Comparison between Clinical and Bacteriological Profile of Febrile Neutropenic and Non Neutropenic Pediatric Leukemic Patients

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Abstract

Background: Infection is an important cause of morbidity and mortality in children with leukemia. To improve the quality of care and survival, it is important to understand the clinical presentation and bacteriological profile during febrile episodes of these patients. The aim of this study was to compare the clinical presentation and bacteriological profile of febrile neutropenic and non-neutropenic pediatric leukemic patients.

Materials and methods: This was a cross sectional observational study conducted at Chittagong Medical College Hospital (CMCH) over a period of 12 months. Study population (n=60) were all hospitalized pediatric leukemic patients who were febrile and on anticancer chemotherapy. By purposive sampling two groups were made. Group A (n=30) was febrile neutropenic and group B (n=30) was febrile non-neutropenic patients. The Clinical presentation, bacteriological profile and antibiotics susceptibility patterns in both groups were analyzed.

Results: Mean (±SD) age of the patients was 6.41±3.05 years. Acute Myeloid Leukemia (AML) patients were high in Group-A (60%) and Acute Lymphoblastic Leukemia (ALL) patients were high in Group-B(80%). Gastroenteritis, skin infection and sepsis were more in group A than group B ($p<0.05$). Upper respiratory tract infections were significantly more in group B than group A ($p<0.05$). Among 60 samples, 7 (12%) were blood culture positive for bacteria. The isolated organisms were E. coli, Klebsiellaspp, Salmonella, Staph aureus and others. Amikacin Meropenem and Vancomycin were the effective agents.

Conclusion: Febrile neutropenic episodes were more common in AML patients undergoing chemotherapy. Gram negative sepsis, gastroenteritis and skin infection were high in febrile neutropenia, but upper respiratory tract infections were high in febrile non neutropenia.

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Introduction

Leukemia is the most common malignancy of pediatric populations, representing about 35% of all childhood cancers. Intensified antileukemia treatment and invasive procedures increases susceptibility to infections. Bacterial infections are common and potentially serious complications of cancer treatment.[1] Despite effective antimicrobial treatment of infections, this still is the leading cause of treatment-related morbidity and mortality.[2]

Intense chemotherapy with cytotoxic drugs usually results in myelosuppression and a resultant high risk of neutropenia.[3] Chemotherapy-Induced Neutropenia (CIN) is the most serious hematological toxicity of cancer chemotherapy. It is associated with the risk of life-threatening infections, as neutropenia blunts the inflammatory response, allowing bacterial multiplication and invasion.[4] In neutropenic patients, infection may occur with minimal signs and symptoms, and may rapidly progress to sepsis with multi-organ failure. Fever during chemotherapy induced neutropenia can be the first sign of bacterial infection and therefore requires prompt and careful attention. The most important sites of infection in these patients are oral mucosa, pharynx, lower esophagus, lung, skin including sites of vascular access, bone marrow aspiration site, tissue around the nails, perineum and anus. These usually arise during the first course of induction chemotherapy, and are directly proportional to the duration and severity of the neutropenia. Pediatric leukemic patients with fever, even when not neutropenic, are known to be at an increased risk of infections.[5] Different studies conducted in home and abroad shows,clinical presentation and bacteriological profile of febrile neutropenic and non-neutropenic pediatric leukemic patients that differ from place to place. Karanwal et al observed that, the most common presenting features in febrile neutropenia were fever (95.7%) followed by respiratory

symptoms (29.6%) mucosa damage (6.1%) Gastro intestinal diseaes (6.1%) consciousness disturbance (1.7%) and rash (1.7%).[6] In Pakistan, Taj M. et al.in their study on febrile neutropenic subjects who suffered pediatric hematological malignancy found clinically documented infections were (46.01%) and microbiologically documented infections were (35.39%), while no focus was identified in (18.58%). Gram negative infections accounted for (85%) and Escherichia coli was the commonest isolate.[7] Gram positive microorganisms were isolated in (15%) cases and most common was Staphylococcus aureus.

But, there are less data in our setting regarding clinical presentation, bacteriological spectrum and antibiotics sensitivity pattern of pediatric leukemic patients during febrile episode. So, the present study was aimed to compare the clinical presentation, bacteriological profile and antibiotics sensitivity pattern of febrile neutropenic and febrile normal neutropenic pediatric leukemic patients.

