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ORIGINAL RESEARCH

Infectious Complications in Paediatric Acute Lymphoblastic Leukemia During Chemotherapy: A Prospective Observational Study from Central India

[1]Ankita Kataria, [2]Charity Lamin, [3]Preetibala Badoule, [4]Dharmanshu Chaube, [5]Preeti Malpani

[1,2,3]3rd year PG Resident, [4]Assistant Professor, [5]HOD and Professor, Department of Paediatrics, MGM Medical College, Indore, Madhya Pradesh, India

Corresponding author
Ankita Kataria
3rd year PG Resident, Department of Paediatrics, MGM Medical College, Indore, Madhya Pradesh, India
Email: ankitakataria.334@gmail.com

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ABSTRACT

Background: Infections are a major cause of morbidity and mortality among paediatric patients undergoing chemotherapy for acute lymphoblastic leukemia (ALL). This study aims to evaluate the incidence, types, and outcomes of infections in paediatric ALL patients during various chemotherapy phases. **Methods:** A prospective observational study was conducted on 75 paediatric ALL patients receiving chemotherapy in a tertiary care hospital. Patients were stratified as per National Cancer Institute (NCI) criteria. Data on socio-demographics, risk stratification, chemotherapy phases, infection types, microbiological profiles, and outcomes were collected and analyzed. Data analysis was performed using SPSS version 29. **Results:** This study had a mean age of 6.16 ± 3.09 years, with a male-to-female ratio of 1.42:1. High-risk patients constituted 52%. Infections occurred in 88% of patients, with bloodstream and respiratory tract infections each accounting for 37.88%. Fever (96.9%) and febrile neutropenia (90.9%) were the most common presentations. Overall mortality was 12%, with septicemia (55.6%) and pneumonia (44.4%) being the leading contributors. Culture-positive infections were found in 36% of cases, predominantly Candida species (13.3%) and Staphylococcus aureus (5.3%). Deceased patients had significantly lower mean total leukocyte count (TLC = 1297.78/µl) and absolute neutrophil count (ANC = 134.44/µl) compared to survivors ($p < 0.0001$). **Conclusion:** Infections significantly impact mortality in pediatric ALL patients undergoing chemotherapy, especially among high-risk patients with neutropenia. Early identification and management, along with monitoring hematological parameters, are crucial for improving outcomes.

Keywords: Paaediatric ALL, Chemotherapy, Infections, Febrile neutropenia, Septicemia, Candida, Leukocyte Count

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most prevalent cancer in children, representing around 25–30% of all pediatric malignancies [1]. Although advancements in chemotherapy have led to significant improvements in survival rates, now exceeding 85% in high-income countries [2], these therapies often cause profound immunosuppression. As a result, patients become highly susceptible to a variety of infections, which can disrupt treatment and negatively affect outcomes and quality of life [3].

Infectious complications, particularly during neutropenic phases, continue to be a leading cause of illness, hospital admission, treatment interruptions, and mortality in pediatric ALL patients[3,4]. Common complications include febrile neutropenia, bloodstream infections, pneumonia, and invasive fungal infections. In low- and middle-income countries, these risks are further intensified by contributing factors such as poor nutrition, inadequate hygiene, limited access to healthcare, antimicrobial resistance, and scarcity of supportive care resources[5,6].

Despite their clinical importance, there is limited region-specific research especially from Central India on the patterns, causative pathogens, and outcomes of infections during ALL treatment. Gaining insight into the local infectious disease landscape is essential for guiding empiric treatment, strengthening supportive care strategies, and minimizing infection-related mortality[6,7].

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This prospective observational study was conducted to evaluate the incidence, types, and microbiological profiles of infectious complications in pediatric ALL patients receiving chemotherapy at a tertiary care center in Central India. It also aimed to examine the association between these complications and key hematological parameters—specifically total leukocyte count (TLC) and absolute neutrophil count (ANC)—to identify potential prognostic indicators for adverse outcomes.

