The Journal of Teachers Association

ISSN 1019-8555 (Print) & ISSN 2408-8854 (Online)
Frequency: Bi-Annual
DOI: https://doi.org/10.62469/taj.v037i01.006

OPEN ACCESS

Website: www.tajrmc.com
Email: editor@tajrmc.com
Volume-37 | Issue-1 | Jan-Jun 2024

Infections during induction therapy of childhood acute lymphoblastic leukemia with MRC-11 protocol

Farid Hossain[1]*, Be-Nazir Ahmmad[2], Rejaul Karim[2], Ruhul Amin[2], Muhammad Solaiman Mollah[3], Rustam Ali[4], Afiqul Islam[5]

[1]Department of Pediatrics, 250 bedded General Hospital, Noagon, Bangladesh
[2]Department of Pediatrics, Rajshahi Medical College, Rajshahi, Bangladesh
[3]Department of Pediatrics, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh
[4]Department of Pediatrics, Upazila Health Complex, Rohonpur, Gomostapur, Rajshahi, Bangladesh
[5]Department of paediatric Hemato-oncology, BSMMU, Dhaka, Bangladesh

Abstract: ***Background:*** During the induction phase of childhood acute lymphoblastic leukemia infections are the major cause of morbidity and mortality. The infection risk is high during induction phase because of the use of intravenous line, mucositis and chemotherapy induced profound neutropenia and immunodeficiency. ***Methods:*** This hospital based observational study was done from February 2015 to June 2015 in the Department of Pediatric Hematology-oncology in BSMMU to observe the type, frequency and outcome of infections and to determine the microbiological profile involved in infections during induction therapy of childhood acute lymphoblastic leukemia. Total 20 diagnosed cases of childhood ALL who were admitted for chemotherapy aged <12 yrs. of both sexes included in this study. Children with fever ≥ 38○ C lasting for 1 hour once with or without local symptoms of infection like cough, dysuria, diarrhea, cellulitis etc. during induction therapy were included. All baseline investigations were done for evaluation. ***Results:*** Mean age of the patients was 5.4±4 years having male predominance. 36 episodes of infections among 20 patients were observed. Isolated febrile episodes 27.8% and clinically documented infections 72.2%. The most common site was the Respiratory system (33.2%) of episodes then thrombophlebitis (13.9%), GIT (13.9%), Genitourinary system (5.6%), soft tissue infection (2.8%), ear infection (2.8%). ANC <500/mm3 was the major risk of infections. Microbiologically documented infections found 7 episodes (19.4%) out of 36 episodes. Gram negative bacilli such as Pseudomonas (42.9%), *E. coli* (28.4%) was predominant organism. ***Conclusion:*** Children less than 5 years were mostly vulnerable. Most of the infections occurred during induction associated with neutropenia (ANC <500/mm3). Gram negative bacteria were predominant organisms involved in infections. The Respiratory system was the commonest site of infection. Outcome of infectious episodes were satisfactory with or without modification of antibiotic regimen.

Keywords: Induction Therapy, Lymphoblast, Infection, Leukemia, Myelosuppression, Chemotherapy, Malignant.

Original Researcher Article

Correspondence:
Dr. Farid Hossain
Department of Pediatrics, 250 Bedded General Hospital, Noagon, Bangladesh
Email: farid_n02@yahoo.com
https://orcid.org/0009-0007-6363-2063

How to cite this article:
Hossain F, Ahmmad BN, Karim R, Amin R, Mollah MS, Ali R, Islam A; Infections during induction therapy of childhood acute lymphoblastic leukemia with MRC-11 protocol. Taj 2024;37 (1): 34-40.

