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PATTERN OF INFECTIONS DURING INDUCTION THERAPY IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA: EXPERIENCE IN A TERTIARY CARE PEDIATRIC HOSPITAL OF BANGLADESH

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ABSTRACT

Background: Post-chemotherapy neutropenia in leukaemia patients is a most common complication since it makes these patients vulnerable to infections. So infections are the major cause of therapy associated morbidity and mortality in children with acute lymphoblastic leukemia during chemotherapy. **Methods:** This retrospective study conducted on post induction therapy acute lymphoblastic leukaemia children and analyzes the medical records of 237 ALL children. **Results:** Among all the 237 cases, 134(56.6%) patients acquired infections during induction therapy, Amongst the 134 infected patients, 63(47%) had clinically documented infection, 54(40%) had fever of unknown origin and rest of the 17(13%) had microbiologically documented infection. Almost 90% patients developed neutropenia with or without infection. Most of the infections occurred during the period of 8th to 17th day of induction. Ten percent patients died of Infection & bleeding-associated complications. **Conclusions:** Our study suggests that infection is the most frequently encountered chemotherapy-related complication in children with Acute Lymphoblastic Leukemia which leads to temporary withheld of scheduled chemotherapy. Gram negative infection is the more common than Gram positive infection. **Recommendation:** Prophylactic measures including proper isolation as well barrier nursing & maintenance of patient`s personal hygiene, appropriate management of infection using antimicrobials are very crucial to avoid as well as shorten the period of chemotherapy withheld and there by ensure better treatment outcome & reduce the chance of relapse of the disease in children with Acute Lymphoblastic Leukaemia.

KEYWORDS: Leukaemia, Induction, Infection.

INTRODUCTION

Acute Lymphoblastic Leukaemia is the most common malignancy in children worldwide. Chemotherapy and stem cell transplantation are the established therapeutic options for these children which causes neutropenia and carry an increased risk of infections.[1,2,3] Morbidity and mortality due to infections are common during chemotherapy for Childhood Acute Lymphoblastic Leukaemia. Bacteria, virus and fungus are the common causative organism.[4,5,6] Infections increase the risk of relapse due to interruption of treatment and the need for a decreased dose of the chemotherapeutic agents.[7] Over recent years, significant progress in antibiotics has improved the outcome of leukaemia treatment.[8] In spite of the progress in the development of antibiotics, infections are still a major concern for health care professionals in the management perspective of this disease.

The epidemiological studies of infections in hospitals have identified the most common germs and helped us **to** make a better prognosis after treatment of chemotherapy-associated infections. This is thanks to a correct prediction of the type of infection at the immediate onset of fever before culture results are available. On the other

hand, late - making and wrong predictions cannot only lead to spread of infection, but can also result in failure of chemotherapy, delayed completion of remission, and poor treatment outcome. So, we perform this study in our hospital to identify the pattern of infections and their antibiotic resistance amongst the patients of Bangladesh.

METHODS AND MATERIALS

This is a comprehensive review of retrospective data conducted in the Department of Pediatric Hematology and Oncology of Dhaka Shishu(Children) Hospital, Bangladesh Institute of Child Health of Dhaka, Bangladesh between January 2013 to June 2016. Total two hundred and thirty seven (237) Acute Lymphoblastic Leukaemia patients treated with Modifies UK ALL 2003 Protocol Regimen A & B according to risk categorization.

Diagnosis

After thorough clinical evaluation CBC with peripheral blood film and bone marrow study were done for morphological diagnosis of Acute Lymphoblastic Leukaemia including FAB type. Then immunophenotyping were done those are financially capable. Chest X-ray and other relevant investigations were done for risk stratification and management purpose.

Blood culture was done if patients presented with fever.

Risk Stratification

All the patients were stratified into Low risk(LR), and high risk (HR) on the background of parameters of risk categorization including age,sex,total count of WBC, CXR, immunophenotyping and morphological response after second shot of induction chemotherapy.

