

# Severe infections during maintenance chemotherapy of childhood Acute Lymphoblastic Leukemia and their correlation with serum immunoglobulin status

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June 26, 2020

## Abstract

**Background:** Few studies have looked into the impact of hypoglobulinaemia on infectious complications in childhood acute lymphoblastic leukemia (ALL). We conducted this prospective study to analyse the profile of severe infections during maintenance chemotherapy in Indian children and their correlation with serum immunoglobulin levels. **Methodology:** Children [?]14 years with ALL on maintenance chemotherapy were recruited and serum immunoglobulin levels were measured at the time-of-recruitment in this study conducted between 1st April 2018 and 31st March 2019. Children were followed up for severe infection for a period of 6 months or till completion of treatment whichever was later. Statistical analysis was done to find out risk factors of severe infection including serum immunoglobulin status. **Results:** We recruited 199 children undergoing maintenance chemotherapy (58, 52, 47, and 42 children in 0-6, 7-12, 13-18 and 19-24 months of maintenance period) and followed them up for a mean (SD) 9.7(2.961) months. 56.8%, 80.4%, and 86.4% children had hypo-IgG, hypo-IgA, and hypo-IgM at the time-of-recruitment. Ninety-one (45.7%) children developed 147 episodes of severe infections of which 54 (59.3%) were respiratory. Univariate analysis showed younger age, female gender and normal IgG group had significantly increased risk of severe infection ( $P=0.024$ ,  $0.007$ ,  $0.049$ , respectively), in multivariate analysis female gender had significantly increased risk of severe infection ( $P=0.025$ ). **Conclusion:** Significant proportion of Indian children on ALL maintenance chemotherapy developed severe infection and hypoglobulinaemia. However, hypoglobulinaemia did not significantly increase the risk of severe infection. Younger children and female gender had significantly increased risk of severe infection during maintenance.

## Introduction

Modern chemotherapy has increased the survival of childhood acute lymphoblastic leukemia (ALL) upto 90%;<sup>1-4</sup> but it comes with the consequences of immune defence abnormalities and increased susceptibility to infections.<sup>5</sup> Infection is an important cause of morbidity and mortality in children with ALL during chemotherapy, especially in developing countries.<sup>6</sup> Reduction of intensity of chemotherapy for ALL had resulted in a major reduction in infectious morbidity,<sup>7</sup> explaining the possibility that serum immunoglobulin levels and specific antibody levels may be less affected in children treated with reduced dose chemotherapy.<sup>8</sup> Few studies have focussed on the effect of chemotherapy on serum immunoglobulin levels, and its effect on infective complications.<sup>9-12</sup> Many studies on infection and immunosuppression in ALL are without stratification for the period and intensity of chemotherapy. Maintenance chemotherapy bears the accumulation of previous intensive chemotherapy and reduced reserve for hematopoiesis and is of the longest

duration of continuation treatment. Children are less intensively monitored during this period of chemotherapy due to reduced intensity of chemotherapy and less frequent use of parenteral chemotherapeutic agents. Continuation of maintenance chemotherapy as outpatient treatment also poses significant risk of exposure to infections via community contacts. There is scarcity of data correlating immunosuppression especially hypoglobulinaemia with occurrence of infections during maintenance chemotherapy. Most of such studies in paediatric ALL are from developed countries, where infections and related mortality are less. Role of intravenous immunoglobulin (IVIG) in reducing infectious complications and improving outcome of infections is still unclear, so is the timing of IVIG for prophylaxis or treatment.<sup>9,13</sup> This study aimed to monitor ALL children for severe infections during maintenance chemotherapy in the Indian setting and to find out the risk of severe infections with hypoglobulinaemia.

## Methodology:

This prospective observational study was carried out in the Department of Pediatric Oncology, of a Regional Cancer Centre, in India from 1<sup>st</sup> April 2018 to 31<sup>st</sup> March 2019 after obtaining institutional review board and Ethical Committee approval. All consecutive ALL children [?]14 years at diagnosis and receiving maintenance chemotherapy during the study period were included after obtaining written informed consent. Children with pre-existing primary or acquired immunodeficiency were excluded. Data regarding diagnosis, treatment, and infections requiring admission and inpatient care (severe infection) during maintenance phase were recorded. Total duration of maintenance chemotherapy was divided into four phases – 0 to 6 months, 7 to 12 months, 13 to 18 months and 19 to 24 months and period of maintenance at the time of recruitment was recorded. Serum immunoglobulin levels were measured by turbidimetric method using Vitros<sup>®</sup> kit (Ortho diagnostics) at recruitment and compared to age-matched reference ranges. All recruited children were followed up for development any severe infection for a period of 6 months from the date of recruitment, or till completion of maintenance treatment, or occurrence of any event or death due to any cause.

