Management of children with acute leukemia and an elevated white blood cell count at diagnosis hyperleukocytosis

1.0 Introduction:

Newly diagnosed children with acute leukemia and hyperleukocytosis are at increased risk of early mortality due to severe cerebral, pulmonary and metabolic complications. Prompt reduction of the white blood cell count in these patients can be achieved by early start of chemotherapy or leukapheresis. Currently, there are no clear guidelines on the best management of such patients and particularly on when to perform leukapheresis. The following are empirical guidelines on the management of children with acute leukemia presenting with a white blood cell (WBC) count > 100,000/mm³. These guidelines will be used by Haematology/Oncology fellows & nurses, CCU fellows and nurses and the dialysis team.

2.0 Definitions

Hyperleukocytosis
Initial WBC > 100,000 /mm³

Leukapheresis
A therapeutic leukapheresis is a procedure where abnormal leukocytes are separated and removed from whole blood while the remainder of the blood is returned back to the patient.

3.0 Clinical Practice Guideline

All recommendations are Grade B.

Table 1. Grades of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>At least one randomized controlled trial, systematic review, or meta-analysis.</td>
</tr>
<tr>
<td>B</td>
<td>At least one cohort comparison, case study or other experiment study.</td>
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<tr>
<td>C</td>
<td>Expert opinion, experience of a consensus panel.</td>
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3.1 DIAGNOSIS OF HYPERLEUKOCYTOSIS

Definition: Initial WBC > 100,000 /mm³ at presentation or at relapse in children with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) or chronic myelogenous leukemia (CML).

Clinical symptoms:

- Neurologic: headache, seizure, decreased level of consciousness (ranging from mild confusion and somnolence to stupor and coma)
- Respiratory: cough, dyspnea, respiratory distress.

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- Vascular: cerebral thrombosis (especially in AML), retinal vein haemorrhage/thrombosis, renal vein thrombosis, acute limb ischemia, myocardial infarction and priapism.

Investigations:
- careful assessment for thrombocytopenia, coagulopathy and tumor lysis syndrome.
  NB: Platelets have to be counted manually since a high white blood cell count can result in the false elevation of automated platelet counts (depending on the machine used) due to the presence of white blood cells fragments.
- chest radiographs may be normal or show diffuse infiltrates.
- pulse oximetry may be helpful in demonstrating hypoxemia.
- consider a head CT if there is a high suspicion of intracranial haemorrhage (ICH): use contrast with caution in case of renal failure.

Hyperleukocytosis is considered a medical emergency. Children with symptoms due to leukostasis or with an extremely elevated WBC (as indicated below) require urgent admission to the medical/surgical critical care unit (CCU) for leukapheresis after consultation with the CCU staff. The Haematology/Oncology fellow and staff should be taking major responsibility for these patients upon arrival at the Emergency.

3.2 TREATMENT

3.2.1 Supportive measures:
- prevention and treatment of the acute tumor lysis syndrome including:
  - hydration with 0.9% sodium chloride IV at 3L/m²/day (or 200mL/kg/day if the child weighs less than or equal to 10kg). Contraindicated if child presents in acute renal failure. See Fluid and Electrolyte Administration in Children.
  - mannitol or furosemide to maintain urine output of at least 80% of input (especially for children with a weight of less than or equal to 10kg).
  - avoid potassium, calcium and phosphate in IV fluids
  - Rasburicase should be started immediately; there is no need for alkalinization with rasburicase (See SickKids' Formulary: Haematology/Oncology guideline: Rasburicase Use). Uric acid levels should be sent on ice after rasburicase use.
  - monitor serum creatinine, urea, urate, potassium, phosphate, calcium, sodium, albumin, and bicarbonate concentrations every 4 hours initially; glucose PRN.
- DIC and/or thrombocytopenia should be corrected aggressively:
  - keep the platelet count above 50 x 10⁹/L to reduce the risk of intracranial hemorrhage (the combination of thrombocytopenia and hyperleukocytosis is a risk factor for CNS hemorrhage).
- Avoid the transfusion of packed RBC: RBC transfusions worsen hyperviscosity and have been associated with increased morbidity and mortality in patients with hyperleukocytosis. In contrast, transfusion of platelets...
and fresh frozen plasma do not worsen the hematocrit. The judicious use of diuresis and gradual PRBC transfusion (e.g. slow transfusion of 3-5ml/kg of PRBC) is strongly recommended in case of congestive heart failure. Depending on the patient's condition, this can be repeated until hemoglobin level is satisfactory.

