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Original Articles

Infectious Complication During Induction Chemotherapy in Children with Acute Myeloid Leukemia- A Single Center Study

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Abstract:

Background: *Acute Myeloid Leukemia (AML) contributes to about 20% of leukemia. Most of the AML patients suffer from infection.*

Objective: *To evaluate the rate of infection, type and site of infection, organisms responsible for infection and to assess antibiotic sensitivity pattern and infection related mortality in AML.*

Material & Methods: *Newly diagnosed AML patients aged between 1-18 years, admitted to receive induction chemotherapy were enrolled. They received induction of chemotherapy according to Modified MRC' 12 in our department. Patient was on follow-up throughout the induction period and all the infectious complication occurred during this period were analyzed.*

Result: *A total of 38 episodes of infection developed in 34 patients in both cycles of induction (1.12 episodes/ patient). Among the total 38 episodes of infection, fever was the commonest clinical presentation. In both chemotherapy cycles, 7(18.4%) episodes of infection were culture positive. A total of 9 organisms were isolated of which most of them was gram-negative. Fever without focus was found in 15(39.5%) episodes. Profound neutropenia was present in 15(39.47%) episodes and profound neutropenic episodes were found to be culture positive in 5(71.4%) cases. About 6(17.5%) patients died during 1st cycle of induction.*

Conclusion: *Among children with AML, profound neutropenic cases had high susceptibility to culture positive infection. Further prospective study is needed to identify means to prevent infectious complication of AML patients receiving induction chemotherapy particularly in those with profound neutropenia.*

Keywords: *Acute Myeloid Leukemia (AML), Febrile Neutropenia, Septicemia.*

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Introduction

Acute leukemia is the most common childhood malignancy accounting for about 31% of all childhood cancer. Acute Myeloid Leukemia (AML) contributes to about 5% of all childhood malignancy.[1] A United Kingdom- based data reveals about 20% of all leukemia are AML.[2] It is not uncommon in our country as well; as less than 18 years of age, relative incidence of AML was 10%.[3] AML patients receive intensive multi-agent protocol based chemotherapy but limited availability of supportive care, the treatment outcome is not appreciable in our country. Infection is the major cause of morbidity and mortality in pediatric AML

patients. Due to the administration of highly intensive chemotherapy to AML patients most of them suffer from life- threatening infection. Infection not only contributes to mortality but it may lead to prolonged hospitalization, also delay in further chemotherapy administration, decrease quality of life and requirement of toxic and costly antimicrobial compounds.[4]

Reduction of neutrophil count due to the disease itself and chemotherapy induced myelosuppression causing invasion & proliferation of bacteria and also inhibition of the appearance of any inflammatory response.[5] In a study reported that 3.3 infectious episodes occurred per patient during the therapy period while worked on 405 AML children.[4] Gram-positive bacteremia is the most common infective organism.[4] It has also been shown that the use of intensified chemotherapy, the cumulative incidence of infection-related mortality is about 9% to 13%.[6]

Acute myeloid leukemia itself and patients who are in induction or not in remission both are independently high risk for adverse outcome of infection.[7] The combination of intensive chemotherapy and advances in supportive care can improve the survival of children with AML.[8]

Hygiene of the hospital environment, visitor restriction, ventilation of the ward all plays a very important factor for decreasing the growth of infective organisms in chemotherapy- induced neutropenic patient.

However, in our country, there is insufficient data regarding infection in AML patients. This study will help us to gather knowledge about the spectrum of this problem and would help us to know the common infections, causative organisms, antibiotic sensitivity pattern and outcome of these infections.