Materials and methods

This cross sectional analytic study were carried out in the Department of Pediatric Hematology and Oncology, Chittagong Medical College Hospital, from July 2017 to June 2018. Sixty hospitalized pediatric leukemic patients were included by purposive sampling.

Inclusion criteria:

i) Child up to 12 years of old.

ii) Diagnosed case of leukemia either ALL or AML.

iii) Patient who was on anticancer chemotherapy, UKALL protocol for ALL and MRC-97 protocol for AML.

iv) Patient who got admitted for fever or developed fever during hospital stay for chemotherapy.

Exclusion criteria:

i) Patient who had received antibiotics 72 hours before admission.

ii) Those who had absolute neutrophil count (ANC) more than 500 / mm^3 but less than 1500 / mm^3 of blood.

Study was carried out after prior approval of the Ethical Review Committee of Chittagong Medical College. Patient who has enrolled for the purpose of the study, informed written consent was taken from parents or guardian. In case of older child, assent was also taken.

Sixty patients fulfilled the above criteria were evaluated thoroughly by detailed history, physical examination and laboratory investigation (CBC, Blood culture and sensitivity for bacteria). For the purpose of data analysis study subjects were divided into two groups- Group A: This group (n=30) included ANC below 500/ mm^3 of blood and Group B: This group (n=30) included ANC above 1500/mm^3 of blood.

Approximately 5 ml of venous blood was collected just after clinical examination. Blood for CBC was carried out by automated hematology analyzer (XS-800i, Sysmex, Japan). Blood culture for bacteria was done by automated (BACTEC) blood culture system (Organon Teknika, USA). Antibiotic susceptibility testing was interpreted by disc diffusion method. Results were interpreted according to the Clinical and Laboratory Standards Institute's guide line.

All the necessary information and clinical data were collected from each of the study population and were recorded systematically in a predesigned questionnaire. All data were analysis using windows based computer software devised with SPSS-23 (SPSS Inc, Chicago, IL, USA). Group comparison of data were evaluated by using statistical methods- Chi square test, Fisher's exact test, t-test The results were presented in tables and pie charts The statistical terms included in this study were mean and median for continuous data and frequency, percentage for categorical. Statistical significance was set at $p<0.05$.

Operational Definition

Neutropenia: The definition of neutropenia was according to the number of patients' Absolute Neutrophil Count (ANC). Neutropenia was defined as ANC < 1500 / µL.[8]

- Mild neutropenia is ANC from 1000-1500 / µL
- Moderate neutropenia is from 500-1000/µL
- Severe neutropenia is ANC < 500 / µL.

Febrile Neutropenia: Febrile neutropenia was defined by the following criteria.[8] A single oral temperature 38.3 ^{0}C (101.0^0 F) or an oral temperature 38.0^0 F (100.4^0 F) sustained for >1 hour or that occurs twice within a 24 hour period. An ANC < 500 / mm^3 or ANC <1000 / mm^3 expected to decrease to <500 /mm^3 over the subsequent 48 hours.

Sepsis: The systemic inflammatory response to an infectious processwas defined as sepsis.[9]

Skin Infection: Skin infection was defined as inflammation of skin, uncomplicated with typical superficial infections and complicated infections usually with deep involvement.[10]

Oral Mucositis: Erythematous and ulcerative lesions of the oral mucosa was defined as oral mucositis.[1]

Gastroenteritis: defined as inflammation of the gastrointestinal tract - stomach and small intestine, symptoms included diarrhea, vomiting, and abdominal pain.[11]

Results

Chemotherapy Regimens of Leukemia

Patients were diagnosed cases of acute leukemia on chemotherapy. Patients with ALL were treated with UKALL regimen- A and regimen- B, AML were treated with MRC- 97 protocols. Their distribution was shown in Figure I.

