

CAUSES OF MORTALITY IN CHILDREN WITH ACUTE LYMPHOCYtic LEUKEMIA

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ABSTRACT

Fifty five deaths between January, 1982 to September, 1989 in children with acute lymphoblastic leukemia (ALL) were evaluated to determine the cause of mortality. Fifty cases died during remission. Infection alone was responsible for death in 26 of 55 (47.3%) cases while hemorrhage was seen in 7 (12.7%) children. Infection and hemorrhage together were responsible in another 13 cases. Gastrointestinal tract and pulmonary system were the major sites of bleeding. Infections either alone or in combination with other factors were responsible for death in 42 of 55 (76.5%) of children.

Septicemia (n = 11), gastrointestinal (n = 15) and pulmonary infections (n = 10) and meningitis in 2 cases were the major sites of infections. Pseudomonas and Klebsiella in 6 cases each accounted for 54.5% of isolates.

Key words: Mortality, Acute lymphoblastic leukemia, Hemorrhage, Infection.

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With newer developments in management, over 60% of children with acute lymphoblastic leukemia are being cured(1-3). However, prior to introduction of chemotherapeutic agents, practically every child with acute lymphoblastic leukemia succumbed within 3-6 months of diagnosis(4). Hemorrhage and infection accounted for mortality in majority of cases from fifties to mid sixties. Liberal use of platelet transfusions have helped to prevent major bleeds in centres having these facilities. Therefore infections have emerged as a major cause of mortality. Vital information on causes of mortality in children from our country will be of interest where infections in general population are very common and supportive facilities for these patients are limited.

Material and Methods

Records of children with acute lymphoblastic leukemia, who died between January, 1982 to September 1989 were evaluated. During this period 287 children were admitted at AIIMS with diagnosis of acute lymphocytic leukemia and chemotherapy was initiated. Clinical, laboratory and pathological data was recorded and the final cause of death was determined. Each case was independently evaluated for cause of death by two authors. Any difference regarding the cause of death between two authors was resolved either by mutual discussion or by referral to a third author.

Diagnosis of ALL was based upon the clinical features and predominance of lymphoblasts (40%) in the peripheral blood and/or bone marrow, corroborated by cytochemistry. All these children were investigated and treated by combination chemotherapy. During the study period children were treated with three regimens (II, III and IV) and details of these protocols have

been given in our previous study(5). Postmortem lung aspirates, biopsy from various organs were performed to evaluate the factors responsible for mortality. However, postmortem cultures and histopathological studies did not help to identify the underlying factors responsible for mortality.

Definitions of potential causes of death in children with ALL as described by Hersh *et al.*(6) in their series was strictly followed (Table I) in the present study.

Results

Fifty five children (38 boys and 17 girls) died of acute lymphoblastic leukemia during the seven year study period.

Age and sex distribution of children who died was similar to that of children getting admitted with ALL for management at AIIMS(7). Fifty children died during initial or subsequent induction therapy while only 5 (9%) died during maintenance phase. In five cases, no definite cause of

TABLE I—Causes of Death—Definitions

Fatal infections	Clinical, radiological and laboratory evidences of overwhelming infections or evidence of vital organ involvement.
Septicemia	Positive blood culture in last seven days prior to death.
Pneumonia	Extensive clinical and radiological lung involvement and death secondary to respiratory failure.
Fatal hemorrhage	Minor bleed in the vital areas or severe visceral bleed leading to shock and death.
Organ failure	Impairment of vital organ not compatible with life, which is not secondary to infection/hemorrhage.
Aspiration	Development of respiratory failure following aspiration of food/vomitus.
Unknown	When cause of death could not be identified.

death was identifiable. Multiple causes of death were identified in 16 (28.1%) cases while in 34 (61.8%) cases a single cause of death could be identified (Table II).

Infection

Infection alone accounted for 47.3%

TABLE II—Causes of Death in ALL

Diagnosis	No. of patients	%
Infection alone	26	47.3
Infection & aspiration	3	5.5
Infection & hemorrhage	13	23.6
Hemorrhage alone	7	12.7
Aspiration alone	1	1.8
Unknown cause	5	2.1

(n = 26) of the deaths and in combination with other factors, it was responsible in 76.5% (n = 42) cases (Table II). Common sites/types of infection were gastroenteritis with or without septicemia in 15, pneumonia in 10, and meningitis in 2. Eleven of these children had septicemia alone. Abscess, hepatitis, disseminated tuberculosis and fulminant tonsillitis were seen in one case each. Bacterial isolation from various sites of infection was possible in 22 (52.2%) cases. *Pseudomonas* and *Klebsiella* were isolated in six cases each. *E. coli* was cultured in 2 cases while *Proteus*, *Shigella*, *V. cholera*, *Acinetobacter* and *Enterobacter* was isolated in one case each. Among the Gram positive organisms,

Staphylococcus (coagulase positive) was isolated in two cases. Total leucocyte counts (TLC) were 1000/ml in 27 (64%) of children out of the 42 children who died because of infection either alone or in combination with hemorrhage or aspiration. The TLC in these patients was recorded within 72 hours prior to death (Table III).