Material & Methods

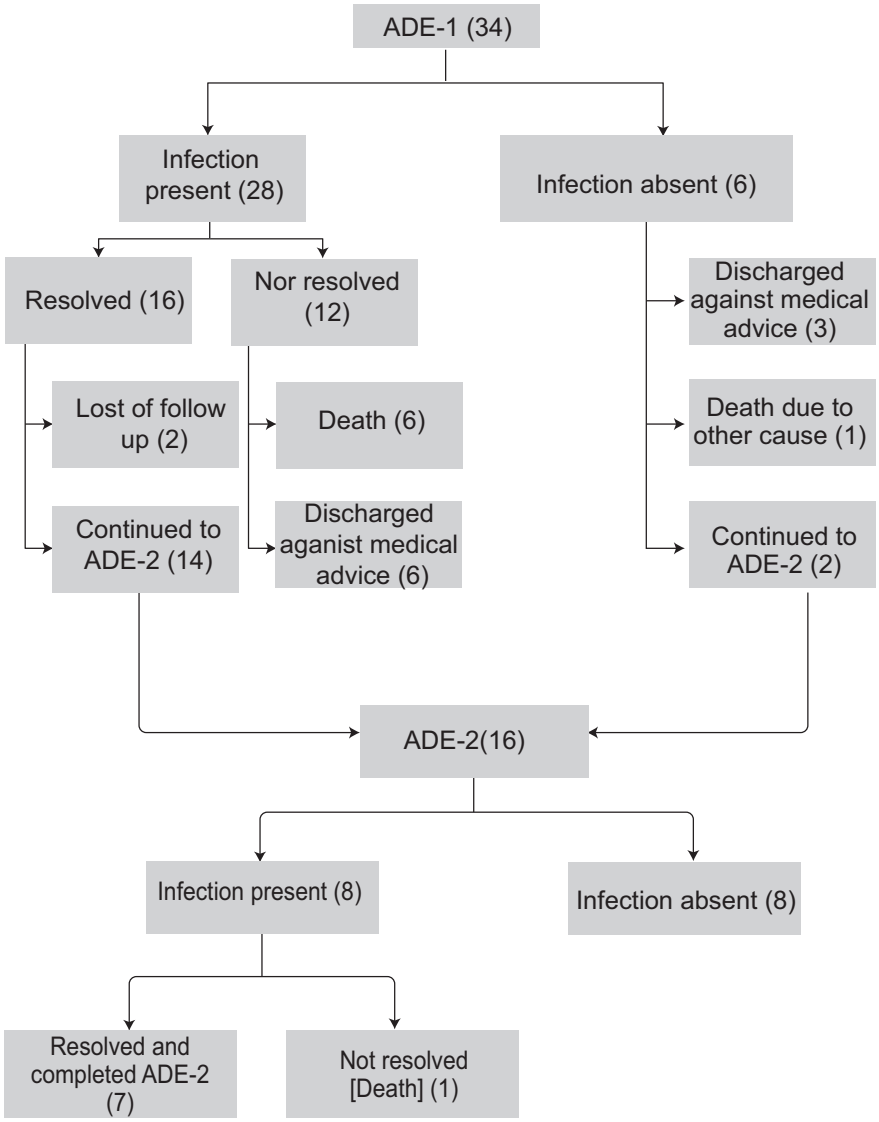
Newly diagnosed children with AML age 1 to 18 years who were initially admitted into the Department of Pediatric Hematology and Oncology, BSMMU for induction from May 2017 to August 2018 for therapy and who fulfilled the inclusion criteria were enrolled in to this study. Informed written consent from the parent or caregiver was obtained at the time of study enrollment. Ethical permission was taken from local ethical review committee. Data were collected using a preformed data collection sheet (questionnaire). Demographic data regarding age, sex and medical data regarding initial presentation during admission was collected from caregiver or parents. Clinical information by general physical and systemic examination was taken. Baseline investigations were done prior to starting of therapy. Chemotherapy was given to all patients with AML according to Modified MRC- 2012. Induction of chemotherapy consisted of 2 cycles known as ADE-1 and ADE-2. ADE-1 of Modified MRC-2012 consists of Inj. Daunorubicin, Inj. Etoposide and Inj. Cytarabine. ADE-2 of MRC- 2012 consists of Inj. Daunorubicin, Inj. Etoposide Inj. Cytarabine & Intrathecal chemotherapy with Inj. Cytarabinein both the cycles of Induction. All patients were provided general supportive management like hydration, alkalinization, allopurinol, phosphate binder, oral care, anal care etc, and patients were monitored regularly.