MATERIAL AND METHODOLOGY

This is a prospective observational study conducted over one year in the Hemato-oncology Unit of the Department of Paediatrics at Maharaja Yashwantrao Hospital (MYH) and Chacha Nehru Bal Chikitsalaya (CNBC), Indore, following ethical clearance. The study included 75 children under 18 years diagnosed with acute lymphoblastic leukemia (ALL).

Inclusion criteria

All children under 18 years of age diagnosed with acute lymphoblastic leukemia receiving chemotherapy and admitted in Hemato-oncology unit.

Exclusion Criteria

Parents/guardians not consenting to participation.

Data Collection:

a. Informed consent was obtained.
b. Data on infections, including type, site, microbiological profile, and outcomes, were collected.
c. Patients developing complications in different phases were counted separately.
d. Laboratory tests (CBC, culture etc.) were done as indicated.

Data Analysis:

a. SPSS version 29 was used.
b. Continuous variables were summarized as mean ± SD or median (IQR).
c. Categorical variables were expressed as numbers and percentages.
d. Chi-square test and t-test were applied; p-value < 0.05 was considered statistically significant.

RESULT

Table 1: Socio-demographic data of the study group

Baseline socio-demographic data	Number of patients (n=75)	Percentage (%)	Remark	
Gender	Male	44	58.7%	Male:Female ratio= 1.42:1
	Female	31	41.3%	
Age	0-5 years	37	49.3%	Mean age = 6.16 ± 3.09 years.
	6-10 years	30	40.0%	
	11-18 years	8	10.7%	

Table 2: Distribution of patients as per risk stratification and stage of chemotherapy

Distribution of patients	Number of patients (n=75)	Percentage (%)	
Risk group	High risk	39	52.0
	Intermediate risk	26	34.7
	Standard risk	10	13.3
Stage of chemotherapy	Induction phase	32	42.67
	Consolidation phase	20	26.67
	Interim maintenance	15	20.0
	Delayed intensification	4	5.3
	Maintenance	4	5.3