Article history:
Received: December 26, 2023
Revised: January 18, 2024
Accepted: February 25, 2024
Published: April 17, 2024

Article at a glance:

Study Purpose: *The purpose of the study was to determine the Infections during induction therapy of childhood acute lymphoblastic leukemia with MRC-11 protocol.*

Key findings: *Febrile episodes: 27.8% isolated, 72.2% clinically documented. Common sites: Respiratory (33.2%), thrombophlebitis (13.9%), GIT (13.9%), Genitourinary (5.6%), soft tissue (2.8%), ear (2.8%).*

Newer findings: *Respiratory tract as the predominant infection site. Clinically documented infections rose to 72.2% from 52%, while isolated febrile episodes dropped to 27.8% from 48%. Gram-negative infections now predominate over Gram-positive.*

Abbreviations: *ANC: Absolute Neutrophil Count, ALL: Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, BSMMU: Bangabandhu Sheikh Mujib Medical University, SD: Standard Deviation.*

INTRODUCTION

The most common childhood malignant neoplasm are Leukemias which are about 41% of all malignancies. In western countries the incidence of Leukemia in children <15 years is approximately 4 in 100,000. About 77% of all cases of childhood leukemias are Acute Lymphoblastic Leukemia (ALL), about 11% are Acute Myeloid Leukemia (AML) and Chronic mixed leukemia are about 3-5%[1]. Twenty years before, this disease in more than 80% of cases was fatal within 6 months of diagnosis and almost all patients died within 2 years. The increased updated diagnostic methods, help in the development of more effective therapy. Advances in supportive care have substantially improved the outlook for children with leukemia. With the modern multimodal therapy and improved supportive care, 70-80% patients have gone remission lasting more than five years and many of them eventually are cured.[2]

Patients usually present with anemia, neutropenia and thrombocytopenia as a result of their disease and suffer from infection and bleeding from the outset. Induction chemotherapy prolongs periods of myelosuppression. As a result, patients are at risk of infection and bleeding for a long period. Mortality due to infection is most frequent between induction therapy and the attainment of remission.[3] The most common side effect of chemotherapy in children with ALL is myelosuppression due to cytotoxic effect.[1] In most of the cases; neutropenia is dose limiting side effect of many common cytotoxic regimens. Neutrophils play a critical role in protecting the body from infection by the micro-organisms that colonize in the oropharynx, gastrointestinal tract, and skin and it also play an important role in acute response to most infections and inflammatory diseases. Chemotherapy induced marrow failure leading to neutropenia are at great risk for over-whelming bacterial infection, especially Gram-positive skin flora, including staphylococcus aureus, Staph. albus and Staph. epidermidis & Gram-negative bowel organisms including E. coli, klebsiella protease, and Pseudomonas.[2]

In acute leukemia generally fever is due to infections, though it may occur due to administration drugs such as cytosine arabinoside, blood or blood products. Fever and neutropenia is an iatrogenic complication of anti-cancer cytotoxic therapy. Serious infection is usually associated with febrile neutropenia. Such patients should urgently be treated with broad spectrum antibiotics.[4] Infections usually occur when absolute neutrophil count is <500/mm^3 (ANC) and those mm^3 are at greater risk with ANC 100/mm^3. Severe and prolonged neutropenia increases risk of fungal infections.[5, 6] Major causes of morbidity and mortality are bacterial and fungal infections in children during chemotherapy of ALL. The risk of death increases due to infections and interruption of treatment may also increase the risk of relapse need to decrease the dose of the chemotherapeutic agents. During neutropenia there are many reports that infectious complications may occur but the information of incidence and the spectrum of infections encountered are much less available during the entire course of leukemic treatment. Patients with leukemia have more infections and their infections are more severe compared with healthy children. During chemotherapy Pneumonia, Bacteremia and Respiratory tract infections are the most common illness suffered by febrile patient with leukemia.[7]