## Definitions:

### Hypoglobulinaemia:

Serum immunoglobulin levels below the reference range for that age group. For Indian children [?]5 years age, reference serum immunoglobulin values were available for comparison<sup>14</sup> while for children >5 years age, Indian reference serum immunoglobulin values were not available and hence compared to international reference values.<sup>15</sup>

### Severe infection:

Any infection during maintenance chemotherapy which required inpatient treatment

### Treatment protocol

Patients were treated using modified BFM (Berlin-Frankfurt-Munster) 95 protocol (Supporting information file). Children with ALL were divided into standard and high-risk (HR) groups. HR children were: age [?]10 years, total leukocyte counts (TLC) [?]50,000/cumm, T acute lymphoblastic leukemia (T ALL), mixed phenotype acute leukemia (MPAL), liver or spleen [?]5 cm below costal margin, t(9;22)(q31;q34.1) positive (BCR-ABL), other unfavorable cytogenetic abnormality, hypodiploidy (chromosome number [?]44), central nervous system (CNS) positive disease (blasts in cerebrospinal fluid at diagnosis or cranial nerve abnormality), or poor prednisolone response (absolute blast counts [?]1000/cumm on day 8 of prednisolone). All other children were classified as standard-risk (SR) children. All HR children except HR due to hepatosplenomegaly received prophylactic cranial radiation (CRT) of 12 Gy after Phase II B (reconsolidation). Children with CNS positive disease received 18 Gy CRT. Maintenance chemotherapy comprised of vincristine (1.5 mg/m<sup>2</sup> every 4 weeks), prednisolone (60 mg/m<sup>2</sup> for 7 days every 4 weeks), 6-mercaptopurine (6MP) (50 mg/m<sup>2</sup> daily) and methotrexate (20 mg/m<sup>2</sup> weekly) in both SR and HR groups. SR group also received intrathecal (IT) methotrexate every 8 weeks during maintenance chemotherapy.

### Statistical analysis

Continuous variables were expressed in terms of mean, median, standard deviation and range. Categorical variables were presented using frequency and percentages. Chi-square test was used to compare severe infection, infection involving respiratory system, infection involving systems other than respiratory system, between children with normal immunoglobulin levels and hypoglobulinaemia and different age groups and risk groups. Logistic regression analysis was performed to find the risk of severe infection with respect to different parameters. P-value <0.05 was considered as significant.

## Results

One-hundred ninety-nine children undergoing ALL maintenance therapy having baseline characteristics as described in Table 1 were recruited. Median age was 72 months (range – 19-186 months). Male: female ratio was 1.28:1, 55.3% children (n=110) were HR and 44.7% (n=89) children were SR. Ninety-four (47.2%) children received CRT, of which 93 received prophylactic 12 Gy CRT and one child received 18 Gy of CRT due to initial CNS positive status.

Ninety-one (45.7%) children developed a total of 147 episodes of severe infections during maintenance chemotherapy. Respiratory system was the most common site affected (59.3% of children and 55.8% of episodes with severe infection) (Table 2). Gastrointestinal and central nervous system were the most common non-respiratory systems involved. Febrile neutropenia without any evident focus of infection was second most common presentation (24.1% of children with severe infection and 19% of total episodes of severe infection). Leucopenia (TLC<1000/cumm) was present in 40 episodes (27.2%) and in 35 children (38.5%) with severe infection. Five children required inotrope support while intensive care unit (ICU) admission for ventilator support was needed for 4 children. Three (3.3% of children with severe infection) children succumbed to death during severe infection and two of these deaths were due to respiratory infections. Eight children (8.7%) had culture positive infections, Escherichia Coli and Pseudomonas Aeruginosa being the common organisms. Severe infections were high during the initial months of maintenance phase chemotherapy compared to the later months (Figure 1). This may be due to the more severe immunosuppression resulting from the intensive reinduction and reconsolidation chemotherapy phases preceding the maintenance phase.

