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Clinical profile and short-term outcome of pediatric hyperleukocytic acute leukemia from a developing country

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Hyperleukocytosis is a medical emergency and is defined as peripheral blood leukocyte count exceeding 100 x10^9/L. Acute hyperleukocytic leukemia (AHL) is reported in 5-22% of children at diagnosis with mortality rate 4-24%. Ischemic complications of hyperleukocytosis are related to leukostasis in brain and lung with metabolic complications related to tumor lysis syndrome (TLS). There were only a few published reports on hyperleukocytosis in children. The data on hyperleukocytic leukemia in children from Pakistan is scarce. The aim of this study was to report frequency, severity, clinical presentation, treatment and short-term outcome of all children with AHL in two pediatric oncology centers in Karachi.

Medical records of all eligible participants were retrospectively reviewed to collect the pertinent demographic, clinical and outcome data on structured data collection sheet from 2009 to 2015, after approval from ethical review committee (1234-Peds-ERC). The cohort of AHL was divided into two groups, based on the WBC counts: (Group I - 100-199, Group-II - >200 x10^9/L); primary outcome (group 1 - alive, group II - expired).

The secondary outcomes were defined as occurrence of complications that occurred during the first 14 days after presentation as described by Lowe et al. Pulmonary leukostasis syndrome was defined as the triad of infiltrate on CXR, tachypnea and hypoxia. Neurological event was defined as any neurological complications that met the National Cancer Institute criteria. Tumor lysis syndrome (TLS) was defined as either laboratory TLS (LTLS) or clinical TLS (CTLS). LTLS was defined as presence of at least two of the features, namely hyperuricemia (serum uric acid >8mg%), hyperphosphotemia (serum phosphorus >6.5mg%), hyperkalemia (serum potassium >6meq/l), and hypocalcaemia (serum calcium <7 mg%). CTLS required the presence of LTLS in addition either one of the three clinical complications, namely renal dysfunction, arrhythmias, features of leukostasis (seizure/intracranial bleed and/or priapism).

After establishing diagnosis of acute hyperleukocytic leukemia, all patients received standard treatment including hyperhydration, allopurinol, cytoreduction and organ-supportive care, as needed. Cytoreduction therapy was performed at the discretion of attending pediatric oncologist. Decision to perform leukapheresis was based on a multidisciplinary team consensus including oncologist, intensivist, and hematologist.

The overall frequency of pediatric oncology patients, who presented with hyperleukocytosis (>100 x10^9/L) during the study period, was determined by dividing the number of admissions to pediatric oncology patients with hyperleukocytosis with the total number of admissions to the pediatric oncology unit. For analysis, SPSS version 20 (IBM, Chicago, USA) was used. Frequencies with percentages were computed for qualitative variables and mean SD and median (IQR) were computed for numerical variables.
quantitative variables depending whether the data was distributed evenly or skewed, respectively. The risk factors associated with hyperleukocytosis (100-200 x 10^9/L) and for increased mortality was calculated with Chi-square test for categorical variables and independent t-test used for continuous variables, with p-value ≤ 0.05 was considered significant.

During the study period, 1,045 patients were diagnosed as acute leukemia and 13.97% (146/1045) had hyperleukocytosis at presentation. Majority (94.5%, n=138) of these patients were diagnosed as ALL, of which 44.5% (n=65) had extreme hyperleukocytosis (<200 x10^9/L). Patients' demographics, clinical and laboratory characteristics are summarized in Table I. The initial median WBC was 181 x10^9/L (IQR, 130.45-298.3). The overall incidence was high in age group between 1-10 year (61.7%, 90/146) with male preponderance (76%, 111/146). Duration of illness was >30 days in nearly 50% of patients, indicating late presentation. Majority (74.6%, n=109) patients developed one or more complications in this cohort with infectious complications being the most common (45.2%, n=66). Laboratory TLS developed in 39% (n=57) and clinical TLS was observed in 17.1% (n=25), respectively. The complications related to leukostasis were observed in 27% (n=4), 24.6% (n=36) and 22.6% (n=33) as isolated neurological and isolated pulmonary complications and combined neuro-pulmonary complications, respectively. The intensive-care resources were utilized in 26% (n=38), with 20.5% (n=30) and 4.1% (n=6) patients requiring vasoactive-inotropic support for hemodynamics plus mechanical ventilation and mechanical ventilation alone, respectively. Four patients (2.7%) required leukapheresis as a short-term cyoreductive intervention in conjunction with other therapies. Only one patient required intermittent hemodialysis for brief duration. The frequency of pulmonary and neurological insults, secondary to leukostasis in children with acute leukemia, varies from 4% to 20% in different pediatric reports. Recently, Kong et al. reported 10% and 4% of neurologic and pulmonary complications in their cohort of childhood acute lymphoblastic leukemia with hyperleukocytosis, respectively. Lowe et al. reported 6% and 9% of neurologic and pulmonary injuries due to leukostasis in their cohort, respectively. However, there was no difference in the incidence of pulmonary complications between two groups. Most of the presently reported patients required only hydration, allopurinol and chemotherapy along with intense monitoring. The leukapheresis was done only in 4 cases without any complication. Despite being invasive, this procedure is a safe and effective if performed by experienced staff. A very high frequency of infection-related complications was observed during the induction-remission phase, consistent with the fact that sepsis has been identified as a major cause of morbidity and mortality in children with cancer. This highlights the importance of education and training in preventing, recognizing and treating infections in such high-risk group.