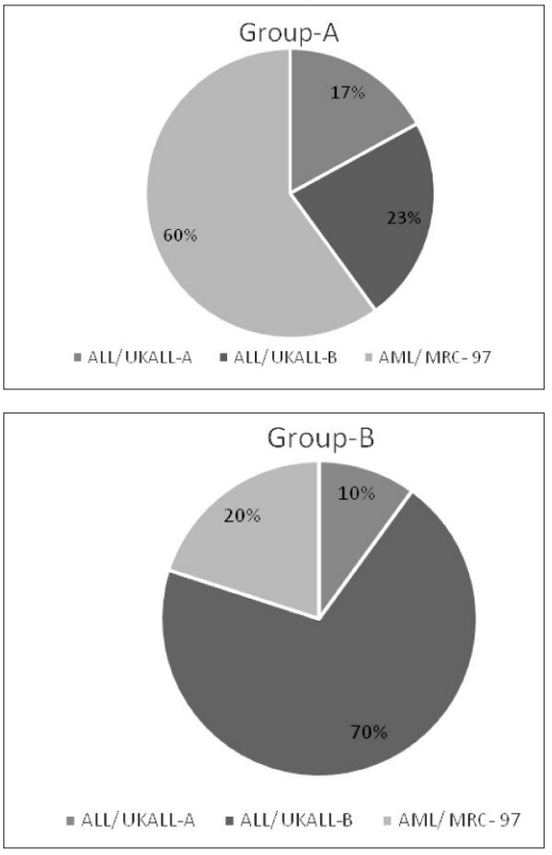

Fig 1 Chemotherapy regimens of leukemia by study groups

Group A: Febrile neutropenic, Group B: Febrile non neutropenic ALL: Acute Lymphoblstic Leukemia. AML: Acute Myeloblastic Leukemia. UKALL: United Kingdom Acute Lymphoblstic Leukemia. MRC: Medical Research Council.

Major Symptoms of the Patients

Dyspnea, diarrhea, and abdominal pain were significantly more prevalent among Group- A compared to Group-B ($p< 0.05$).Runny nose was significantly more prevalent among Group- B compared to Group- A ($p< 0.05$) (Table I).

Table I Distribution of the major symptoms of the patients by groups

Symptoms	Study group		p value
	Group – A (n=30)	Group – B (n=30)	
Cough	18 (60%)	15 (50%)	0.82 NS
Runny nose	8 (27%)	17 (57%)	0.047 S
Dyspnea	8 (27%)	2 (7%)	0.03 S
Diarrhea	7(23%)	3 (10%)	0.049 S
Vomiting	6 (20%)	2 (7%)	0.243 NS
Abdominal pain	7 (23%)	1(3%)	0.04 S
Dysuria	6 (20%)	3 (10%)	0.143 NS
Bleeding	6 (20%)	5 (17%)	0.243 NS

Group A: Febrile neutropenic, Group B: Febrile non neutropenic, NS: Not Significant, S: Significant.

Major Signs of the Patients

Respiratory (Crepitation, Rhonchi) GIT (Abdominal distension, tenderness, absence of bowel sound) skin infection were prominent signs among the patients. Most of these were significant among the Group-A compared to Group-B (Table II).

Table II Distribution of the signs of the patients by group.

Signs	Study group		p value
	Group-A (n=30)	Group-B (n=30)	
Dehydration	6 (20%)	2(7%)	0.06 NS
Lymphadenopathy	20 (67%)	14 (48%)	0.35 NS
Oral mucositis	7 (23%)	4(13%)	0.06 NS
Skin infection	6(20%)	1 (3%)	0.04 S
Crepitation	8 (27%)	2 (7%)	0.038 S
Rhonchi	8 (27%)	3 (10%)	0.04 S
Abdominal distension	7 (23%)	1 (3%)	0.02 S
Abdominal tenderness	6 (20%)	1(3%)	0.04 S
Hepatomegaly	5 (17%)	4 (13%)	0.195 NS
Splenomegaly	5 (17%)	3 (10%)	0.448 NS
Absence of bowel sound	6 (20%)	1 (3%)	0.04 S

Group A: Febrile neutropenic, Group B: Febrile non neutropenic, NS: Not Significant, S: Significant.

Disease Profile

Sepsis, gastroenteritis and skininfectionweresignificantly more prevalent among Group- A compared to Group-B ($p< 0.05$).Upper respiratory tract infectionsweresignificantly more prevalent among Group-B compared to Group- A($p<0.05$) (Table III).

Table III Disease profile of the patients by groups

Signs	Study group		p value
	Group A (n=30)	Group B (n=30)	
Sepsis	18 (60%)	4 (13%)	0.035 S
Gastroenteritis	7 (23%)	3 (10%)	0.049 S
Skin infection	6(20%)	1(3%)	0.04 S
Oral mucositis	7(23%)	4(13%)	0.06 NS
URTI	8(27%)	17 (57%)	0.047 S
Tonsillitis	6 (20%)	3 (10%)	0.448 NS

Group A: Febrile neutropenic, Group B: Febrile non neutropenic.