Chemotherapy

Administered according to Modified UK ALL 2003 (Regimen A & B) protocol as table I.

Table I: Modified UK ALL 2003 (Regimen A & B) protocol.

Chemotherapy Agents	Low Risk (Regimen A)	High Risk (Regimen B)
Inj. Vincristine	1.5 mg/m2/day ivon day 2, 9,16,23,30.	1.5 mg/m2/day ivon day 2, 9,16,23,30.
Inj.LAsperaginase	6000 iu/m2/day im/iv drip on day 2,4,6,8,10,12,14,16,18.	6000 iu/m2/day im/i.v drip on day 2,4,6,8,10,12,14,16,18.
Dexamethasone	6-10 mg/m2/day po in 3 divided doses from day 1to 28 & then tapering for 7 days.	6-10 mg/m2/day po in 3 divided doses From day 1to 28 & then tapering for 7 days.
Inj. Daunorubicine	N/A	25 mg/m2 iv infusion over 1 hour on day 2, 9, 16, 23.
Triple intrathecal therapy	Inj. Hydrocortisone(25 mg)+Inj. Cytosar(30 mg)+ Inj. MTX(age <2 years: 4 mg, 2 years 10 mg,3 years & above 12 mg) on day 1,8,15,22and 28.	Inj. Hydrocortisone(25 mg)+Inj. Cytosar(30 mg)+ Inj. MTX(age <2 years: 4 mg, 2 years 10 mg,3 years & above 12 mg) on day 1,8,15,22and 28.
6-Marcaptopurin	75 mg/m2/day orally from day 29 to 35.	75 mg/m2/day orally from day 29 to 35.
Cotrimoxazole	240-480 mg (according to body surface area) 12 hourly 2 days in a week.	240-480 mg (according to body surface area) 12 hourly 2 days in a week.

Follow-up

Clinical follow-up, complete blood count with blood film study twice in a week and other relevant investigations given to all the patients as per schedule after starting chemotherapy.

Assessment & management of complications including infection

Fever was defined as single axillary temperature of more than 38 degree centigrade or a temperature of more than 38 degree centigrade for four hours.

Infectious complication was defined as fever requiring antibiotic &/or antimycotic&/or antiviral treatment. Infectious episodes were categorized as microbiologically or clinically documented infection or as fever of unknown origin(FUO). Isolation of clinically significant organisms by culture of blood and specimen from other sites was the basis of microbiological documented infection. The term clinical documented infection was applied if fever was associated with clinical evidences of infection like pneumonia, oral ulcer, skin infection, septic arthritis, dysentery & loose motion, septicemia and otitis media and others. Fever of unknown origin was leveled when there was no of clinical radiological and microbiological evidences of infection.Neutropenia was defined as a neutrophil count of <500/cmm.

During clinical and laboratory follow-up fever, specific infective focuses, neutropenia and thrombocytopeniaetc were noticed and appropriate investigations like blood culture & others were done and management (Antimicrobials & other supportive) were given.

Management of infections were done by antimicrobials-initially broad spectrum antibiotic either single or in combination, then antiviral as well antifungal agents

were added empirically where indicated, Subsequently antibiotic was changed according to blood & other clinical sample culture & sensitivity pattern where implicated. Few patients were responded against infection on addition of antifungal agent.

Scheduled chemotherapy was postponed temporarily for about 5 to 12 days in presence of infections.

Data entry & Statistical calculation

The incidence and duration of fever, other infective focuses, neutropenia and temporary postponed of scheduled chemotherapy were recorded in pre-coded data sheet, and analysis was done by SPSS version 16.

RESULTS

Patient's characteristics

Among 237 patients the age of 10 patients were <1 year, of 180 patients were 1-10 years and of 47 patients were >10 years (Table II).

Table II: Age and Sex Distribution of study patients (n=237).

