

Sites of Infections and choice of antimicrobial drugs in acute leukemia in Indian Children

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Abstract: In this study children with acute leukemia were evaluated for the incidence and sites of infection, correlation with absolute neutrophil count, causative organisms and to standardize the initial empirical antimicrobial therapy as per culture sensitivity pattern. A total 40 children in the age group 6 month to 12 year with acute leukemia relapse were included in this study. A total 82 infectious episodes including 61 febrile episodes were investigated for infectious etiology. We found that the frequency of infections increased significantly with the degree of immunocompromisation specially neutropenia (ANC < 500/cmm). The skin and soft tissue was the commonest site of infection (26.83%), followed by respiratory tract (21.95%). *Staphylococcus nonhemolytic coagulase-negative* (34%), followed by *Klebsiella* (17%) were the most common organisms isolated from blood. *Staphylococcus non-hemolytic coagulase-negative* was also the commonest isolate (26%) from other sites of infection. Most strains were sensitive to Cloxacillin, cephalosporin and aminoglycosides. For the treatment of febrile episodes, empirical use of beta-lactamase resistant penicillin e.g. Cloxacillin or cephalosporin combined with an aminoglycosides with a broad spectrum antifungal like fluconazole in selective cases at the first sign of infection is recommended.

Key words: Infection, acute leukemia, children, antimicrobial therapy.

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I. Introduction

Children with leukemia are susceptible to various infectious complications. The host is immunocompromised by both malignancy and cytotoxic treatment. As a result, infections become an important cause of morbidity and mortality.

In the recent era with the judicious use of antibiotics and supportive treatment, the rate and duration of remission and survival have improved greatly. To optimize survival, the pattern of infection must be determined in these patients so that effective empiric therapy must be instituted at the earliest sign of infection.1

With this background this study was conducted to determine the incidence of infection in relation to the severity of immunocompromisation specially the absolute neutrophil count, to determine the common site of infection of these immunocompromised patients, and to identify the pathogens isolated in febrile patients with acute leukemia and their sensitivity pattern to common antibiotic regimen.

II. Materials and methods

The study was conducted at inpatient pediatric ward, medical college Kolkata. A total number of 40 children, suffering from acute leukemia, in the age group upto 12 year, admitted during the period January 2007 to February 2008, formed the study group.

Diagnosis of leukemia was based on blood and bone marrow examinations. All patients were put on standard chemotherapy. Complete blood count with actual platelet count, blood cultures, chest x-rays and urinalysis were done in all patients. Cultures from other sites such as wound discharge, ear discharge, throat swab, stool, and vaginal discharge were done in selected cases. Viral studies were not done because of financial constraints.

A significant febrile episode was defined as three oral temperature elevations above 38.0 C over a period of 24 hour or a single temperature elevation above 38.50C, which could not be attributed to any blood transfusion, chemotherapy or allergic reactions etc.

The diagnosis of pneumonia was considered if the patient had a compatible chest x-ray examination and clinical presentation. Often the etiologic agent could not be identified because gram staining and culture of the sputum were not done. Septicemia was defined as the presence of at least one positive blood culture in a patient. Gastrointestinal tract infections included oral infections such as thrush or significant ulcerations containing pathogenic organisms, positive throat swab culture, dental infections and enteritis. Genito-urinary tract infections included all those patients with urinary tract infections and vulvar abscess. Urinary tract

infection was considered to be present if the patient had clinical presentation and with pus cells of greater than 10 cells in urinalysis or greater than or equal to 100,00 col/ml of a single organism cultured from the urine. The presence of cellulitis was established based on clinical signs.

The patient was said to be in remission if there was freedom from symptoms and physical findings attributable to leukemia, normal peripheral blood cell values, 1,000/mm. or more neutrophils and 150,000/ mm. or adequate platelets, hemoglobin of 10 grams or more, no demonstrable blast and bone marrow blast less than 5% with megakaryocytic, granulocytic and erythroid activity intact. Patient was on relapse when there was a reappearance of leukemia in the blood, bone marrow, skin, CNS testes or other visceral organs.

Patient was on induction therapy when the initial chemotherapy led to a complete remission usually within 4-8 weeks. On suspicion of infection, all patients were started on a combination of aminoglycosides and Cephalosporins or beta-lactamase resistant penicillin given intravenously. Antibiotics were adjusted according to the results of culture and sensitivity test and the therapeutic response. No post-mortem examination was done in any of these patients.

III. Results and analysis

There were 47 hospitalizations for a total of 40 patients of which 34 children (85%) had acute lymphoblastic leukemia (ALL) and 24 had acute myelogenous leukemia (AML). Four patients were readmitted because of repeated infections from different foci. Twenty-eight children were male and 12 were female, with a male to female ratio of 2.3:1.