The mortality rate was 20.5% (n=30) in this cohort. The early mortality in children with hyperleukocytic acute leukemia has been reported to be 4% to 27%. There are few other reports, which are consistent with the currently reported results.
Table I: Patients’ characteristics of acute hyperleukocytic leukemia.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All 100,000-200,000</th>
<th>&gt;200,000</th>
<th>p-value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=146 (%)</td>
<td>N=81 (%)</td>
<td>N=65 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10 years</td>
<td>50 (61.7%)</td>
<td>40 (61.7%)</td>
<td>0.068</td>
<td>-</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>31 (38.3%)</td>
<td>25 (38.5%)</td>
<td></td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>61 (49.4%)</td>
<td>21 (32.3%)</td>
<td>0.156</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>38 (46.9%)</td>
<td>39 (60%)</td>
<td></td>
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<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pre B cell ALL</td>
<td>40 (49.4%)</td>
<td>21 (32.3%)</td>
<td>0.067</td>
<td>-</td>
</tr>
<tr>
<td>T cell ALL</td>
<td>2 (2.5%)</td>
<td>3 (4.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>1 (1.2%)</td>
<td>2 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of illness before diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10 days</td>
<td>13 (16.0%)</td>
<td>13 (20%)</td>
<td>0.858</td>
<td>-</td>
</tr>
<tr>
<td>10-30 days</td>
<td>27 (33.3%)</td>
<td>21 (32.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30 days</td>
<td>41 (50.6%)</td>
<td>31 (47.7%)</td>
<td></td>
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</tr>
<tr>
<td><strong>CNS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>I</td>
<td>68 (84%)</td>
<td>59 (90.8%)</td>
<td>0.067</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>0 (0%)</td>
<td>2 (3.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>13 (16%)</td>
<td>4 (6.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Therapeutic Intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydration + Steroids</td>
<td>76 (93.6%)</td>
<td>60 (92.4%)</td>
<td>0.065</td>
<td>-</td>
</tr>
<tr>
<td>Hydration + Steroids + Leukapheresis</td>
<td>3 (4.6%)</td>
<td>3 (4.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3 (3.7%)</td>
<td>2 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ICU Interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>5 (7.7%)</td>
<td>5 (7.7%)</td>
<td>0.106</td>
<td>-</td>
</tr>
<tr>
<td>Mechanical Ventilation + Inotropes</td>
<td>15 (18.5%)</td>
<td>15 (23.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation + Inotropes + RRT</td>
<td>1 (1.5%)</td>
<td>1 (1.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotropes</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>64 (79%)</td>
<td>44 (67.7%)</td>
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<td></td>
</tr>
<tr>
<td><strong>Laboratory Data</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (mg/dl) mean (+/- SD)</td>
<td>7.44 (2.38)</td>
<td>7.83 (+/-2.16)</td>
<td>0.071</td>
<td>-0.720 (-1.482-0.073)</td>
</tr>
<tr>
<td>Platelets (c/mm) median (IQR)</td>
<td>132.6 (117.1-163.7)</td>
<td>7.31 (4.68-11.57)</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Platelets (c/mm) median (IQR)</td>
<td>31 (19-54.5)</td>
<td>3.42 (+/-0.89)</td>
<td>0.004 -0.371 (-0.623-0.119)</td>
<td></td>
</tr>
<tr>
<td>LDH (IU/L) median (IQR)</td>
<td>2668 (1313-5704)</td>
<td>4.51 (+/-2.53)</td>
<td>0.269 -0.459 (-1.107-0.310)</td>
<td></td>
</tr>
<tr>
<td>Uric Acid (mg/dl) median (IQR)</td>
<td>5.9 (3.97-9.2)</td>
<td>9.0 (+/-0.95)</td>
<td>0.822 -0.036 (-0.355-0.282)</td>
<td></td>
</tr>
<tr>
<td>Potassium (meq/L) mean (+/- SD)</td>
<td>4.03 (+/-0.75)</td>
<td>4.23 (+/-0.89)</td>
<td>0.004 -0.371 (-0.623-0.119)</td>
<td></td>
</tr>
<tr>
<td>Phosphorus (mg/dl) mean (+/- SD)</td>
<td>4.11 (+/-1.39)</td>
<td>4.51 (+/-2.53)</td>
<td>0.269 -0.459 (-1.107-0.310)</td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl) mean (+/- SD)</td>
<td>8.9 (+/-0.91)</td>
<td>9.0 (+/-0.95)</td>
<td>0.822 -0.036 (-0.355-0.282)</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl) median (IQR)</td>
<td>0.6 (0.5-0.8)</td>
<td>0.63 (0.54-0.98)</td>
<td>0.028</td>
<td>-</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>24 (29.6%)</td>
<td>25 (38.5%)</td>
<td>0.293</td>
<td>0.674 (0.338-1.344)</td>
</tr>
<tr>
<td>CNS</td>
<td>3 (3.7%)</td>
<td>11 (16.9%)</td>
<td>0.189</td>
<td>0.516 (0.050-0.709)</td>
</tr>
<tr>
<td>Infectious</td>
<td>3 (16.5%)</td>
<td>28 (43.1%)</td>
<td>1.168</td>
<td>1.618 (0.605-2.252)</td>
</tr>
<tr>
<td>Renal</td>
<td>14 (17.3%)</td>
<td>18 (27.7%)</td>
<td>0.546</td>
<td>0.247 (0.124)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Alive</td>
<td>66 (81.5%)</td>
<td>50 (76.9%)</td>
<td>0.541</td>
<td>1.320 (0.590-2.951)</td>
</tr>
<tr>
<td>Dead</td>
<td>15 (18.5%)</td>
<td>15 (23.1%)</td>
<td>0.236</td>
<td>0.647 (0.336-1.244)</td>
</tr>
</tbody>
</table>