Characteristics	Patient evaluated
Number of patients	237(100%)
Age	
<1 year	10(04%)
1-10 Years	180(76%)
>10 Years	47(20%)
Sex	
Boy	154(65%)
Girl	83(35%)

Presenting Features

Almost 81% pediatric patients with Acute Lymphoblastic Leukaemia were presented with fever, 43% were with bleeding, 91% with pallor, 74% with organomegaly, 68% with lymphadenopathy in our study population. Laboratory investigations revealed total leucocyte count was <50,000/cmm in 68% and >50,000/cmm in 32%, Blast cells were detected in peripheral blood of 91%, ANC was <1000/cmm in 26% and >1000/cmm in 74% of our patients and none presented with blast cell in CSF (Figure I).

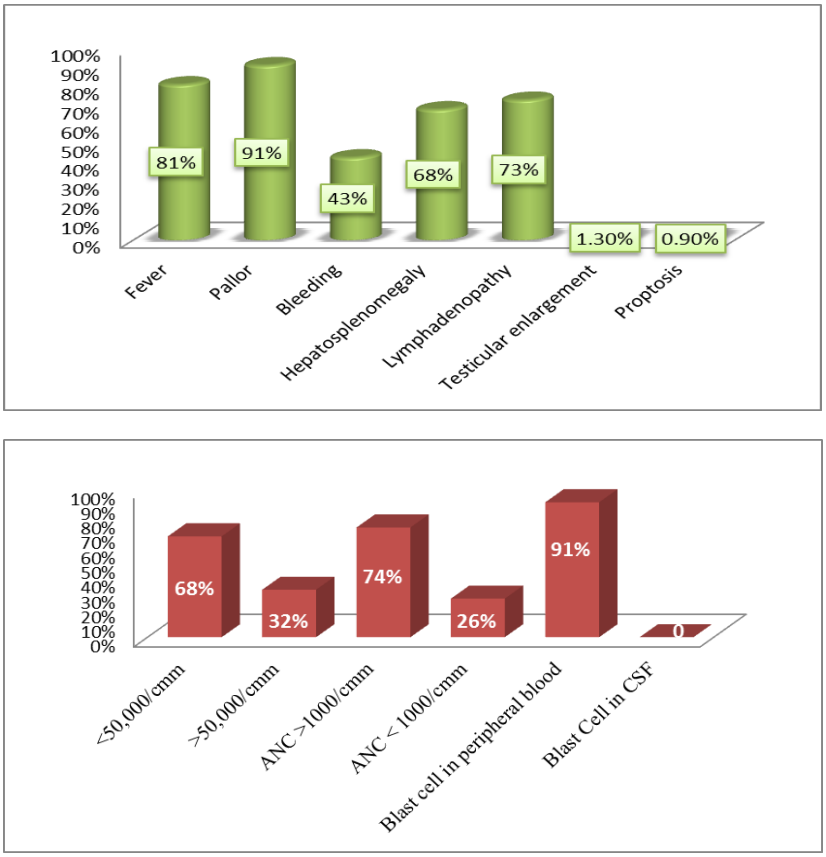

Figure I: Presenting features of study subjects (n=237).

Infections

According to infection criteria 134(56.5 %) oftotal 237 patients had clinically and microbiologically documented infections as well as fever of unknown origin. Infections were randomly seen in all the risk categorized groups including standard & high risk. The totalincidence of infection episode was 183 and range was 0-2in each patient during induction period.

Amongst the 134 infected patients, 63(47%) had clinically documented infection, 54(40%) had fever of unknown origin and rest of the 17(13%) had microbiologically documented infection (Figure II).