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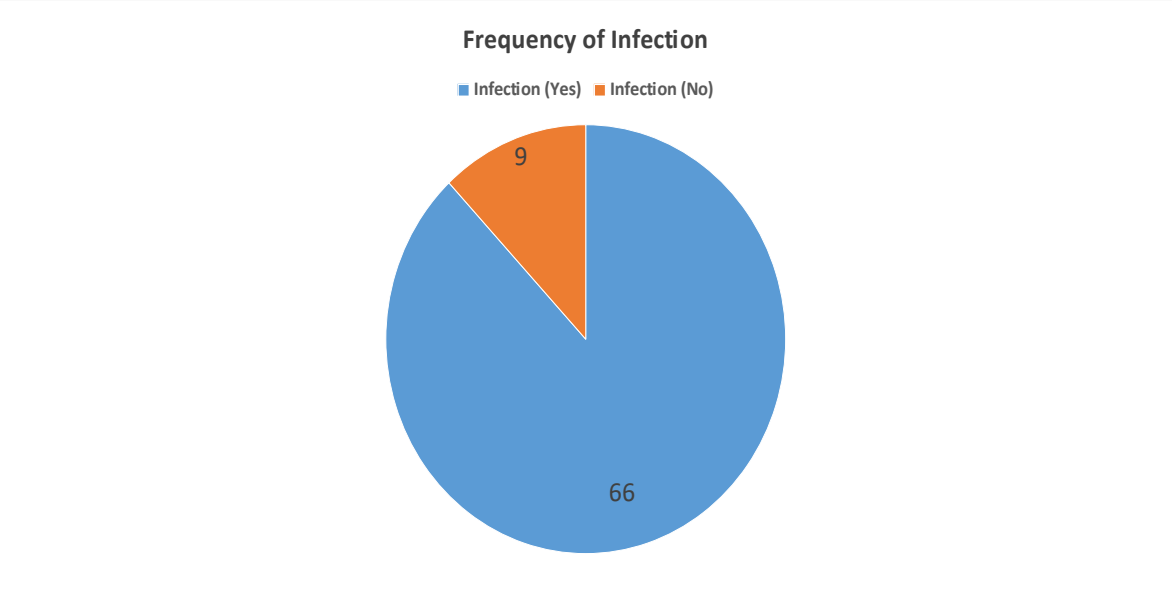
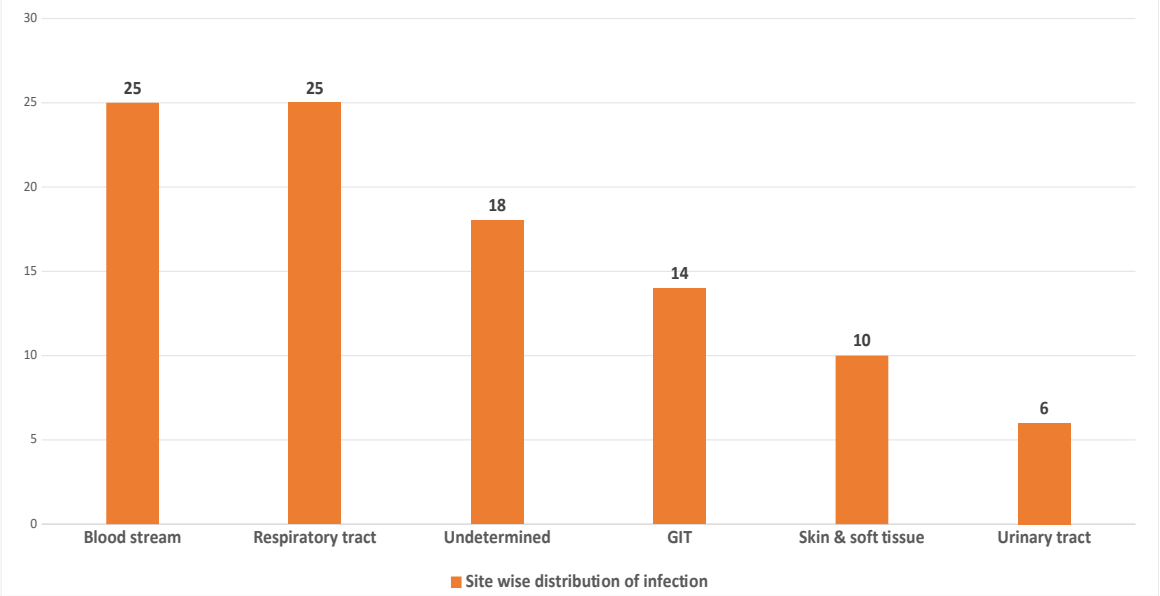


Graph 1: Frequency of Infection



Graph 2: Site wise distribution of infection (n=66)

Table 3: Outcome of the study group

Outcome	Number of patients (n=75)	Percentage (%)
Death	9	12.0
Discharged	66	88.0

Table 4: Distribution of infectious complications and their correlation with the outcome of treatment(n=66)

Types of infection	Death (n=9)		Discharge (n=57)		Total (n=66)	
	Number of patients with complication	Percentage (%)	Number of patients with complication	Percentage (%)	Total number of patients with complication	Percentage (%)
Fever	9	100	55	96.5	64	96.9
Febrile neutropenia	9	100	51	77.3	60	90.9
Septicemia	5	55.6	12	21.1	17	25.8
Pneumonia	4	44.5	19	33.4	23	34.8
Fungal sepsis	3	27.3	8	14.1	11	16.7
Urinary tract	3	33.34	3	5.3	6	9.1