As per our departmental protocol, patients received packed red cell blood transfusion if Hb% was ≤8gm/dl and platelet transfusion if count was ≤10,000/mm3. Oro-nasal examination, perineum (peri-anal area and urethral orifice) urine, stool, cannula or procedure site examination and other physical examination were done routinely on each patient to identify any focus of infection. CBC parameter were done in each patient every alternative day to check Hb% (≤8gm/dl), platelet count (≤50, 000/mm3), and absolute neutrophil count(≤500/mm3). While any patient become symptomatic to infection or if any focus of infection found then septic work-up was sent including complete blood count with peripheral blood film, blood Culture (automated culture), chest radiography, urine R/E & C/S, stool C/S was done in case of diarrhea, C/S from I/V cannula site (when indicated), culture of wound, was done when indicated. For complete blood count and blood culture venous blood was collected. Automated Blood culture and sensitivity was done (BACTEC9240) using Becton Dickinson machine in all infectious episodes.

All data was recorded systematically in preformed data collection form & compiled. Statistical analysis test was performed by using SPSS, version 22. Data was presented in tabular or diagrammatical form. All the variables were qualitative so, relative risk (RR) were measured. A p-value <0.05 was considered as significant.

Results:

Among newly diagnosed 34 AML cases who were admitted to receive chemotherapy during this study period, 28 patients had infection during cycle ADE-1 and 8 patients during cycle ADE-2. No infection developed in 3 patients & 9 patients took discharge against medical advice at ADE-1 & 2 were lost to follow up after 1st cycle.



Algorithm of patient selection to follow-up

In a total of 34 patients, 23(67.65%) patients were in <10 year age group and 11(32.35%) patients were in ≥10years age group. Mean age was 8.13 ±4.60 years. Male to female ratio was 1.4:1. At diagnosis hyperleukocytosis (≥100,000/mm^3) was present in 6(17.6%) patients.

Thirty four patients who received cycle ADE-1, 28(82.4%) patients developed infection and 6(17.6%) patients had no infection; but in cycle ADE-2, 8(50%) patients were found to be infected out of total 16 patients who were able to receive the cycle.

Table I shows that in total of 38 infectious episodes' commonest clinical presentation was fever 35(92.1%). Cough 7(18.4%) & diarrhea 6(15.8%) were the next common clinical presentation. Abdominal pain, I/V cannula site infection, soft tissue swelling and chemosis were infrequent.

Table-I

Distribution of the study subjects by clinical presentation during infectious episodes (n=38)

Clinical presentation	Frequency (%)
Fever	35 (92.1)
Cough	7 (18.4)
Diarrhea	6 (15.8)
Abdominal pain	3 (7.9)
Infection at I/V cannula site	3 (7.9)
Chest pain	1 (2.6)
Soft tissue swelling	1 (2.6)
Chemosis	1 (2.6)

There was no association found to infection with hyperleukocytosis (≥100,000/mm^3) at presentation, RR 95% CI 1.015(0.682-1.50); P- value was insignificant (0.943).

Among the total 38 episodes, severe neutropenia (ANC<500/mm^3) was found in 25(65.8%) episodes. Increasing trend of culture positive infection was seen in profound neutropenic (ANCd"100/mm^3) patients but was not found to be statistically significant (P- value 0.08). (Figure-1)

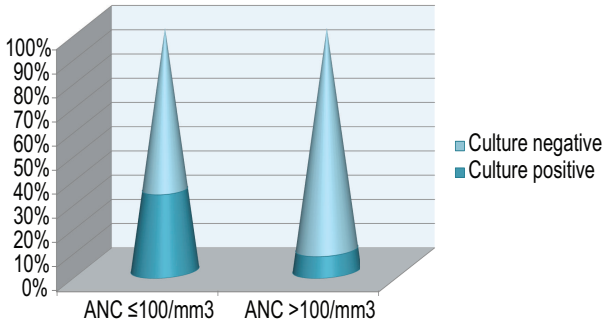


Fig.-1: *Association of culture positivity with profound neutropenia*

In all the episodes, 15(39.5%) were fever of unknown origin, 4(10.5%) episodes were septicemia, 4(10.5%) were gastro-intestinal symptoms,3(7.9%) had pnemounia. Other sites of clinically suspected infection were eye, urine and I/V cannula site infection. Combined focus of infection (blood &/or pulmonary &/or GIT &/ or UTI was present in 9 episodes of infection.