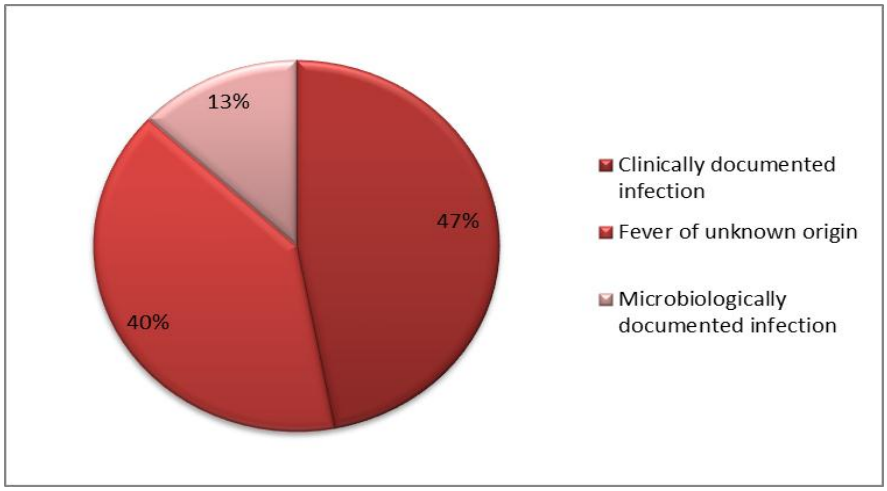

Figure II: Pattern of Infections (n=134).

Pattern and incidence of clinically documented infections are summarized in table III.

Table III: Type and sites of clinically documented infections (n=63).

Characteristics	Value in number	Value in percentage
Clinically documented infection	***63(237)***	***47%***
Oral ulcer	31(63)	49%
Pneumonia	20(63)	32%
Upper respiratory tract infection	23(63)	36.5%
Acute supporative otitis media	04(63)	06.3%
Diarrhea	07(63)	11%
Skin including I/V canulla site infection	13(63)	20.6%
Herpes Zoster & Simplex, Mumps	05(63)	08%
Pyogenic Meningitis	02(63)	03%

In the category of MDI, out of total 17 patients Gram negative bacilli were more frequent than gram positive bacilli. Among the Gram negative bacteria, Acinetobacter was most frequent organisms followed by Escherichia coli & Klebsiella pseudomonas. Most common site of isolation Gram negative bacteria is blood.

White Blood Cell count & relevant findings

Lowest leucocyte count and neutrophil percentage during induction period were 80/cmm and 10% respectively in most cases along with bone marrow depression. The median duration of leucopenia with neutropenia, fever and antimicrobials administration were 8, 7 and 10 days respectively (Table- IV).

Table - IV: Duration of neutropenia, fever, antimicrobials administration and temporary postponed of chemotherapy (n=134).

Parameters	Range	Median
Leucopenia & neutropenia	4 to 11 Days	8 Days
Fever	3 to 9 Days	7 Days
Antimicrobials administration	7 to 18 Days	10 Days
Temporary postponed of chemotherapy	5 to 12 Days	7 Days

Outcome of infections

Majority of infected patients responded to antibacterial, some patients needed antiviral and antifungal agents indicating presence of viral as well as fungal infection as there were no facilities for viral & fungal isolation microbiologically in our setup. Total 73 (40%) febrile

neutropenic episodes improved with first-line antibiotic therapy, modification to second or third-line antibiotic therapy was required in rest of the episodes.

Oral thrush was responded mostly by local as well systemic antifungal.

About 70% of infection episodes occurred during day 8 to day 17(around 10th day) of induction and rest of the 30% infection episodes occurred during the middle half of induction period.

Chemotherapy postponed temporarily in about 60% of the patients with infection and median period of chemotherapy postponed was 7 days (range 5 to 12 days).

Ten percent patients died due to infections refractory to antimicrobials including antibiotic, antifungal & antiviral and due to bleeding mostly intracranial.

DISCUSSION

The present study was to evaluate the infectious complications and risk factors during induction chemotherapy in childhood Acute Lymphoblastic Leukaemia. Febrile neutropenia is considered to be the major toxicity of chemotherapy which leads to overall morbidity like infections and mortality.[9,10] Infectious complications have been the most frequent manifestation of chemotherapy toxicity in children with Acute Lymphoblastic Leukaemia.[11-17] Our study also supports this finding. Thrombocytopenia along with bleeding manifestations was also common toxicity of chemotherapy.

