Coag Neg Staphylococcus	2%	01
Klebsiella	3%	02
Micrococcus Species	2%	01
Stenotrophomonas maltophilia	2%	01

length of hospital stay was 15.14 ± 12.45 days, ranging from 2 to 67 days. The cohort was predominantly male (67%) compared to female (33%). Most participants were diagnosed with B-cell (ALL), with 58% classified as high-risk (HR) and 23% as standard-risk (SR). The majority of cases (69%) occurred during the induction phase of cancer treatment, followed by delayed intensification (13%), consolidation (10%), interim maintenance (9%), and maintenance (2%). Mostly patients underwent conservative treatment. Blood culture results showed positive cultures in 31% of participants, while 64% had negative results. Among the identified organisms, E. coli was the most frequent pathogen, found in 25% (n = 16) of cases. The clinical outcomes revealed a recovery rate of 89%, with 11% of participants expired. The mean heart rate was 125.25 bpm, hemoglobin level 7.5 g/dL, serum creatinine 0.46 mg/dL, albumin 2.68 g/dL, and ANC 135.9 cells/µL. Table I

Overall mean hemoglobin level was 7.5 ± 1.20 g/dL, mean serum creatinine was 0.46 ± 0.23 mg/dL, reflecting preserved renal function, mean albumin level was 2.68 ± 0.38 g/dL, indicating poor nutritional status and overall average of ANC was 135.9 ± 161.6 cells/µL. Clinically the average heart rate was elevated at 125.5 ± 18.2 beats/minute; suggesting tachycardia among patients and overall average Hospital stay was 15.14 ± 12.45 days, reflecting a prolonged and flatulate duration of hospitalization among patients. Table II

Table II: descriptive statistics of clinical and laboratory characteristics. (n=64)		
Variables	**Mean**	**Standard Deviation**
Hemoglobin	7.5	1.20
Serum Creatinine	0.46	0.23
Albumin	2.68	38.7
Absolute Neutrophil Count	135.9	161.6
Heart Beat	125.5	18.2
Length of Stay	15.14	12.45

The mortality rate was slightly higher in males (7.8%) than females (6.3%) p = 0.357, the phase of cancer treatment not showed the significant effect on mortality, though B-ALL high-risk patients had the highest proportion of mortality (12.5%) p = 0.087. Additionally, the induction therapy, type of steroids, and consolidation therapy did not show the significant association with outcomes (p=>0.05). Conversely, few clinical features were significantly associated with mortality, including patients with blood in stool had higher rate of mortality (36.4%/9.4%), and increased gut wall thickness (>3 mm) also linked with higher mortality rate (12.5%/1.6%) P=<0.05. Furthermore, the positive blood culture was strongly linked to mortality, (12.5% vs. 1.6%) p=0.001, while ascites was not statistically significant (p = 0.113). *Table III*

Additionally, the univariate regression analysis demonstrated that the blood in stool, increased gut wall thickness (>3 mm) and positive blood culture were significantly linked to mortality (p= <0.05). Additionally, the cases with high-risk cancer phase had a significantly higher mortality (p = 0.033), as in high-risk patients, 12.5% died and 43.8% recovered, whereas in the non-high-risk group mortality rate was 1.6%. On the other

Table III: Stratification of risk factors for outcomes. (n=64)

Risk factors		OUTCOME		Total	p-value
		EXPIRED	RECOVER		
Gender	Female	4	16	20	0.357
		6.3%	25.0%	31.3%	
	Male	5	39	44	
		7.8%	60.9%	68.8%	
Phase of Cancer Treatment	B ALL HR	8	28	36	0.087
		12.5%	43.8%	56.3%	
	B ALL SR	0	15	15	
		0.0%	23.4%	23.4%	
	T ALL	1	12	13	
		1.6%	18.8%	20.3%	
Induction	No	4	20	24	0.642
		6.3%	31.3%	37.5%	
	YES	5	35	40	
		7.8%	54.7%	62.5%	
Steroids	Dexamethasone	1	13	14	0.692
		1.6%	20.3%	21.9%	
	Prednisolone	5	25	30	
		7.8%	39.1%	46.9%	
	No	3	17	20	
		4.7%	26.6%	31.3%	
Consolidation	NO	8	50	58	0.847
		12.5%	78.1%	90.6%	
	YES	1	5	6	
		1.6%	7.8%	9.4%	
Ascites	NO	1	21	22	0.113
		1.6%	32.8%	34.4%	
	YES	8	34	42	
		12.5%	53.1%	65.6%	
Blood in stool	NO	5	48	53	0.019
		7.8%	75.0%	82.8%	
	YES	4	7	11	
		6.3%	10.9%	17.2%	
Gut wall thickness	≤3	1	22	23	0.049
		1.6%	34.4%	35.9%	
	>3	8	33	41	
		12.5%	51.6%	64.1%	
Blood culture	Positive	8	17	25	0.001
		12.5%	26.6%	39.1%	
	Negative	1	38	39	
		1.6%	59.4%	60.9%	