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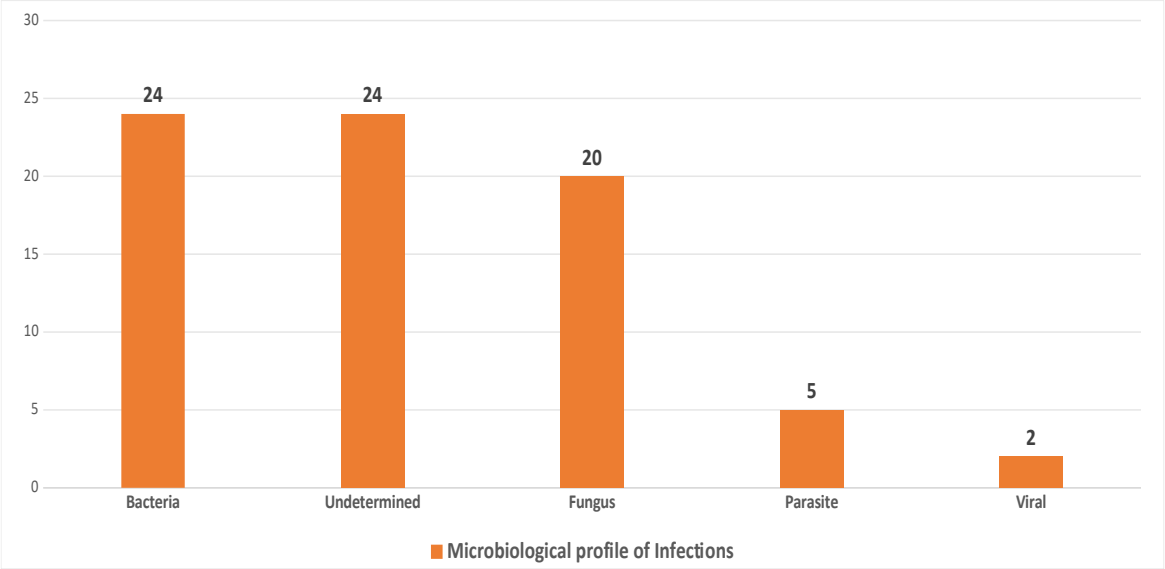
infections (UTI)						
Oral candidiasis	3	33.34	6	10.6	9	13.63
Abscess	2	22.2	8	14.03	10	15.2
Others	1	11.1	6	10.6	7	10.6



Graph 3: Microbiological profile of Infections (n = 66)

Table 5: Culture proven infections

Culture	Culture report	Number of patients	Percentage (%)
Blood culture (n=75)	Sterile	48	64.0
	Candida	10	13.3
	Staphylococcus aureus	4	5.3
	CONS	4	5.3
	Klebsiella	4	5.3
	E.coli	3	4.0
	Pseudomonas	2	2.7
Urine culture (n=15)	Sterile	9	60.0
	Pseudomonas	3	20.0
	E.coli	2	13.3
	Candida	1	6.67
Pus culture(n=10)	Sterile	7	70.0
	Staphylococcus aureus	3	30.0
	Acinetobacter	2	50.0

Table 6: Comparison of Survivors and Non survivors in Terms of TLC and ANC

	TLC (/µl)		ANC (/µl)	
Outcome	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**
Death	1297.78	1219.49	134.44	173.86
Discharge	3481.35	2175.73	1129.09	1160.70

The association of outcome of treatment with TLC and ANC was found to be **significant (p <0.0001)** for both the groups, indicating patient with low level of TLC and neutropenia are at more risk to succumb to the illness contributing to the mortality.

DISCUSSION

This prospective observational study assessed chemotherapy induced complications in paediatric ALL patients admitted to MYH and CNBC, Indore, and explored the pattern and frequency of infections during chemotherapy of ALL and examine their association with hematological parameters. A total of

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75 patients undergoing chemotherapy, classified per NCI risk stratification, were included.

The mean age was 6.16±3.09 years, closely aligning with ***Priyanka aggarwal et al. (2020)***[8], who reported a mean age of 6.5±3.5 years. The majority (49.3%) were aged 0–5 years, similar to findings by ***E. sivakumar and D. rajkumar (2022)***[9] (46.7%). There was a male predominance (M:F ratio=1.42:1), consistent with ***Ayse Pınar Ozturk et al. (2020)***[10], who observed a ratio of 1.44:1.