Out of the total 91 children, who developed severe infections, 42 children were [?]5 years and 49 children were >5 years of age. Proportion of children with severe infection and with respiratory infection was significantly more in [?]5 years age group compared to the older children (P=0.034, 0.015, respectively), while proportion of children who developed severe infection involving systems other than respiratory system was similar in both age groups (P=0.881) (Table 3). Female children developed significantly more severe infections and also respiratory infections during maintenance phase (P=0.008 and 0.046, respectively) (Table 3). In both SR and HR groups, proportion of children with severe infections, respiratory infections, non-respiratory infection, ICU admission and inotrope requirement were similar (P=0.071, 0.288, 0.066, 0.327, 0.249) (Table 3).

Serum immunoglobulin estimation during maintenance phase revealed hypo-IgM in 172 (86.4%) children and hypo-Ig G in 113 (56.8%). (Table 1) In the 6-10 years age group (n=87), 24 (27.6%) children had IgA levels <40 mg/dL and 63 (72.4%) children had normal IgA levels (>40 mg/dL). We could not precisely assess the exact number of children with hypo-IgA in this age group as the cut off for hypo-IgA in this age group was 33 mg/dL, while the lower limit of kit for IgA levels was 40 mg/dL. Among the rest of children (n=112), 80.4% (90) had hypo-IgA and 19.6% (22) had normal IgA levels. One-hundred eighty (90.5%) children had decreased levels of at-least one immunoglobulin class, while 64 (32.1%) children had decreased levels of all three immunoglobulin classes. Proportion of children with hypo-IgG, hypo-IgA hypo-IgM, hypoglobulinaemia of at-least one immunoglobulin class and hypoglobulinaemia of all immunoglobulin classes was significantly high in [?]5 years age group as compared to >5 years age group (P=0.044, <0.001, 0.024, 0.009, <0.001, respectively). For children with hypo-IgA, the difference remained significant even after excluding 6-10 years age group children. (Table 1)

Percentage of children developing severe infections as well as respiratory infections was significantly higher among patients with normal IgG levels compared to those with low IgG levels (P=0.045 and 0.022, respec-

tively) (Table 4). Similarly, non-respiratory infections was significantly higher in a group of children who did not have low levels of any of the immunoglobulin class compared to children who had hypoglobulinaemia of at-least one immunoglobulin class ( $P=0.039$ , respectively) (Table 4).

On univariate analysis for factors influencing the occurrence of severe infection during ALL maintenance phase, younger age at the time of recruitment, female gender, age group  $\leq 5$  years and normal IgG levels were significantly associated with increased risk of severe infection. Odds ratio (OR) (95% CI) was 0.991 (0.984 – 0.99;  $P=0.024$ ) for children with older age (in months) at the time of recruitment, 0.587 (0.329 – 1.046;  $P=0.070$ ) for children in age group  $>5$  years, 2.199 (1.239 – 3.903;  $P=0.007$ ) for female gender and 0.565 (0.319 – 0.998) ( $P=0.049$ ) for hypo-IgG. On multivariate analysis, only female gender had significantly increased risk of severe infection [OR. (95% CI) 1.970 (1.088 – 3.566) ( $P=0.025$ )] (Table 5).

## Discussion

In this study from India, during childhood ALL maintenance chemotherapy, 45% children developed 147 episodes of severe infections requiring inpatient treatment and 1.5% of them suffered infection related mortality. Younger children and female patients had significantly higher risk of severe infection. Holmes *et al* observed 400 febrile episodes among 136 children on Children's Oncology Group protocol during the maintenance chemotherapy period.<sup>9</sup> In a study from Greece by Kostaridou *et al*, 22 (78%) out of 28 children developed infection, though it was not classified as severe requiring admission.<sup>10</sup> We included only infections requiring inpatient care in the present study.

Among the severe infections during maintenance, the system most commonly involved was respiratory system, affected in 59.3% children. This finding was similar to most reports from the developed world. In a study from United Kingdom, Rapson *et al* observed that pneumonia was the most common infection (70% of all infections) during continuation therapy.<sup>11</sup> In a study from Greece by Kostaridou *et al* also 53% of infection episodes involved respiratory system.<sup>10</sup> Luczynski *et al* from Poland reported 39% of total infections were respiratory infections in children with ALL during maintenance chemotherapy.<sup>17</sup> In a study from a middle income country like Egypt, pneumonia was the most common cause of death (33%) in remission during ALL chemotherapy.<sup>6</sup> In our study also pneumonia was the commonest cause of death, accounting for 66% of maintenance deaths.