hand, gender, use of steroids, induction or consolidation phase, and presence of ascites were not significantly linked to the outcome (>0.05). Generally, infectious and gastrointestinal severity markers were the strongest predictors of mortality.

Discussion

Neutropenic colitis is a severe and often life-threatening gastrointestinal complication observed in pediatric patients, those undergoing intensive chemotherapy for acute leukemia. This research study analyzed total 64 patients diagnosed with acute lymphoblastic leukemia ALL who developed neutropenic colitis, evaluating their clinical characteristics, their treatment responses and also risk factors associated with mortality. Overall mean age of patients was 7.15 ± 1.19 years and male (67%) predominance. Parallels demographic profile were documented in the studies conducted by Yozgat et al.[19] and Fike et al.[20]

In this study, laboratory findings revealed that overall study subjects were anemic, free from renal dysfunction, had poor nutritional status, and severe neutropenia, as

Table IV: Univariate logistic regression analysis of clinical and Laboratory characteristics with outcome of patients. (n=64)

Risk Factor	Category (Reference)	OR (95% CI)	p-value
Gender	Male (Female)	0.51 (0.13–2.03)	0.357
Cancer (high risk)	Yes (No)	**7.71 (0.89–66.6)**	0.033
Induction Phase	Yes (No)	0.78 (0.18–3.32)	0.642
Steroid Use	Prednisolone (None)	1.13 (0.23–5.43)	0.692
	Dexamethasone (None)	0.44 (0.04–4.65)	
Overall (Steroid use)	(Yes vs No)	1.12 (0.25 – 5.00)	0.88
Consolidation Phase	Yes (No)	1.25 (0.14–11.3)	0.847
Ascites	Yes (No)	4.94 (0.57–42.5)	0.113
Blood in Stool	Yes (No)	5.49 (1.26–23.8)	0.019
Gut Wall Thickness	>3 mm (<3 mm)	5.34 (1.01–28.3)	0.049
Blood Culture	Positive (Negative)	17.9 (2.14–149.5)	0.001

indicated by mean hemoglobin level of 7.5 ± 1.20 g/dL, mean serum creatinine of 0.46 ± 0.23 mg/dL, mean albumin level of 2.68 ± 0.38 g/dL, mean ANC value of 135.9 ± 161.6 cells/µL, and. Aligning with these findings, in the study of Sahoo et al[21] low albumin levels were observed in 78% of neutropenic enterocolitis patients, suggesting poor nutritional status. Consistently, in another study of Jaime-Pérez et al,[22] a large proportion of patients were anemic (82.9%), with an overall median hemoglobin level of 7.5 g/dL in their study subjects.

In this series, among neutropenic colitis patients, abdominal distension and tenderness (20% and 17% respectively) were the most frequent clinical findings, with average heart rate of 125.5 ± 18.2 beats/minute, suggestive of tachycardia among patients. These findings are corroborating by the study of_Yozgat et al[19] where abdominal pain was the most frequent symptom (81.8%). Similarly, the study conducted by Nematolahi et al[23] also documented abdominal pain as most commonly occurring presentation.

In this study, the patients were predominantly diagnosed with B-cell (ALL), with majority of 58% classified as high-risk (HR) and 23% as standard-risk (SR). Additionally, majority of cases (69%) occurred during the induction phase of cancer treatment, followed by delayed intensification (13%), consolidation (10%), interim maintenance (9%), and maintenance (2%). In line with these findings, in the study conducted by Yildirim et al.[24] pre-B cell (ALL) accounted for approximately 93.6% of cases, suggesting B-cell ALL predominance, with 19.1% HR, and 12.8% of SR cases, however 68.1% cases were intermediate risk. Correspondingly, in the study of Timur et al[25] reported that medium-risk, standard-risk, and high-risk patients were 45.52%, 32.26%, and 22.22% respectively. Additionally, in their study, majority of cases (32.62%) also occurred during induction phase, followed by consolidation phase (19.35%). The high proportion of B-cell ALL reproduces its overall high incidence, whereas the greater proportion of high-risk patients (58%), likely indicating late presentation, higher count of leukocytes and adverse prognostic features at diagnosis, fundamental to higher staging of risk.