Hemorrhage

Hemorrhage alone was responsible in 12.7% cases while hemorrhage with infection caused death in 23.6% cases. Among the various sites of hemorrhage, the gastrointestinal system was the commonest site (65%) cases followed by CNS (25%), pulmonary (15%) and urinary tract (10%). Some patients had more than one site of bleeding. Platelet count was less than 50,000/ μ l in 70% (14 of 20) cases prior to death inspite of platelet supportive therapy in these cases.

Discussion

Infections continue to be the major cause of morbidity in children with acute lymphoblastic leukemia. It was responsible in 82 of 93 febrile episodes in our earlier study(8). Pulmonary infection was seen in 25 cases, while micro-organisms were isolated in 40 (45.5%) cases(8). Infections ac-

counted for 73% of febrile episodes in 78 patients of Viola(9). Thus corticosteroids and use of other chemotherapeutic agents increase the susceptibility of individuals to develop serious infections.

Chemotherapeutic agents impair the immune defence system by multiple mechanisms(10). Incidence of infection in patients receiving all types of antitumor therapy was higher (75%) than in those on no therapy (64%) or those on steroid therapy (66%)(6). However, these differences were not significant but may be explained by the presence of profound granulocytopenia, often associated with acute leukemia(6). Children with persistent absolute neutrophil count of less than 500/ μ l are at higher risk of infection. Only 13.5% of patients with severe neutropenia were free of infection for a period of one month at the time of death(11). Frei and his colleagues reported the mean granulocyte count of 100/ μ l at the onset of *Pseudomonas* septicemia in their series of 41 febrile episodes(12).

In the present series, infection alone or in combination with other factors such as hemorrhage and aspiration was responsible for deaths in 76.4% of cases. In 26 (47.3%) cases, infection alone was responsible for mortality while Hersh and his colleagues observed infection as a cause of death in 70% of their cases(6).

Pseudomonas, *Klebsiella* and *Esch. coli* were the offending organisms in majority of our fatal cases. Similar observations have been made by others(6,9,12). *Pseudomonas aeruginosa* if isolated from any site in leukemic children needs special attention especially if the absolute neutrophil count is below 500/ μ l or in the presence of gastrointestinal ulceration. Isolation of this organism from blood, spinal fluid or bone marrow is of diagnostic significance.

TABLE III—Fatal Infections in ALL — Leucocyte Count

Leucocyte Count/ μ l	n	
< 500	15	} 64%
500-1000	12	
1000-1500	7	
1500-2000	2	
> 2000	6	
Total	42	

Hughes and Memphis have shown that presence of *Pseudomonas* in the nasopharynx, throat, stool, urine or skin is suggestive of impending infection or sepsis(11). Over the years the spectrum of infections in fatal cases has changed drastically in the developed countries. Virtual elimination of fatal *Staphylococcal* infection following introduction of methicillin therapy is an example(6). There has been increase in disseminated fungal, viral and parasitic infections in these cases(6,13,14). However, large studies on viral and fungal infections in these children are not available from our country.

Hemorrhage alone or in presence of infection caused death in 36.3% cases of the present series while hemorrhage was responsible for death in 48% cases of Boggs *et al.*(15). Cerebral hemorrhage was more common in AML than ALL (41% vs 20%) while gastrointestinal hemorrhage was more common in ALL (15% vs 4%). Fatal hemorrhage progressively declined over a period of 10 years in the series of Hersh *et al.*(6), because of better supportive therapy. However, hemorrhage contributed towards death in 52% of their cases. In their series, cerebral hemorrhage was also more common in AML (18% vs 8%) while gastrointestinal hemorrhage in AML has been attributed to frequent occurrence of leukostatic lesions(16).

A high index of suspicion, knowledge of spectrum of infections, early institution of appropriate antibiotics and better availability of supportive facilities along with the newer antibiotics are essential to improve the long term event free survival periods in these children(17-19).

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NOTES AND NEWS

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