In the culture sensitivity pattern *Proteus, Enterobacterspp, Klebsiella, Pseudomonas spp, Staphylococcus spp,* and *E. coli* found in blood cultures. One urine culture were positive for *E. coli* (2.6%) and one I/V cannula site infection were positive Klebsiella (33.3%) (Table-II).

Enterobactereaceae were 100% resistant to amoxiclav, cefoxitin, cefuroxime, cefixime, ticarcillin. Ceftriaxone (80%), ceftazidime (85.7%), co-trimoxazole (80%), cefepime (75%) were resistant to Enterobactereaceae, around 66% organisms resistant to ciprofloxacin, meropenem, & gentamycin. Pipercillin-tazobactum was 40% resistant. Colistin & tigecycline were 100% sensitive & amikacin was 85% sensitive to the Enterobactereaceae.(Figure-2)

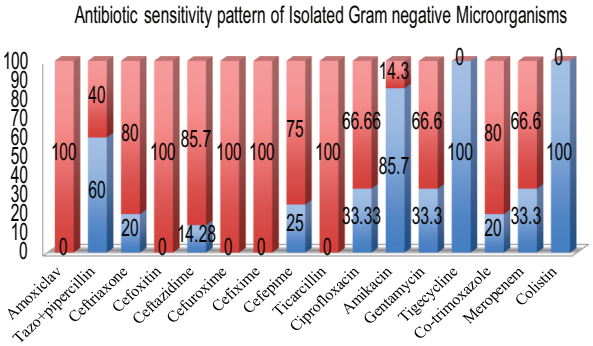


Fig.-2: *Antibiotic sensitivity pattern of isolated Gram negative microorganism.*

Methicillin resistant *Staphylococcus hominis was* isolated in two of the blood samples which are resistant to oxacillin, ciprofloxacin, & co-trimoxazole in both the samples but sensitive to vancomycin, linezolid, levofloxacin, tigecycline,ticoplanin.

Mean duration of neutropenia was 10.45±6.16 days and mean duration of fever 10.29±5.95 days.

A positive correlationis showing between the duration of Neutropenia with duration of fever. According to Pearson Correlation R=0.9483 and p-value is <0.00001. The result is significant.(Figure-3)

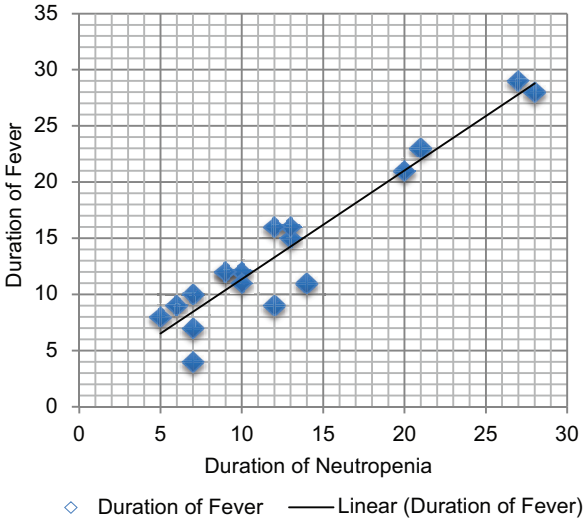


Fig.-3: *Scatter diagram of duration of neutropenia with the duration of fever correlation*

Out of total 34 patients, 22 had completed the chemotherapy cycle ADE-1, of them 16(72.7%) patients survived and 6 (27.3%) died. Sixteen patients who were able to complete cycle ADE-2 15(93.8%) survived & 1(6.3%) died. (Table.III)