The treatment approaches in the conducted study were predominantly conservative with solitary only 2% of patients requiring surgical intervention. This is consistent with existing research that recommends non-operative management as the first-line approach for neutropenic colitis, with surgery reserved for patients with complications such as perforation, severe bleeding, or peritonitis. The relatively low surgical rate observed in our cohort suggests that most cases of neutropenic colitis can be managed with supportive care, including bowel rest, parenteral nutrition, and broad-spectrum antibiotics. Addictingly in the blood culture, E. coli (25%) was the most frequently identified pathogenic organism. In contrast with these findings, in a study Jain et al.[26] reported that 73% of neutropenic enterocolitis patients underwent laparotomy, primarily due to free intraperitoneal gas and cecal perforation, demonstrating surgery as a frequently required intervention in pediatric ALL patients with severe or complicated NE. Consistent with our study, in the study of Cherif et al[27] infections were verified among 66% of patients, based on microbiology present, where 34% had no microbiological documentation, suggesting that blood cultures are frequently negative in neutropenic patients, even in the setting of severe infection. Moreover, in their study,

Escherichia coli was the most common pathogen in 23.1% of the patients.

In present study, mean length of hospital stay was 15.14 ± 12.45 days, reflecting a prolonged and flatulate duration of hospitalization among patients. Moreover, the clinical outcomes revealed a recovery rate of 89%, however 11% of participants expired. Parallel findings were stated in the study of Brunel et al[28] where NEC was associated with significantly longer length of hospitalization (P<0.001), confirming that neutropenic colitis leads to prolonged admissions. However, they found lower 30-day mortality (6.5%) was than our findings. In another study conducted by Gupta et al[29] also revealed prolonged hospital stay, with mean length of 23.9 ± 0.9 days for leukemic patients with neutropenic enterocolitis.

In our study, according to the stratification of risk factors for outcomes, mortality rate was slightly higher in males (7.8%) than females (6.3%); p = 0.357, suggesting that gender is not an independent predictor of mortality in neutropenic colitis among acute lymphoblastic leukemia patients. Consistent with these findings, in the study of Brunel et al[28] although gender distribution was reported and found insignificant (p = 0.5), mortality was associated with clinical severity markers rather than the gender difference, indicating that small gender-based mortality difference is clinically minimal and statistically non-significant. Additionally, according to our findings study, the phase of cancer treatment showed no significant effect on mortality, though B-ALL high-risk patients had the highest proportion of mortality (12.5%) p = 0.087. In line with these findings, the study conducted by Gorschlüter et al[29] demonstrated that in adult cancer patients with NEC, mortality was associated with complications, clinical severity, and intensity of chemotherapy, rather than the specific phase of treatment. Treatment timing alone was not a decisive prognostic factor, as the patients receiving high-dose or intensive regimens had worse outcomes. Furthermore, in this study, presence of blood in stool, increased gut wall thickness (>3 mm), and positive blood culture were significantly linked to mortality (p= <0.05). Consistent findings were documented in the study conducted by Muñoz-Ramírez et al[30] where gastrointestinal bleeding was independently associated with significantly higher mortality in leukemic patients with NEC (p = 0.05), with an increased relative risk of death in the presence of bleeding (RR ≈ 2.3), suggestive of adverse prognostic indicator in patients with leukemia and neutropenic colitis. Consistently, in the study of Cartoni et al[31] mortality rate was significantly higher among patients (60%) when bowel wall thickness exceeded 10 mm compared to those with thickness below or equal to 10 mm (4.2%), P <.001.

Besides all its contribution our research study has some limitations like relatively small sample size and study was conducted at only one institution, which may limit the generalizability of the findings. Therefore, future research would focus on multi-center studies with the larger sizes to validate these findings and would explore additional risk factors that may influence outcomes in pediatric patients with NC.

Conclusion

Study revealed that the patients with ALL who develop neutropenic colitis during chemotherapy, the condition is linked to a significant risk of mortality. The certain factors, including high-risk leukemia, signs of severe gastrointestinal involvement like blood in stool and increased gut wall thickness, and the presence of systemic infection, were observed to be closely linked with adverse outcomes. Overall findings underscore the close monitoring of disease severity, gastrointestinal complications, and infections condition are very important. Hence early identification and management of high-risk patients may improve the outcomes. Future larger, multicenter studies are recommended to validate these observations and improve the prognostic models for this high-risk complications.

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