URTI: Upper Respiratory Tract Infections, NS: Not Significant, S: Significant.

Among the 60 respondents, 7 (12%) were positive for blood culture. Culture positivity was higher among Group-A than Group-B. It was significant (p=0.04) (Table IV).

Table IV Frequency of culture positivity by groups

Culture result	Study group		Total (n=60)	p value
	Group- A (n=30)	Group- B (n=30)		
Positive	6 (20%)	1 (3%)	7 (12%)	0.04 S
Negative	24 (80%)	29 (97%)	53 (88%)	

Group A: Febrile neutropenic, Group B: Febrile non neutropenic, S: Significant.

In 7 blood culture positive cases, 5(71%) gram-negative agents and 1(14%) gram-positive agents were isolated in Group-A, 1 (14%) gram-negative agents were isolated in Group-B. Gram-negative and Gram-positive microorganism were shown (Table V).

Table V Type of organisms by Group

Type of organisms		Group- A (n=6)	Group- B (n=1)
Gram positive	Staphylococcus aureus	1 (16%)	0 (0%)
Gram negative	Klebsiella species	1 (16%)	1 (100%)
	Escherichia coli	2 (33%)	0 (0%)
	Salmonella	1 (16%)	0 (0%)
	Other (Enterobacter group, not defined)	1 (16%)	0 (0%)

Group A: Febrile neutropenic, Group B: Febrile non neutropenic, MDI: Microbiologically Documented infection.

Discussion

In present study, febrile neutropenic episodes were more in AML patients on MRC 97 chemotherapy and febrile non neutropenic episodes were more in ALL patients on UKALL regimen B chemotherapy (Fig 1). Jacob et al. also found that AML is the most common cause of Febrile neutropenia.[12] Among the therapeutic regimens of acute leukemia, AML patients receive more cytotoxic and intense chemotherapy than ALL patients, and they are high risk group for development of febrile neutropenia.[1]

Runny nose was significantly more prevalent in group- B (Table I) and respiratory and skin infection were significantly prevalent in Group-A (Table ii) . Chemotherapy induced neutropenia is the most common risk factor for infection in patients with leukemia.[6] Variable sites of infections may be associated with different invasive procedures that provide a portal of entry for pathogens.[13] High incidence of mucositis was reported in neutropenic children, possibly due to their higher mitotic index in the oral mucosa compared with adults, with a higher risk of mucositis with chemotherapeutics.[14]

In this study, gastroenteritis, skin infection, and sepsis were statistically more in febrile neutropenia, upper respiratory tract infections were significantly more in febrile non neutropenia (Table III). Which is similar to Taj M.et al. where 52% of febrile neutropenia were associated with sepsis.[7]

Gram-negative organisms were the predominant cause of infections in febrile neutropenia and febrile non neutropenia in our study (Table V). Another study reported that in children with cancer, Viridans Streptococci, Pseudomonas spp. and Esch.coli are the most frequently isolated organisms.[14] Tezcan et al. also observed that among children with neutropenia and cancer, Staphylococci and Escherichia coli are the most commonly isolated organisms.[15]

Infections due to Gram negative bacteria with high resistance to different classes of antimicrobials are common in cancer patients.[16] In this study the most effective antibiotics against gram negative bacteria were Amikacin, Meropenem, and against gram positive bacteria was Vancomycin. But the microbiological profile of our study was too small to make a comment on the sensitivity pattern.

Limitations

Regarding isolation of organisms, only blood culture for bacteria was done.

Conclusion

Febrile neutropenic episodes were more in AML patients on chemotherapy and febrile non neutropenic episodes were more in ALLpatients on UKALL, regimen B chemotherapy protocol. Sepsis with gram negative bacteremia,gastroenteritis and skin infection were high in febrile neutropenic pediatric leukemic patients. But, upper respiratory tract infections were high in febrile non-neutropenic pediatric leukemic patients. Amikacin, Meropenem and Vancomycin were the most effective antibiotics.

Recommendations

As bacterial infections is the common cause of treatment related death in case of leukemia, so early detection and prompt treatment of infection is very important aspect of leukemia management. Continuous surveillance of locally prevalent pathogens and their susceptibility patterns is essential for formulation of therapeutic regimens of chemotherapy induced febrile patients. A multicenter prospective observational study with a larger sample size with the aim to assess risk factors and outcome is necessary to meet this need.