A total of 61 febrile episodes were evaluated for infective etiology. Organisms were isolated in 40% cases at presentation and 92% cases at induction. This finding is statistically significant ($p < 0.01$). (Table. I)

Table I: Time of infectious episodes

Time of febrile Infection No (%)	Infection not identified No (%)	Infection identified No (%)
	At presentation	
30 (49.18%)	18(60%)	12(40%)
	During induction	
25 (40.99%)	2(8%)	23(92%)
	During remission	
6 (9.84%)	4(66.66%)	2(33.33%)
Total 61	24 (39.34%)	37 (60.66%)

Organisms were isolated more frequently (81.25%) if febrile episode occurred in patients with Absolute Neutrophil Count (ANC) < 500/cmm and a much less chance of isolation of organisms (48.48%) when ANC was >1500. (Table. II)

Table II : Relation with ANC

Absolute neutrophil count t [ANC](cells/cmm)	Febrile episodes	Infection identified No (%)	Infection not identified No (%)
< 500	16	13 (81.25%)	3(18.75%)
500-1500*	12	8 (66.66%)	4 (33.33%)
>1500**	33	16 (48.48%)	17 (51.51%)
Total 61	61	37 (60.66%)	24 (39.34%)

* $p < 0.01$ ** $p < 0.02$

Table. III shows that the skin and soft tissue was the commonest site of infection, accounting for 26.83% of all infection, closely followed by respiratory tract (21.95%).

Table III: Site of infection in acute leukemia patients

Sites of infection	Absolute neutrophil count			Total No (%)
	count< 500/cmm	500-1500/cmm	> 1500/cmm	
Skin and soft tissue	10	7	5	22 (26.83)
Respiratory tract	10	4	4	18 (21.95)
Gastrointestinal including oropharynx	8	5	3	16 (19.51)
Septicemia	4	4	2	10 (12.19)
Genitourinary	3	2	1	6 (7.32)

Others	5	2	3	10 (12.19)
Total	40 (48.78)	24 (29.26)	18(21.95)	82 (100)

Most of the infection (48.78%) occurred when the granulocytopenia was severe (<500/cmm), whereas the incidence of infection reduced considerably (21.95%) when the ANC was more than 1500/cmm.

Sixty seven percent of pathogens isolated were from the blood (Tables IV and IV-A). Gram-positive organisms were responsible for the 50% of the 30 episodes in which organisms were identified in blood and 53% of 15 episodes from other sites. Staphylococcus non-hemolytic coagulase-negative was the most common isolate, accounting for 34% in blood and 26% from other sites (Tables IV and IV-A). Gram-negative bacilli were responsible for 42.30% of

all the infection including blood and other sites. E.coli and Klebsiella were the gram negative bacilli cultured most frequently from blood and different sites of infection. In only one episode multiple organisms was cultured from blood (Tables IV).

Table IV: Blood culture results in acute leukemia

Organisms	Number
Gram Positive Pathogens	
Staphylococcus non-hemolytic coagulase-negative	10
Staphylococcus non-hemolytic coagulase-positive	4
Bacillus subtilis	1
Gram Negative Pathogens	
Klebsiella	5
Escherichia coli	3
Enterobacter	2
Pseudomonas sp	2
Fungal	
Candida species	2
Mixed Pathogens	
Pseudomonas sp. and Escherichia coli	1
Total	30

Table IV-A: Culture results in acute leukemia from other sites

Organisms	Sites	Number
Gram Positive Pathogens		
Staphylococcus (non-hemolytic coagulase-positive)	Wound discharge	4
Staphylococcus (non-hemolytic coagulase-negative)	Wound discharge	1
Alpha-hemolytic Streptococcus	Throat swab	1
Bacillus subtilis	Wound discharge	2
Gram Negative Pathogens		
Escherichia coli	Stool	1
	Urine	2
Pseudomonas sp	Ear	1
Klebsiella species	Urine	1
	Wound discharge	2
Total		15

Table V shows that Staphylococcus coagulase-negative or positive has acceptable sensitivity to Cloxacillin and Amikacin (72-75%) and suitable for empiric regimen, whereas vancomycin and linezolid having excellent (100%), is a good option for resistant Staphylococcus infection. Third generation cephalosporins (cefepime, ceftazidime) have pretty well efficacy (75-100%) against gram negative organisms. Levofloxacin has got excellent and wide sensitivity against both gram positive and gram negative organism and therefore a candidate for future empirical therapy.