Patients classified in the high-risk group (52%) were more frequently affected by complications, followed by intermediate risk group (34.7%) and standard risk group (13.3%), in consistent with ***Ulku Miray Yildirim et al., (2023)***[11] (49% HRG) and ***Ayse Pınar Ozturk et al., (2020)***[10] (63.7% HRG). However, no statistical significance was found between risk group and infection episode (P <0.078). In our study,majority patients were undergoing early phases of chemotherapy i.e., induction phase (42.67%) and consolidation (26.7%) and less patients were in later phases of chemotherapy i.e., interim maintenance (20%), delayed intensification (5.3%) and maintenance phase (5.3%). This is in consistent with the phase distribution reported by ***H. Inaba et al., (2016)***[3].

In the present study, 88.8% patients had infection episode, many of which suffered from more than one infection while undergoing chemotherapy. Comparatively, a retrospective analysis conducted by ***Joanna Zawitkowska et. al. (2019)***[7] reported that 92% ALL children had microbiologically documented bacterial infections during chemotherapy. The overall infection-related mortality rate in this cohort was 2.4%, primarily due to fungal infections.

We observed that the most common documented site of infection were blood stream (37.88%) and respiratory tract (37.88%). The site of infection in 27.28% patients could not be identified despite microbiological and radiological investigations. The other site of infections identified in our study were gastroinestinal system (21.21%), skin & soft tissue (15.15%) and urinary tract (9.09%). This was consistent with the study by ***Joanna Zawitkowska et. al.,* (2019)**[7] in which most common site of bacterial infection was bloodstream (71.3%), followed by gastrointestinal tract (61%) and urinary tract (33.7%). Similarly, in a study by ***H. Inaba et al., (2016)***[3], febrile neutropenia was the most common infection related complication (46%), followed by documented infections of the respiratory tract (16%), bloodstream (7%), and gastrointestinal tract (6%).

In our study, the majority of paediatric ALL patients (88%) were successfully discharged following chemotherapy, while the overall mortality rate was 12%. This outcome is favorable when compared to prior studies such as those by ***Bhargab Jyoti Saikia et. al. (2020)***[12] and **Suzy *Abdelmabood et. al., (2020)***[13], which reported mortality rates of 21% and 23%, respectively. The overall infection-related mortality rate in study conducted by ***Joanna Zawitkowska et. al. (2019)***[7] was 2.4%.

Among the infectious complications, fever and febrile neutropenia were the most prevalent, observed in 96.9% and 90.9% of cases, respectively. Notably, all nine patients who succumbed to their illnesses had both fever and febrile neutropenia, underscoring the critical nature of these conditions. The incidence of febrile neutropenia was more in high risk group patients. A statistical significance (P<0.003097) was seen between high risk and febrile neutropenia . However, no statistical significance was seen between phase of chemotherapy and febrile neutropenia. Similarly, fever was a complication seen in all study participants (100%) in a study by ***E. Sivakumar, D. Rajkumar (2022)***[9]. A study by ***H. Inaba et al., (2016)***[3] had febrile neutropenia as the most common infection related complication (46%), with it's significant association to risk group and phase of chemotherapy ($P < 0.001$).

Septicemia emerged as a particularly lethal complication in our study (25.8% cases in total), present in 55.6% of deceased patients compared to 21.1% of survivors. Pneumonia was another significant contributor to mortality in our cohort, identified in 44.5% of deaths, compared to 33.4% of survivors. Fungal infections, including fungal sepsis and oral candidiasis, were also notable in our study. Fungal sepsis was present in 27.3% of deaths and oral candidiasis was observed in 33.34% of deceased patients, while occurring in 16.7% and 13.6% respectively of the total patients studied. Urinary tract infections (UTIs), though less frequent (9.1%), were associated with a high mortality rate in our study; 50% of patients with UTI died. Abscess was seen in 15.2% patients undergoing chemotherapy. In a comparative analysis, ***H. Inaba et al. (2016)***[3] highlighted that bloodstream infections were a significant concern in paediatric ALL patients, particularly during induction therapy, with a reported incidence of 6%. Pneumonia was commonly observed during reinduction II, especially in patients receiving high dose cytarabine. Invasive fungal infections and urinary tract infections were also documented throughout various phases of therapy.