During the past few decades, the spectrum of microbial agents isolated from febrile neutropenic children are changed. These results in new intensive chemotherapeutic regimens that can induce oral mucositis, widespread use of indwelling vascular catheters, the use of prophylactic antibiotics with Gram negative coverage and Gram-positive bacteria have been isolated more frequently. In contributing to the morbidity and death of patient with leukemia non-bacterial infections have also assumed a greater place. There is common an accompanying bacterial infection in a neutropenic child suffering from an acute viral infection and the risk of subsequent bacterial infection. A wide range of viral and parasitic infections are susceptible to occur in the immunocompromised patient. Mixed infections are not uncommon, such as those of bacterial-fungal or bacterial-viral etiology. Herpes viruses and measles are particularly troublesome in children with leukemia, but severe and life-threatening infections may also be caused by other viruses.[7] Nosocomial infections cause considerable morbidity and mortality, hospital stay and increase healthcare cost. Monitoring of nosocomial infections and

infection rates that differs in different patient populations and in different hospitals is of great importance to establish preventing measures.[8]

Aims and objectives

To identify distribution, frequency and outcome of infections during induction phase of childhood acute lymphoblastic leukemia.

MATERIALS AND METHODS

This hospital based observational study was done from February 2015 to June2015 in the Department of Pediatric Hematology and oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Shahbag, Dhaka. Total 20 pediatric ALL Bone-marrow confirmed diagnosed patients of 1 to 12 years old of both sex receiving induction therapy with MRC-11 protocol are enrolled. Patient having fever (axillary temperature greater than 38.5^{0}C or ≥38^{0}C for at least 1 hour once) with or without local symptoms of infections like cough, diarrhea, dysuria, cellulitis etc. during induction therapy are included. Age >12 years, Childhood malignancy other than ALL and Patients on therapy of ALL other than induction phase, fever due to other causes without infections are excluded. Informed written consent was taken from each parent and purpose of the study was explained to them and relevant information was documented in a preformed questionnaire. Percentage calculations are done to find out the proportion of the findings. Further statistical analysis of the results was done by using computer software devised as the statistical package for social science (SPSS). The results were presented in frequency, percentage, mean standard deviation and range.

RESULTS

Table 1: Distribution of study subjects according to age group (n=20)

Age in years	No. of patients (n=20)	Percentage
1 – 4	11	55.0
5 – 8	5	25.0
9 – 12	4	20.0
Mean ±SD= 5.4±4.0, Range= (1-12)		

The study includes 20 children with acute lymphoblastic leukemia and they were divided into three age groups. The age group of 1 – 4 years had the maximum number 11(55.0%), 5(25.0%) belonged to 5 – 8 years and 4(20.0%) belonged to 9 – 12 years. The mean (±SD) age was 5.4±4.0 years varied from 1 year to 12 years. The results are shown in the above table

.

Table 2: Sex distribution of the study subjects (n=20)

Sex status	No. of patients (n=20)	Percentage
Male	14	70.0
Female	6	30.0

The above table shows the sex distribution of study patients and found more than a two third (70.0%) of the patients was male and 6(30.0%) was female. Male to female ratio was 2.3:1.

Table 3: Time of fever onset (n=36)

Time of fever onset	No. of episodes (n=36)	Percentage
1st week	15	41.7
2nd weeks	12	33.3
3rd weeks	6	16.7
4th weeks	3	8.3

The onset of fever was divided into four groups. 15 episodes (41.7%) were within the 1st week, 12 episodes (33.3%) during the 2nd weeks, 6 episodes (16.7%) during the 3rd weeks and 3 episodes (8.3%) during the 4th weeks.

Table 4: Distribution of the primary sites of infection of the episodes (n=36)

Primary sites of infection	No. of episodes (n=36)	Percentage
No focus	10	27.8
Respiratory system	12	33.2
GIT	5	13.9
Thrombophlebitis	5	13.9
Genitourinary system	2	5.6
Ear infection	1	2.8
Soft tissue infection	1	2.8

Table 4 shows the distribution of the primary sites of infections. The Respiratory system was the most common site 12(33.2%) of infectious episodes. Other primary sites were without focus 10(27.8%), Thrombophlebitis 5(13.9%), GIT 5(13.9%), Genitourinary system 2(5.6%), Ear infection 1(2.8%), Soft tissue infection 1(2.8%) of the infectious episodes

.