### 3.2.2 Reduction of the white blood cell count:

There are two ways to achieve a prompt reduction of the WBC in a patient diagnosed with acute leukemia: early start of chemotherapy or leukapheresis. While the relative merits and risks of both methods remain to be conclusively proven, we recommend starting chemotherapy promptly in all patients with hyperleukocytosis and to use leukapheresis for patients meeting the additional indications listed below.

#### i) Early start of chemotherapy

- Start induction chemotherapy as soon as the diagnosis of leukemia has been confirmed. Keep in mind that in cases of leukemia with hyperleukocytosis: diagnostic tests including morphology, flow cytometry, molecular tests and cytogenetics can be performed on a sample of peripheral blood; early start of therapy should not be postponed because of the delays associated with scheduling a diagnostic bone marrow aspirate.
- Be prepared for a prompt diagnosis and treatment of acute tumor lysis syndrome associated with the chemotherapy-induced breakdown of large number of leukemic blasts in patients with hyperleukocytosis (see supportive measures).
- Special arrangements must be made for antineoplastic therapy that must be initiated after 15:30 hours on weekends or statutory holidays. The Haematology/Oncology staff (or delegate i.e Haem/onc fellow) must contact a pharmacist to discuss the urgent need for antineoplastic therapy. Delays in the availability of the antineoplastic therapy should be expected since it may be necessary to call in additional pharmacy staff to prepare the required doses.
- Chemotherapy should not be delayed until after leukapheresis, as this procedure may take a long time to organize.

#### ii) Leukapheresis

**Definition:**
A therapeutic leukapheresis is a procedure where abnormal leukocytes are separated and removed from whole blood while the remainder of the blood is returned back to the patient\(^6\). A double blood volume processed is expected to reduce the initial WBC by 50%. Total Blood Volume is calculated as 100ml/kg for infants<1 month of age, 80 ml/kg for children between 1 month-10 years and 70 ml/kg for >10 years.

**Indications:**
- All patients with Acute Lymphoblastic Leukemia (ALL) or Acute Myeloid leukemia (AML) with WBC > 100 x 10^9/L and clinical signs or symptoms of hyperleukocytosis
- Asymptomatic patients with ALL and a WBC > 400 x 10^9/L\(^7\)
- Asymptomatic patients with AML and a WBC > 200 x 10^9/L .

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Contraindications:

- Leukapheresis is contraindicated in cases of acute promyelocytic leukemia (APL) due to the risk of catastrophic complications associated with the degranulation of the promyelocytes.
- **Massive intracranial haemorrhage.** A small intracranial bleed could be secondary to hyperviscosity and IS NOT a contraindication to leukapheresis, since the amount of citrate (used in the circuit) that goes into the patient circulation is minimal.

Preparation of leukapheresis:

The method requires the placement of a temporary double lumen central venous line (CVL) typically in the critical care unit (refer to the sickkids heparinization policy and procedure for choice of CVL; consult with the apheresis nurse if unclear), the performance of the leukapheresis procedure by the apheresis team as ordered by the hematology/oncology team and the availability of sufficient amounts of blood products in blood bank. As a result, if a decision is made to perform leukapheresis then the Haem/Onc fellow should:

- notify the attending physician (Haematology/oncology)
- alert the apheresis team (through locating) ASAP
- inform blood bank
- arrange for an urgent admission to CCU for: 1) CVL placement, and 2) Leukapheresis
- pre-leukapheresis (within 2 hrs) order STAT CBC (no need for diff), ionized calcium, albumin, potassium, phosphate and magnesium

In case of a possible delay in preparing for leukapheresis: start chemotherapy in the meantime and monitor WBC frequently.