Microbiological profile of patients suggest that some patients contracted infection from multiple organism, either at the same time or separately while undergoing a certain phase of chemotherapy. Organism could not be determined in 36.4% of the infections despite microbiological and clinical examination. In the rest, bacterial infections (36.4%) was most commonly observed infection, followed by fungus (30.3%), parasite (7.5%) and viral infection (3.03%). ***Joanna Zawitkowska et. al., (2019)***[7] also found similar observation in their study where 53.2% children were reported to have a microbiologically documented bacterial infection during chemotherapy while 18.4% children experienced viral infection and 20.4% children had fungal infection. The most common site

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of bacterial infection was bloodstream (71.3%), followed by gastrointestinal tract (61%) and urinary tract (33.7%).

Overall positive cultures in blood were obtained from 27 cases (36%). The most commonly isolated pathogen in blood was Candida (13.3%), followed by Staphylococcus aureus (5.3%), CONS (5.3%), Klebsiella (5.3%), E.coli (4%) and Pseudomonas (2.7%). Urine culture were sent from 15 patients. Positive urine cultures were obtained from 6 cases (40%). The most commonly isolated pathogens in urine was Pseudomonas (20%), while the rest were E.coli (13.3%) and candida (6.67%). Pus culture were sent from 5 patients. Staphylococcus aureus (40%) was obtained from 2 pus culture, while the rest were sterile culture (60%). In a study by ***Joanna Zawitkowska et. al., (2019)***[7], it is seen that among the bacterial infection (53.2%), gram-positive (57.5%) and gram negative isolates (38.4%) were recovered from microbiologically confirmed cultures from bloodstream. Organism obtained were Staphylococci species (46%), Escherichia coli (17%), Klebsiella (8%), Pseudomonas species (7%) and others. Candida was responsible for 80% of the total fungal infection (20.4%). ***E. Sivakumar, D. Rajkumar (2022)***[9] also did a study on 45 patients and the microbiological profile of these patients showed no growth in 40 children, while klebsiella growth was found in 6.7% patients and pseudomonas growth was seen in 4.5% patients. These differences could be explained by different prophylactic measures and a smaller group size.

Critically, a statistically significant association was found between patient outcomes and both total leukocyte count (TLC) and absolute neutrophil count (ANC). The mean TLC among deceased patients was markedly lower (1297.78/µl ± 1219.49) compared to those who survived (3481.35/µl ± 2175.73). Similarly, the mean ANC was substantially reduced in deceased patients (134.44/µl ± 173.86) versus survivors (1129.09/µl ± 1160.70). The differences in TLC and ANC between survivors and non-survivors were both highly significant ($p < 0.0001$). Similar finding was seen by ***Roland a ammann et. Al. (2010)***[14] and ***Mohamed badr et. Al. (2016)***[15] which showed significant association of febrile neutropenia with the occurrence of complications and mortality, highlighting the clinical significance. These findings highlight the prognostic importance of hematologic parameters during chemotherapy for paediatric ALL. Severe leukopenia and neutropenia at critical phases of treatment predispose patients to life-threatening infections and complications, thereby significantly increasing the risk of mortality.

CONCLUSION

Infectious complications remain a major cause of morbidity and treatment delay in paediatric ALL patients receiving chemotherapy. This study highlights the high burden of infectious complications during chemotherapy in paediatric ALL patients, with febrile neutropenia, bloodstream infections, and pneumonia being the most common. Infections occurred predominantly during the early phases of treatment and were more frequent in high-risk patients. Gram-negative and fungal pathogens were significant contributors to morbidity and mortality. Critically, lower total leukocyte and absolute neutrophil counts were strongly associated with poor outcomes, emphasizing their prognostic relevance. Early identification, infection surveillance, and optimized supportive care are vital to reduce infection-related mortality, particularly in resource-limited settings. Further multicentric studies are warranted to guide tailored interventions for infection prevention in similar settings.

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