ALL = Acute Lymphoblastic Leukemia; AML = Acute Myelogenous Leukemia; CML = Chronic Myelogenous Leukemia; CNS = Central Nervous System; ICU = Intensive Care Unit; RRT = Renal Replacement Therapy; WBC = White Blood Cells; LDH = Lactate Dehydrogenase.
### Table II: Risk factors of mortality among hyperleukocytosis patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Alive N=116 (%)</th>
<th>Expired N=30 (%)</th>
<th>P-value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10 years</td>
<td>73 (62.9%)</td>
<td>17 (56.7%)</td>
<td>0.345</td>
<td></td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>43 (37.1%)</td>
<td>13 (43.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>90 (77.6%)</td>
<td>21 (70%)</td>
<td>0.472</td>
<td>1.484 (0.606-3.629)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (22.4%)</td>
<td>9 (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre B cell ALL</td>
<td>49 (42.2%)</td>
<td>12 (40)</td>
<td>0.728</td>
<td></td>
</tr>
<tr>
<td>T cell ALL</td>
<td>59 (50.9%)</td>
<td>18 (60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>5 (4.3%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td>3 (2.6%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of illness before diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-10 days</td>
<td>21 (18.1%)</td>
<td>5 (16.7%)</td>
<td>0.858</td>
<td></td>
</tr>
<tr>
<td>10-30 days</td>
<td>37 (31.9%)</td>
<td>11 (36.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30 days</td>
<td>58 (50%)</td>
<td>14 (46.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>104 (89.7%)</td>
<td>23 (76.7%)</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (1.7%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>10 (8.6%)</td>
<td>7 (23.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Therapeutic Intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydration + Steroids</td>
<td>109 (94%)</td>
<td>29 (96.7%)</td>
<td>0.849</td>
<td></td>
</tr>
<tr>
<td>Hydration + Steroids + Leukapheresis</td>
<td>2 (1.7%)</td>
<td>1(3.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>5 (4.5%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ICU Interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>6 (5.2%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation + Inotropes</td>
<td>2 (1.7%)</td>
<td>28 (93.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation + Inotropes + RRT</td>
<td>1 (0.9%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotropes</td>
<td>1 (0.9%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>106 (91.4%)</td>
<td>2 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory Data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (mg/dl) mean (+/- SD)</td>