Possible complications:

i) Hyperviscosity and subsequent stroke:

The leukapheresis circuit requires priming. In order to reduce the risk of hyperviscosity: use reconstituted whole blood (RWB, with added FFP) with a hematocrit closest to the patient’s hematocrit, or use the following specific parameters: if the patient’s Hct <0.15 use RWB with Hct of 0.18; patient’s Hct 0.15-0.25 use RWB with Hct 0.2; patient’s Hct 0.25-0.35 use RWB with Hct 0.3; patient’s Hct >0.35 use RWB with Hct 0.4; regular RWB (when Hct is not specified on the REQUISITION FOR BLOOD PRODUCTS) has Hct of 0.4 to 0.5. To calculate the patient’s actual Hct use this formula: Hct= Hb x 3÷1000. After the procedure is completed do not return the priming solution (RWB) into the patient. As a replacement solution use a combination of FFP, or 5% albumin, and platelets. The apheresis team has corresponding guidelines. Confirm the details of the procedure for each patient.

ii) Hypocalcemia, hypokalemia and thrombocytopenia:

- Heart rate & blood pressure are monitored at least every 15 minutes during the procedure; CBC, hematocrit, ionized calcium, magnesium, potassium, phosphate and albumin are monitored prior to, half-way through and immediately following the procedure.
- Calcium infusions, except those required to counteract the effect of citrate toxicity, are contraindicated unless
there is symptomatic hypocalcemia (hyperleukocytosis may be associated with hyperphosphatemia, in which case infusion of calcium may result in precipitation of calcium phosphate). Calcium infusions should never be given at the same time with bicarbonate infusions.

- In case of severe hypokalemia (K ≤ 2.5) may give potassium infusions very cautiously. Stop IV K as soon as the serum potassium concentration reaches the lower limit of normal for age especially after the start of chemotherapy.
- During leukapheresis transfuse platelets via peripheral IV (during and after the procedure PLT count is expected to drop). If the post-leukapheresis CBC shows PLT < 50 x 10^9 --> transfuse more platelets.

-iii) Hypomagnesemia^a^: correct accordingly.

-iv) Hypovolemia, hypotension and restlessness: consider normal saline (NS) bolus.

-v) Hypervolemia, hypertension, edema and hypoalbuminemia: anticipate need for a Foley catheter and diuretics, with or without albumin infusions.

-vi) Blood transfusion reaction: fever, chills, irritability, rash, dyspnea: all patients are premedicated with Diphenhydramine (Benadryl). Give more Benadryl and hydrocortisone. In case of anaphylaxis: stop procedure, notify MD, start NS bolus, give epinephrine and start oxygen.

-vii) Dysrhythmias: sinus bradycardia^b^, ST changes and prolonged QT interval^b^, Monitor ECG during procedure; obtain STAT calcium, potassium.

-viii) Respiratory distress and decrease in oxygen saturation may occur due to pulmonary emboli or to worsening pulmonary leukostasis^b^ (after the procedure) or fluid overload: obtain chest x-ray, ECG; consider decreasing IV fluids; may need VQ scan/spiral chest CT. Systemic inflammatory response syndrome can also cause respiratory distress: consult with the Hem/Onc staff for management.

.ix) Chilling: Blood that is removed during the procedure cools slightly causing the patient to suffer chills. The leukapheresis machine is accompanied by a blood warmer, but to minimize chilling, warm blankets may need to be applied^c^. Chilling can also be due to citrate toxicity and/or to a blood transfusion reaction.

-x) Femoral vein thrombosis^b^: can be prevented by removing the femoral line as soon as feasible. Consult thrombosis service for treatment with heparin.

**After leukapheresis:**

If the WBC has decreased and there are no symptoms secondary to hyperleukocytosis, there is no need to perform a second leukapheresis procedure even if the WBC remains above 100 x 10^9/L. Continue to avoid a transfusion of packed...
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RBC even after leukapheresis unless the WBC is lower than 100 x 10⁹/L or the lack of RBC transfusion would result in a life-threatening clinical situation.

Currently, there are conflicting data that leukapheresis is effective in the immediate management of hyperleukocytosis. Therefore, these guidelines are only empirical and appropriate clinical judgment should be used.

4.0 Related Documents

SickKids' Formulary Haematology/Oncology Guideline==> Rasburicase Use

5.0 Statement of Evidence

The literature search was done initially in 2006 and again in the fall of 2008 on Pubmed using key words: hyperleukocytosis, children, leukemia, leukapheresis. The recommendations were derived in part by conclusions from the literature and in part by general local consensus. These guidelines are driven from 3 pediatric retrospective case series⁵,⁷,⁸. All recommendations are Grade B.

Table 1 serves as a guideline to the hierarchy of evidence available; with meta-analysis considered to be the highest level of evidence and expert opinion considered to be the lowest level of evidence that can be used to support each recommendation in this CPG.

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6.0 References:


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Internal Reviewer:
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Attachments:
  Revision History.docx