Table 5: Profile of infectious complications (n=36)

	No. of episodes	Percentage
Clinically documented infections	26	72.2
Fever of unknown origin	10	27.8

Table 5 shows that 26 episodes (72.2%) of the infections documented clinically and 10 episodes (27.8%) fever occurred due to unknown origin.

Table 6: Distribution of isolated bacteria is according to the site of culture

Organism isolated	Blood culture	Ear swab	Swab from the skin lesion	Urine culture	Stool culture
E. coli	1	0	o	1	0
Pseudomonas aeruginosa	1	1	1	0	0
Staphylococcus aureus	0	0	1	0	0
Coagulase negative *staphylococcus*	0	1	0	0	0

Table 6 shows microbiologically documented infections found 7 episodes (19.4%) out of 36 episodes. Gram negative bacilli such as Pseudomonas (42.9%), *E. coli* (28.4%) were predominant organism.

Table 7: Result of antimicrobial sensitivity for isolated microorganism

Name of the organism	Sensitive antibiotics
E. coli	Imipenem, Meropenem
Pseudomonas aeruginosa	Cefepime, Ceftazidime, Gentamicin, Imipenem, Meropenem, Ciprofloxacin
Coagulase negative Staphylococcus	Ceftazidime, Gentamicin, Imipenem, Meropenem
Staphylococcus aureus	Ceftazidime, Amikacin, Imipenem, Meropenem

Table 7 shows most sensitive antibiotics were cefepime, ceftazidime, amikacin, imipenem, meropenem, ciprofloxacin, and gentamicin.

Table 8: The outcome of infectious episodes (n=36)

No. of episodes	Success without modification	Success with modification	Death
36 (100%)	9(25%)	26(72.22%)	1(2.8%)

Treatment outcome analysis showed that 9 episodes (25%) resolved with the combination of first line antibiotics (The 4th generation of cephalosporin with or without aminoglycoside eg. ceftipime, amikacin) while 26 episodes (72.22%) required modification of the treatment. Modification of therapy was usually done by adding ceftipime and vancomycin in majority of the episodes. Carbapenem with or without aminoglycoside were also given in few episodes. Amoxicillin- clavulanic acid or ciprofloxacin were given to few episodes with or without carbapenem. According to c/s results or clinical status all these modifications were done. Amphotericin B was also given in 4 episodes (11.11%). In this study outcome of 1 episode (2.8%) was death of the patient.

Table 9: Duration of treatment received during episodes of infection (n=36)

Duration of treatment (day)	No. of episodes (n=36)	Percentage
7 – 10	24	66.7
7 – 14	12	33.3
Mean ±SD =10.1±2.4, Range = (7-14)		

Table 9 shows that two thirds (66.7%) of the children received 7 to 10 days of treatment and one third 12(33.3%) received 7 to 14 days of treatment. The duration of treatment received was mean (±SD) 10.1±2.4 days varied from 7 to 14 days.

Table 10: Absolute neutrophil count (ANC) of the episodes (n=36)

ANC/mm^3	No. of episodes (n=36)	Percentage
0 – 100	11	30.6
100 – 500	18	50.0
500 – 1000	3	8.3
>1000	4	11.1

Table 10 shows very severe neutropenia (0-100/mm^3) were 11 episodes (30.6%), severe neutropenia (100-500/mm^3) were 18 episodes (50.0%), moderate neutropenia (500-1000/mm^3) were 3 episodes and no neutropenia (>1000/mm^3) were 4 episodes (11.1%).

Table 11: CXR finding of the episodes (n=36)

CXR findings	No. of episodes (n=36)	Percentage
Normal	27	75.0
Pneumonitis/consolidation	9	25.0

Table 11 shows documented radiological evidence of infection was 9 episodes (25.0%).