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Contribution of authors

M-Conception, data collection, manuscript writing & final approval.

AKM RK-Concept, design, critical revision & final approval.

RU-Data analysis, interpretation of data & final approval.

Disclosure

Al the authors declares no competing interest.

References

1. Kuo FC, Wang SM, Shen CF, Ma WJ, Ho TS, Chen JS et al. Blood stream infections in pediatric patients with acute leukemia: Emphasis on gram negative bacterial infections. J of microbiology, immunology and infection. 2015; 8 (1): 13-14.

2. Christensen, MS., Heyman, M., Möttönen, M., Zeller, B., Jonmundsson, G., Hasle, H et al. Treatment related death in childhood acute lymphoblastic leukaemia in the Nordic countries: 1992-2001. Br J Haematol .2005;131(1): 50-58.

3. Lie, SO., Abrahamsson, J., Clausen, N., Forestier, E., Hasle, H., Hovi, L et al. Long-term results in children with AML: NOPHO-AML Study Group-report of three consecutive trials. Leukemia. J Lab Physicians. 2005;19(12):2090-2100.

4. Smiley, Katherine, MK.,Forestier, E., Hasle, H., Hovi. Etiology and clinical course of febrile neutropenia in children with cancer. J PediatrHematolOncol. 2015;31 (4): 623-629.

5. Mullen, Buchanan, GR. Early hospital discharge of children with cancer treated for fever and neutropenia: Identification and management of the low-risk patient. J ClinOncol. 2004;8(12): 1998–2004.

6. Karanwal, Kumar, S., Aditya, HG., Isolation, identification and profile of antibiotic resistance of bacteria in childhood febrile neutropenia patients.J Pediatr.2013; 9(7):514-521.

7. Taj, M., Farzana, T., Shah, T., Maqsood, S., Ahmed, S. S. Shamsi, T.S., et al. Clinical and Microbiological Profile of Pathogens in Febrile Neutropenia in Hematological Malignancies: A Single Center Prospective Analysis. Journal of Oncology. 2015 ;19(4):537-544.

8. Agrawal, A., Feusner, J. Supportive Care of Patients with Cancer' In: Lanzkowsky, P., Lipton, JM., Fish, JD (eds) Lanzkowsky's Manual of Pediatric Hematology and Oncology, London: Elsevier Inc. 2016;620- 628.

9. Stoll, B., J., Shane, A., L., Infections of the Neonatal Infant, In: Robert, M, K., Bonita, F, S., Joseph, W, S., Nina, F, S., Richard, E, B., (eds) Nelson's textbook of Paediatrics, Canada: Elsevier Inc. 2016; 909- 917.

10. Esposito, Bassetti, E., Concia, G., Simone, F., Rosa, P.,Grossi, A et al. Diagnosis and management of Skin and Soft-Tissue Infections (SSTI). A literature review and consensus statement: An update. Journal of Chemotherapy. 2017;131(1):50-58.

11. David, Vivas, JR.,Potro, E., Diaz-Mediavilla, J., Alvarez, A. Predominance of gram-positive microorganisms as a cause of septicemia in patients with hematological malignancies. Infect Control J.2017;15 (3): 10-14.

12. Jacob, Lin, H. Febrile neutropenia in pediatric hematological malignancies: Clinical and microbiological profile and outcome in high risk patients- A single center study in South india. J Lab Physicians.2014; 7 (1): 116-120.

13. Yasufuku, Shigemura, T., Tanaka, K., Arakawa, S., Miyake, H., Fujisawa, M et al. Risk factors for refractory febrile neutropenia in urological chemotherapy. J Infect Chemo.2013; 19 (2): 211-216.

14. Hana, Patricia, MF., Katherine, MK., Kumar, S., Aditya, HG. Etiology and clinical course of febrile neutropenia in children with cancer. J PediatrHematol Oncol.2009; 31 (4): 623-629.

15. Tezcan, Kupesiz, A., Ozturk, F. Episodes of fever and neutropenia in children with cancer in a tertiary care medical center in Turkey. Pediatr Hematol Oncol.2006; 23 (3): 217-229.

16. Almaziny, M.A.,Merabi, Z.,Rahman, M. Isolation, identification and profile of antibiotic resistance of bacteria in childhood febrile neutropenia patients European Journal of Experimental Biology.2014;4(2):1-6.