Table V: Drug sensitivity pattern of important organisms

Organisms	Cloxacillin	Amikacin	Netilmycin	Cefepime	Ceftazidime	Vancomycin	Linezolid	Levofloxacin
Staphylococcus (non-hemolytic coagulase-negative) (n=11)	8 (72.77%)	8 (72.77%)	10 (90.90%)	7 (63.63%)	7 (63.63%)	10 (90.90%)	11 (100%)	8 (72.77%)
Staphylococcus (non-hemolytic)	6 (75%)	6 (75%)	7 (87.50%)	6 (75%)	5 (63.50%)	8 (100%)	8 (100%)	7 (87.50%)

coagulase-positive) (n=8)								
Klebsiella species (n=8)	-	4(50%)	-	6(75%)	6(75%)			8(100%)
Escherichia coli (n=6)	1(16.66%)	5(83.33 %)	-	5(83.33%)	5(83.33%)	-	-	6(100%)
Pseudomonas sp (n=3)	-	1(33.33 %)	-	1(33.33%)	3(100%)	-	-	2(66.66%)

IV. Discussion

Infection in the immunocompromised host is an important problem in present day medicine. Acute leukemia has a high frequency of infectious complications further influenced by therapy.¹⁻¹³ Infection not only influences the outcome of chemotherapeutic response but also the morbidity of these patients. Thus, prevention and treatment of infection are vital in the management of acute leukemia.

Neutropenia is probably the most important factor predisposing to infection in cancer patients. In patients with neutrophil count of 500/cu mm, both the incidence and the rate of recurrence of infection increase significantly.³ Granulocytopenia usually occurs in acute leukemia either because of leukemic process or a result of intensive chemotherapy.

Pickering LK has shown in his study that chemotaxis, phagocytosis and intracellular bactericidal activity are markedly reduced.⁴ In our study, the episode of infection was more frequent in those with an ANC of < 500/cu mm. Remission significantly influenced the occurrence of infection. In our study, the incidence of infection in patients on complete remission was markedly lower than in those with induction or relapse. The infection rate in patients on induction is still lower than that of patients on relapse. The result of this study indicates that the decrease in infectious episode was associated with an improved ANC. This decrease may also be associated with the recovery of both the quantity and the function of the granulocytes.⁴ In addition to the deficiencies created by the malignant process itself, many patients acquire deficiencies in host defense mechanism as a consequence of their therapy.

Corticosteroids are administered as part of the chemotherapeutic regimen in acute leukemia. In a study by Qi-nan et al in 1989, they had observed that the incidence of infection and mortality were greater among those on corticosteroids than those not receiving corticosteroids.⁵ This agent has a profound effect on host defense mechanisms, including decreasing antibody production, suppressing acute and chronic inflammatory response reducing delayed hypersensitivity reactions and impairing wound healing.⁶

Since corticosteroids are often a component of chemotherapeutic regimen, strict vigilance should be exercised in monitoring such patients.

The distribution of infections according to site in this study is very different from other investigators.^{3,7,8} In our study skin and soft tissue was the commonest site of infection, closely followed by respiratory tract, whereas the workers like Sickes EA et al. find that respiratory tract is most commonly affected in these patients.⁷ Application of various invasive procedures

frequently and failure to maintain local asepsis may be responsible for this. Contrary to a report by Bodey GP, multiple organisms were uncommon in our patients.⁹

The spectrum of organisms is constantly changing due to modification in chemotherapy. With the incorporation of semi-synthetic anti-staphylococcal penicillins into routine antibiotic regimens, the frequency of fatal *S. aureus* infections decreased. However, in a recent report by Elihu A, Gollin G, this organism has re-emerged as an important pathogen because of widespread use of intravenous catheters.¹⁰ The poor anti-staphylococcal coverage of most routine antibiotic regimens also contributes.¹¹

E. coli and *Klebsiella* were the most common cause of gram-negative bacillary infections. Several studies including the one by Wang SM et al, have indicated that fungal infections are increasing in frequency, not only in leukemic but in other patients with compromised host defense mechanisms.¹² However, fungal organisms were responsible for only a small portion of the total infections in these study. The most frequent fungal infection was oral candidiasis. This was known to develop in patients with cellular immunodeficiencies and in patients treated with cancer chemotherapeutic agents or steroids.

Viral infections were diagnosed infrequently in this study. There were three episodes of measles and one episode of herpes zoster infection.

V. Conclusion

This study clearly indicated that the incidence of infection is inversely proportional to the absolute neutrophil count. Infection in acute leukemia was more prevalent before and during the induction phase of chemotherapy. The skin and soft tissue was the commonest site of infection, thereby reflecting the need for more stringent aseptic precaution and cautious attitude of health care providers. The Gram Positive Pathogens esp. *Staphylococcus non-hemolytic coagulase-negative*, followed by Gram Negative Pathogens including *E. coli*

and Klebsiella were the most common organisms isolated. They remain sensitive to beta-lactam, cephalosporins and aminoglycosides.

Strict asepsis during any invasive procedure, careful attitude during cytotoxic drug delivery, so that no extravasation occurs, and effective local wound care in time is strongly recommended in order to reduce the incidence of soft tissue infection. It is recommended that a combination of beta-lactam and aminoglycosides be instituted as an empiric drug therapy for infections in acute leukemia. However, better diagnostic technique is required if fungal and viral infections are considered.

Newer broad spectrum antibiotics have a definite advantage in terms of efficacy. However, emergence of antibiotic resistance and superinfection needs careful consideration. These matters will aid in preventing infection or improving the outcome of infection.

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