DISCUSSION

The most common form of childhood malignancy is Leukemia. With the modern multi-modal therapy and improved supportive care, 70-80% patients have gone into remission lasting more than five years and many of them are eventually cured.[2] Aggressive multiagent chemotherapy may induce several toxic effects like tumor lysis syndrome, hepatotoxicity, nephrotoxicity, mucositis and myelosuppression.[3] In most of the cases of neutropenia are the dose limiting side effect of many common cytotoxic drugs. These patients are at a great risk of overwhelming infection and they should be treated promptly with broad spectrum antimicrobials.[9]

In this study, total 20 patients were enrolled who showed signs and symptoms of infections like, fever, cough, diarrhea and vomiting, soft tissue swelling etc. during induction therapy. In this study population 5.4±4 (Table 1) was the mean age, but in Santolaya M, Alvarez A *et al*. it was 7±4 years.[10] Among the study group 70% cases were male; indicating male preponderance (Table 2), similarly Santolaya M, Alvarez A *et al*. also revealed that males were predominant in numbers (56%).[10] In our study, total 36 infectious episodes (Table-3) were observed in which most of the infectious episodes were in 1st and 2nd week of induction, which was similar to a previous study done by Judith M Chessells and Alison D Leiper.[11] We found in Table 4 & 5 isolated febrile episodes were 27.8%, clinically documented infections were 72.2%. The Respiratory system was the most common site (33.2%) of infection. GIT infection 13.9%, thrombophlebitis 13.9%, genitourinary system infection 5.6%, ear infection 2.8%, and soft tissue infection 2.8% were observed. In a previous study done by R. Jagarlamudi *et al* showed that documented infections 52%, 48% isolated febrile episodes clinically without focus.[12] The Respiratory system was the most common site (35.7%), skin, soft tissue, thrombophlebitis (13%), GIT (7%), Genitourinary system (6%) were observed in that study.[12]

In our study (Table 6) microbiologically documented infections found 19.4%. Gram negative bacilli such as Pseudomonas aeruginosa, E. coli were the predominant organisms. Other organisms were Staphylococcus aureus, coagulase negative staphylococcus. In the previous study done by Meir *et al*. showed 37% microbiologically documented infections. They found Gram positive cocci were the most frequently isolated organisms followed by Gram negative bacilli.[13] In another study done by Katerina Katsimpardi *et al*. showed that P. aeruginosa, K. pneumonia and E. coli were the most commonly isolated organisms.[14] In our study (Table 7) we found that isolated Gram positive organisms were sensitive to ceftazidime, imipenem, meropenem and isolated Gram negative bacteria were sensitive to cefepime, ceftazidime, meropenem, imipenem, gentamicin, ciprofloxacin and amikacin. In the study done by Meir *et al*. showed that Gram positive bacteria were sensitive to vancomycin, cephalothin, oxacillin, clindamycin and gentamycin. Gram negative bacteria were sensitive to imipenem, gentamycin, piperacillin, tobramycin and azotronem.[13]

We found in Table 8 that 25% episodes of infections resolved with the first line combination of antibiotics (ceftipime, amikacin) and 72.22% infectious episodes required modification of treatment and 2.8% episodes ended in death. In a study done by S. Mahmood *et al*. showed that 72% of episodes were resolved with first line antibiotic combination and 24% episodes needed modification of antibiotics. In that study outcome of 4% episodes ended in death of the patients.[15] The mean duration of treatment (Table 9) of infectious episodes was 10.1±2.4 days in our study. In a previous study done by S. Mahmood *et al*. also showed that the average length of antibiotics was 8.4 day.[15] We found in table 10 that 30.6%, 50%, 8.3% and 11.1% episodes were associated with very severe neutropenia (ANC<100/mm^3), severe neutropenia (ANC 100-500/mm^3), moderate neutropenia (ANC 500-1000/mm^3) and no neutropenia (ANC >1000/mm^3) respectively. Meir *et al*. found 31%, 44% and 25% episodes were associated with ANC<100/mm^3, ANC<500/mm^3 and ANC>500/mm^3 respectively.[13]

In this study (Table 11) 25% episodes were radiologically documented and, in another study, done by S. Mahmood *et al*. found 10.8% episodes were radiologically documented.[15] The limitations of our study were that small sample size, short study period, virus and fungus were not isolated in our study. The Comparison of our results with those studies published previously in other centers of the world has shown many similar and a few different findings. We should emphasize the importance of frequency, severity and outcome of infections in such critically ill patients over the years in order to detect changing epidemiologic patterns. Empiric therapy should be continuously modified based on this data.