This study showed that the rate of infection was 56.5 % which correlates with the other study done abroad,[5,18,19] but few other studies showed very high incidence of infection[20] and as low as 27%.[21] This variation of infectious complications might be related to environmental like isolation & barrier nursing, genetic factors,[22] chemotherapy protocol, ANC, use of medical devices like CVCs etc.

There were significant correlation of infection episodes with ANC at diagnosis & D8, D15& D22, duration of neutropenia ($P<0.001$), status of isolation & barrier nursing, use of central venous line and presence of thrombocytopenia along with bleeding manifestation. No correlation was found between infection and following variables: risk categorization, gender, immunophenotype, morphological type or treatment response.[22]

Among the all sorts of infectious episodes in our observation, clinically documented infections (CDI) were the most frequent (47%), there after fever of unknown origin (FUO) (40%) followed by microbiologically documented one (13%). These findings were similar to the some other studies[11,18,19] but lower than the few study (20), Some studies showed fever of unknown origin (FUO) was the most frequent[18,22] and few study showed microbiologically documented infection rate is more(33-40%).[20,23] These variations might be explained by meticulous clinical evaluation as well investigations.

Oral ulcer was the most frequent in the group of clinically documented infections (CDI) followed by upper respiratory tract infection and then pneumonia in our study. But some studies showed that pneumonia was the most frequent[7,18,20] and few other studies found the upper respiratory tract infection more common.[18] The incidence of oral ulcer was not addressed in most of other studies.

In the group of microbiologically documented infections, Gram negative bacteria are the most frequently isolated organism in our study in contrast to the Gram positive organism by other studies,[7,11,16,18,24,25] but similar to the finding of some studies.[19,20,22,23,26] This variation is might be due to differences of geographical, environmental as well as inherited host susceptibility factors to different organisms. Most common site of isolation of Gram negative bacteria in our study was blood which is similar to other study.[19] Among the Gram negative bacteria; Acinetobacter was most frequent organisms followed by Pseudomonas aerogenosa, Escherichia coli & Klebsiela pseudomonas which are commonly found in other non-oncological patients in our Hospital. Pseudomonas aerogenosa and E coli was the more common isolated organism by other study.[19,20,26]

Most of the infections (about 70%) were documented from day 8 to day 17(around 10th day). On the other hand neutropenia also persisted during this period. So it could be postulated that this neutropenic period is more susceptible for all sorts of infections. This finding is also supported by other studies.[22]

Our strategy was to postpone scheduled chemotherapy temporarily in every patient with infection over a period of 5 to 12 days (mean 7 days). This strategy is supported by other study done abroad.[22] To postponed scheduled chemotherapy temporarily might have negative impact on favorable outcome and could pave the way of relapse.

Total 73 (40%) febrile neutropenic episodes improved with first-line antibiotic therapy, modification to second or third-line antibiotic therapy was required in rest of the episodes. This finding is similar to few other studies.[19]

Our study also showed that mortality rate is low (10%) as in other studies[18] with the evidences that severe infection with septicemia & disseminated intravascular coagulation is the one of the common cause of death during induction phase.[27] Intracranial and other severe internal hemorrhage due to marked thrombocytopenia as well disseminated intravascular coagulation was another important cause of mortality.

CONCLUSION

Our study suggests that infection is the most frequently encountered chemotherapy-related complication in children with Acute Lymphoblastic Leukemia which leads to temporary withheld of scheduled chemotherapy. Gram negative infection is the more common than Gram positive infection. Fungal & viral infections are not uncommon.

RECOMMENDATION

Prophylactic measures including proper isolation as well barrier nursing, maintenance of patient`s personal hygiene, appropriate management of infection using antimicrobials are very crucial to avoid as well as shorten the period of chemotherapy withheld and there by ensure better treatment outcome & reduce the chance of relapse of the disease in children with Acute Lymphoblastic Leukemia.

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