Table-II
List of microorganism identified according to site infection

Site of infection	Positive	No. of episodes of infection	Microorganism
Blood (n=38)	7(18.4%)	1	*Proteus*
		1	*Enterobacter spp.*
		1	*Klebsiella*
		1	*Pseudomonas spp.*
		2	*Staphylococci hominis.*
		1	*E. coli*
Urine (n=38)	1(2.6%)	1	*E.coli*
Stool (n=8)	0	0	
Swab form local wound			
[I/V cannula site] (n=3)	1(33.3%)	1	*Klebsiella*

Table-III
Infectious episodes and outcome in two different cycles

Induction cycle	n	Outcome		RR 95% CI	p-value
		Death	Improved		
ADE-1	22	6(27.3%)	16(72.7%)	4.36(0.58- 32.79)	0.15
ADE-2	16	1(6.3%)	15(93.8%)		

p-value reached from relative risk= not significant

Discussion:

Infection in pediatric acute myeloid leukemia is the commonest and dreadful condition, which need immediate medical attention because it may hasten death of AML patients before remission is achieved. AML is a bone marrow disease, causing abnormal proliferation and differentiation of myeloid precursor and ultimately hamper defense mechanism of the body.[1] So, after receiving highly intensive myelosuppressive therapy most of the AML patient suffers from infection. Both the cycles of induction, out of 34 AML patients' total 38 episodes of infection developed. It was about 1.12 episodes of infection per patient. A total of 34 patients, 28(82.4%) patient developed infection during ADE-1 and out of 16 patients, 8(50%) patients developed infection during ADE-2 cycle of induction. Bochennek et al.[4] found 3.3 episodes of infection per patient while he worked on 405 AML children; their rate of infection was higher than the present study probably as they covered the full period of chemotherapy not merely the initial induction period.

Prolonged and profound neutropenia is the major cause of infection in immune-compromised patients; as AML patients receive highly intensive myelo-suppressive therapy thus ultimately leads to invasion and colonization of different pathogens as well as opportunistic microorganism that complicates the outcome of the AML patients and reduces survival rates. In this study, we found a total of 38 episodes of infection; of these, 25 (65.8%) episodes were associated with severe neutropenia and among the severe neutropenic episodes 15(60%) were found to be profound neutropenic. A significant positive correlation was found with duration of neutropenia and duration of fever.

In this current study, culture- positive bloodstream infections were found in 18.4% episodes. A study conducted in this department on febrile neutropenic ALL children had found 6(20%) culture positive episodes.[9] Subburaj et al.[8] found in about 19% culture-positive bloodstream infections and also reported that 10% to 30% bloodstream infection found in other

studies. Both studies are consistent with the present study finding. For the purpose of this study, multiple culture or 2nd culture was not sent in most of the episodes due to economic constraints of the patients, probably that might be the cause of less culture positivity in our study findings.

In this study, it was found that gram-negative organisms were 77.7%. *E.coli, Proteus spp., Enterobacter spp., Pseudomonas spp., Klebsiella spp*. were gram- negative organisms. Ahmed et al.[9] also found a high rate of gram-negative infection in febrile neutropenic ALL children during working in this department. Lima et al.[10] reported that among the causative microorganism most of the infections occurred with gram-negative bacteria. Commonly observed organisms were *Escherichia coli, Pseudomonas aeruginosa* and less commonly gram-positive organisms; especially *Staphylococcus epidermidis & Staphylococcus* aureus.[11] reported a higher incidence of gram -negative organism (57%) than gram-positive organism (34%). Biswal et al.[12] and Subburaj et al.[8] also reported that gram-negative bacilli were the commonest cause of infection in febrile neutropenic AML patients. All the above study result is consistent to the present study findings.

But in contrast to the present study Bochannek et al.[4] has reported gram-positive bacteremia most frequently. Cumulative incidence of *Streptococcus viridians* related bacteremia found >40% with use of high-dose cytarabine and mucositis.[2] The cause of more gram-positive infection probably due to prophylactic use of ciprofloxacin at the completion of chemotherapy cycle, which inhibited gram-negative infection, but in this present study, the patients did not receive any prophylaxis after the ending of each chemotherapy cycle and also not received high dose cytarabine ($\geq$1000 mg/m^2 BSA). More gram-negative infection than gram-positive infection was found in this study. Actually, isolates and their sensitivity may vary from center to center.