CONCLUSION

Children less than 5 years were mostly vulnerable. Most of the infections occurred during induction associated with neutropenia (ANC <500/mm^3). Gram negative bacteria were predominant organisms involved in infections. The Respiratory system was the commonest site of

infection. Outcome of infectious episodes were satisfactory with or without modification of antibiotic regimen.

Acknowledgements

At first, I convey my gratitude and thanks to Almighty Allah for giving me the opportunity, energy and patience to carry out this dissertation. I am very much pleased to express my profound gratitude and deep regards to my guide Prof. (Dr.) Afiqul Islam, MBBS, FCPS, MD, Chairman Department of Haemato-oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka for his full support, direct supervision, constructive suggestion and proper guidance to me without which this dissertation could not be prepared. I am grateful to my teacher DR. Helena Begum, Assist. Prof. Dept. of pediatric Hemato- Oncology, BSMMU. For providing me support at all stages of my dissertation. My special thanks to Dr. Baha Uddin, Dr. Asif Masud Chy. for their help for preparing this dissertation.

Authors contributions

FH, RA, MSM: Concept and design, data acquisition and interpretation, drafting and final approval. BA, RK: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work. AI: Principal guide.

Declarations

Funding: All the authors did not receive any financial support for the research, authorship and/or Publication.

Conflict of interest: There was declared no conflict of interest of the authors.

Ethical approval: Ethical approval of the study was obtained from the Ethical Review Committee, BSMMU, Dhaka. The ethical issues were informed and addressed for future development of management to the participants' parents. Verbal consent had been given by the parents of the affected children.

Consent for publication: Had been taken.

REFERENCE

1. David G. Tubergen and Archie Bleyer, the leukemia's In: Behrman RE, kliegman RM, Jensen HB, editors. Nelson textbook of pediatrics, 18th edition, Philadelphia: WB Sounders Company 2007; 2116-2117.
2. Mannan M.A & Islam A et al. Long term survival of children with ALL experience of a semi-specialized center, Bangladesh cancer report, 1991; 12:5-11.
3. Manual of pediatric Hematology and Oncology-P. Lanzkowsky-2nd edition.
4. Bakhshi S, Padmanjali K, Arya L. Infections in childhood acute lymphoblastic leukemia: An analysis of 222 febrile netropenic episodes. Pediatric Hematol Oncol 2008; 25:385-392.
5. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new direction for its management. Cancer:2004; 100:228-237.
6. Gerson SL, Talbot GH, Hurwitz S, et al. Prolonged granulocytopenia:the major risk factor for invasive pulmonary aspergillosis in patients with acute leukaemia. Ann Intern Med. 1984; 100:345-351.
7. Rahiala J, Perkkio M, Riikonen P. Infections occurring during the courses of anticancer chemotherapy in children with ALL: a retrospective analysis of 59 patients. Pediatric Hematol Oncol 1997; 15: 165-174.
8. Aihua W, Shaozhen F, Yonghong Y, Xuzhuang S. Nosocomial infectionsamong pediatric hematology patients: Re of a retrospective incidence study at a pediatric hospital in China. Journal of pediatric hematology/oncology 2008;30:674-678.
9. Hughes WT, Armstrong D, Boidey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin. Infect. Dis. 2002; 34: 730-51.
10. Santolaya M, Alvarez M, Clinviles, et al. Prospective Evaluation of a model of prediction of invasive bacterial infection risk among children with cancer, fever and neutropenia.CID,2002:35;678-83.
11. Chessell M J and Leiper. Infection during remission induction in childhood leukemia. Arch Dis Child 1980; 55: 118-123.