<td>7.49 (+/-2.35)</td>
<td>7.26 (+/-2.51)</td>
<td>0.645</td>
<td>0.225 (-0.741-1.192)</td>
</tr>
<tr>
<td>WBCs (/cmm) median (IQR)</td>
<td>180 (130.8-293.7)</td>
<td>218 (123.2-350)</td>
<td>0.418</td>
<td></td>
</tr>
<tr>
<td>Platelets (c/mm) median (IQR)</td>
<td>31 (19-62)</td>
<td>22.5 (15-42.25)</td>
<td>0.092</td>
<td></td>
</tr>
<tr>
<td>LDH (IU/L) median (IQR)</td>
<td>3158.5 (1740.5-5115)</td>
<td>4897 (1125-7100)</td>
<td>0.600</td>
<td></td>
</tr>
<tr>
<td>Uric Acid (mg/dl) median (IQR)</td>
<td>5.7 (3.9-8.36)</td>
<td>7.6 (4.5-15.05)</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td>Potassium (meq/L) mean (+/- SD)</td>
<td>4.08 (+/-0.77)</td>
<td>3.85 (+/-0.68)</td>
<td>0.168</td>
<td>0.229 (-0.077-0.555)</td>
</tr>
<tr>
<td>Phosphorus (mg/dl) mean (+/- SD)</td>
<td>4.39 (+/-1.98)</td>
<td>3.9 (+/-2.15)</td>
<td>0.309</td>
<td>0.459 (0.431-1.351)</td>
</tr>
<tr>
<td>Calcium (mg/dl) mean (+/- SD)</td>
<td>8.9 (+/-0.89)</td>
<td>9.2 (+/-1.01)</td>
<td>0.176</td>
<td>-0.296 (-0.732-0.139)</td>
</tr>
<tr>
<td>Creatinine (mg/dl) median (IQR)</td>
<td>0.61 (0.5-0.8)</td>
<td>0.56 (0.43-0.9)</td>
<td>0.447</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>31 (26.7%)</td>
<td>18 (60%)</td>
<td>0.001</td>
<td>0.243 (0.105-0.562)</td>
</tr>
<tr>
<td>CNS</td>
<td>8 (6.9%)</td>
<td>6 (20%)</td>
<td>0.041</td>
<td>0.296 (0.094-0.933)</td>
</tr>
<tr>
<td>Infectious</td>
<td>43 (37.1%)</td>
<td>23 (76.7%)</td>
<td>&lt;0.001</td>
<td>0.179 (0.071-0.453)</td>
</tr>
<tr>
<td>Renal</td>
<td>25 (21.6%)</td>
<td>7 (23.3%)</td>
<td>0.833</td>
<td>0.903 (0.347-2.345)</td>
</tr>
<tr>
<td><strong>WBCs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100,000-200,000/cmm</td>
<td>66 (56.9%)</td>
<td>15 (50%)</td>
<td>0.541</td>
<td>1.320 (0.590-2.951)</td>
</tr>
<tr>
<td>&gt;200,000,000/cmm</td>
<td>50 (43.1%)</td>
<td>15 (50%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALL = Acute lymphoblastic Leukemia; AML = Acute Myelogenous Leukemia; CML = Chronic Myelogenous Leukemia; CNS = Central Nervous System; ICU = Intensive Care Unit; RRT = Renal Replacement Therapy; WBC = White Blood Cells; LDH = Lactate Dehydrogenase.
was no mortality related to acute metabolic complications or secondary to leukostasis in early phase of cytoreduction. Many deaths in this study could have been prevented by strict implementation of infection control policy in hospital and prompt broad spectrum antibiotics.

Acute hyperleukocytic leukemia in children is not uncommon and can be managed with appropriate supportive care and monitoring. Most of the deaths were related to sepsis during induction-remission phase of chemotherapy instead of early complications of hyperleukocytosis.

REFERENCES