Higher rate of use of intravenous line made the patient liable to infection with gram-positive organism caused by the patient's own endogenous flora. In this study three patient developed wound infection at I/V cannula site; of them, one patient was found to be culture positive with *Klebsiella spp.* Usually, wound infections occur with gram-positive organisms*;* since AML patients are immunocompromised, it is likely gram-negative bacteria can be found in the wound or probably contamination from his own blood. Ki. et al.[13] also reported that although soft- tissue infection with gram-positive bacteria is higher but gram-negative soft tissue infection is not uncommon at all.

This study also demonstrated an increasing trend of culture positivity in profound neutropenic ($\leq$100/mm^3) patients than neutropenia with neutrophil count >100/mm^3. Osmani et al.[11] evaluated over 156 patients of febrile neutropenia with bacteremia. They found that 74% of bacteremia was observed in high-risk patients (<100/mm^3) and mortality was also slightly more in high-risk febrile neutropenic cancer patients. Subburaj et al.[8] concluded that most of the patients they lost had suffered from sepsis with prolonged neutropenia. Lal et al.[14] found that prolonged duration of hospital stay is the risk factor for culture positive infection in profound neutropenic episodes.

No such relation was seen in any previous studies between the two-induction cycles of MRC-12.We found between the cycles, more patients had suffered from infection in 1st cycle of induction (82.4% vs 50%) &treatment-related death also more in ADE-1 then ADE-2 (85.71% vs 14.28%). Probably, in leukemia a normal bone marrow is replaced with blast cell, and these cells cannot function as normal cell for the defense of the body against microorganism but after receiving chemotherapy at 1st induction cycle when marrow recovery occurs with normal population of cells as well in peripheral blood. Although there is chemotherapy-induced myelosuppression but there is less chance of prolonged and severe infection after the recovery of bone marrow.

The present study also showed that among the isolated organism, all the gram–negative organisms were resistant to cephalosporins except *Enterobacter* and *Pseudomonas. Pseudomonas* was only sensitive to *Cefipime* and *Enterobacter* was sensitive to 3rd generation cephalosporins. Most of the gram-negative organisms were sensitive to protein synthesis inhibitor; Amikacin was sensitive to 85% gram-negative microorganisms. This finding is consistent with the study done by Babu et al.[16] It is really alarming that Meropenem was resistant in 66.7% of micro-organisms. But Ahmed et al.[9] have found 100% sensitivity to meropenem 9 years back in febrile neutropenic ALL children in this department. Study done by Lakhmaiah et al.[15] demonstrated those 85% gram-negative organisms were sensitive to

carbapenem. Both the above study results differ from present one; probably due to wide empirical use of Meropenem in our ward. Gram-positive organisms were resistant to cell wall inhibitor and beta-lactam resistant antibiotic but sensitive to teicoplanin, linezolid, gentamycin, and tigecycline.

It is also alarming that most of the microorganisms were resistant to cephalosporin except 4th generation cephalosporin. Babu et al.[16] also found high degree of cephalosporin resistance in febrile neutropenic patients in his study.

High rate of prolonged and profound neutropenia found in this study and infection related death was also high. Only 16(42.1%) patients received both the cycles of induction. So it was assumed that high suspicion of infection; early intervention and proper location of treatment (in general wards/ Intensive Care Unit) may combat this dreadful condition.

The study identifies a high rate of infection particularly during ADE-1. Severe and prolonged neutropenic cases had a higher rate of infection and mortality. Babu et al.[16] also reported that prolonged neutropenic episodes are more prone to develop infection. Gram-negative organisms are the most commonly identified causative agents. Further study is needed that focus on prevention and optimization of treatment of the problem.

Conclusion

AML patients mostly suffered from prolonged and profound neutropenia. The high rate of infection and infection related death was occurred during the neutropenic episodes and about 15(39.5%) episodes were found fever of unknown origin. Although there are multiple limitations, further study is needed to prevent and optimization of these infectious events.

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