There was no difference in the number of children developing severe infections between SR and HR groups in our study, as maintenance treatment protocols were similar for both groups, consisting of vincristine, steroid pulse and similar 6 MP and methotrexate. This may have abolished the difference observed between various risk groups in studies from the developed world.<sup>7,11,17</sup>

Rapson *et al* from UK, did not find any significant differences in leukocyte counts, mitotic response to phytohaemagglutinin, and serum immunoglobulin levels among patients treated with intensive continuous therapy who had serious infections and those who did not develop any.<sup>11</sup> In our study also regression analysis did not show significant correlation between hypo-IgG, hypo-IgA or hypo-IgM and development of severe infection. Though children with normal IgG levels showed a trend towards severe infection in our study, it did not reach statistical significance in multivariate analysis. Holmes *et al* from USA observed that IgG monitoring and IVIG supplementation did not significantly impact episodes of fever, febrile upper respiratory infection, or positive blood culture rates between groups with IgG levels  $<500$  mg/dL and  $>500$  mg/dL and even in IVIG supplemented group.<sup>9</sup> Our observation on association between hypoglobulinaemia and risk of severe infection was similar to this. Their data also suggested that monitoring or supplementation of low IgG is not indicated for infection prophylaxis in ALL patients during maintenance chemotherapy.

In our study 43.2% children had normal IgG levels during maintenance chemotherapy. Many authors have shown that immunoglobulin levels, especially IgG showed a trend towards normalization in post intensive chemotherapy phase during maintenance period, explaining the possible role of deficiency of immunological parameters other than immunoglobulin as the predisposing factor for severe infections during maintenance chemotherapy<sup>9,17,18</sup>. Abnormality of T cells, NK cells, and other cytokines have been shown in ALL children undergoing chemotherapy in various studies,<sup>10,12,17-24</sup> which also might have contributed to increased risk of

severe infections during maintenance chemotherapy. Severe infection pattern seen in our cohort also could be due to any of these other immune abnormalities, but as we didn't estimate these parameters in our study, a definite conclusion could not be drawn regarding this. Instead of the deficiency of any one particular immune system arm, it may be the combination of deficient immune system parameters which predisposes the ALL children to infections during maintenance chemotherapy.

It has been shown by Van Tilburg *et al* that decline in levels of serum IgG did not correlate well with decline in levels of IgG antibody to vaccine preventable diseases.<sup>8</sup> Children with low IgG may have normal levels of antibody to vaccine preventable diseases or against infections occurred in past and this might have prevented the occurrence of infection in children with hypo-IgG.<sup>8</sup> In our study also, through a similar mechanism, ALL children with hypo immunoglobulin levels might have had normal antibody levels against vaccine antigens or past infections.

Younger children ([?]5 years) had significantly more number of severe infections in our study compared to the older children, though multivariate analysis could not demonstrate statistical significance. Inaba *et al* from St Jude Children's Research Hospital, USA, observed that younger age at diagnosis was associated with significantly increased risk of infection during induction and later part of continuation phase.<sup>25</sup> and our observation was also similar. In addition to hypoglobulinaemia, younger children may also have associated deficiency of other immune parameters contributing to their increased susceptibility to severe infection.

The main strength of our study included that it was a prospective study conducted in a tertiary care cancer centre with a fairly large number of ALL children on maintenance chemotherapy (199 children) and nearly equal number of children in each of the six months period of maintenance (58, 52, 47, and 42 in 0-6, 7-12, 13-18 and 19-24 months of maintenance chemotherapy, respectively) could be recruited. A male to female ratio of 1.28:1 observed in our study, was helpful to compare parameters between both genders.

Limitations of the study were that we could not monitor immunity markers other than serum immunoglobulin and both HR and SR groups received similar maintenance chemotherapy, because of which the difference between the risk groups could not be assessed.

## Conclusion

Significant proportion of Indian children on ALL maintenance chemotherapy developed severe infection and hypoglobulinaemia. However, hypoglobulinaemia did not significantly increase the risk of severe infection. Younger children and female gender had significantly increased risk of severe infection during maintenance. Respiratory infections were the most common infection during maintenance phase and contributed to 66% of infection related deaths.

**Conflict of interest** – None

**Acknowledgement** - None

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Legends:

**Figure 1** – Severe infections during different periods of maintenance phase chemotherapy

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