Leukapheresis for Hyperleukocytosis in Acute Leukemia

**ALGORITHM 1**

### Inclusion Criteria
- New diagnosis or relapse of acute leukemia
- White blood cell count (WBC) ≥ 100,000/μL

### Exclusion Criteria
- Known diagnosis or high suspicion of acute promyelocytic leukemia (APML) or myelogenous leukemia (CML) in chronic phase
- Any symptoms of leukostasis
- Presence of concerning symptoms should be discussed among Oncology/Leukemia, PICU, and Apheresis teams involved.

#### Any symptoms of leukostasis present?

- Yes
  - **Consider:**
    - Hydroxyurea or steroid prophase in discussion with Leukemia faculty member.
    - Leukapheresis as bridge to definitive chemotherapy (as directed by Oncology).

- No
  - **Start definitive chemotherapy regimen to be determined by Oncology team.**
    - In addition may consider leukapheresis, particularly if WBC ≥ 400K, symptoms of leukostasis present, or with concern for treatment delay.
      *See algorithm 2 for Leukapheresis Coordination*

### Start definitive chemotherapy-regimen to be determined by Oncology team.

#### Consider:
- Hydroxyurea or steroid prophase in discussion with Leukemia faculty member.
- Leukapheresis as bridge to definitive chemotherapy (as directed by Oncology).

### Start definitive chemotherapy-regimen to be determined by Oncology team.

#### In addition may consider leukapheresis (excluding APML or CML), particularly if monocytic, symptoms of leukostasis present, or with concern for treatment delay.

*See algorithm 2 for Leukapheresis Coordination*
Leukapheresis Coordination

ALGORITHM 2

- Care conference coordinated between Oncology and PICU team (via call or in person)

- Leukapheresis desired by medical teams

  - Contact Transfusion Medicine ASAP and place Transfusion Medicine Consult in EPIC

  - Discuss timing and venous access options with PICU, Oncology and Transfusion Medicine
    - Consult Apheresis Catheter Guidelines for venous access decision making (*see link at bottom of page)
    - Establishing venous access is often the rate limiting step to initiation of leukapheresis

  - Venous access obtained and catheters in place

- Leukapheresis initiated
  - Set up for leukapheresis by the Transfusion Medicine team generally takes 1-2 hours from time of apheresis RN arrival
  - Coordination of leukapheresis timing between PICU and Transfusion Medicine team is paramount to a successful procedure

**Apheresis Catheter Guidelines: Short Term Use**
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Clinical Management
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TARGET POPULATION

Inclusion Criteria
- New diagnosis or relapse of acute leukemia
- White blood cell count (WBC) ≥ 100,000/µL

Exclusion Criteria
- Known diagnosis, or high suspicion of, acute promyelocytic leukemia (APML) or chronic myelogenous leukemia (CML) in chronic phase

BACKGROUND | DEFINITIONS

Hyperleukocytosis in Acute Leukemia

Definition
- **Hyperleukocytosis**: white blood cell (WBC) count ≥ 100,000/µL
- Indicates increasing risk for leukostasis with subsequent end organ damage (usually affecting central nervous system, lungs and kidneys) and disseminated intravascular coagulation (DIC)

Pathophysiology
- Hyperviscosity of blood
  - Due to high fractional volume of leukocytes and the reduced deformability of blasts
  - Blasts are larger diameter than lymphocytes, with average size of myeloblast being larger than lymphoblast [1]
- Increased adhesion of cells to endothelium
  - Upregulation of adhesion molecules (ICAM, VCAM, E-selectin) and increased cytokine (IL-1b, TNF-α) and enzyme (MMP) release seen with hyperleukocytosis, particularly monocytic (M4/M5) acute myeloid leukemia (AML) [2]

Outcomes in Hyperleukocytosis
- Risk of early complications
  - In AML, the risk of respiratory complications (hypoxia, hemorrhage) and neurologic complications (ischemia, hemorrhage) during induction 1 were significantly higher for patients with WBC > 100,000/µL [3]
In acute lymphoblastic leukemia (ALL), the overall risk of early complications in the first 14 days is rare, with most occurring at presentation rather than developing

- Complications occur at lower WBC levels in AML than in ALL
  - Lowe et al reported neurologic complications (grade 3 or 4 toxicity, predominantly central nervous system, CNS, hemorrhage) in 4/111 ALL patients (3.6%) with WBC < 400,000/µL versus 12/67 patients (17.9%) with WBC ≥ 400,000/µL [4]
  - Abla et al reported neurologic complications (all CNS hemorrhage) in 1/62 ALL patients (1.6%) with WBC < 400,000/µL versus 5/22 patients (22.7%) with WBC ≥ 650,000/µL [5]

- Risk of early death (variably defined as death in first 14 days or during induction)
  - In pediatrics, early death rate in patients with hyperleukocytosis is estimated at 9-17% in AML [3,6] and 4% in ALL (using WBC > 200,000/µL) [4]
    - Mortality is highest in patients with both respiratory and neurologic symptoms
  - The utility of leukapheresis in reducing risk of early complications and/or early death remains unclear (please see page 5 under “Use in hyperleukocytosis” for more information)

**INITIAL EVALUATION**

Assess for symptoms of leukostasis

Concerning symptoms should be discussed among all involved providers (Oncology/Leukemia, Transfusion Medicine, PICU, etc.) to determine if indication for leukapheresis exists

<table>
<thead>
<tr>
<th>Affected System</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Imaging findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system (CNS):</td>
<td></td>
<td></td>
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<tr>
<td>Headache</td>
<td>Papilledema</td>
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<tr>
<td>Dizziness</td>
<td>Retinal hemorrhage</td>
<td></td>
<td></td>
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<tr>
<td>Vision disturbance</td>
<td>Retinal vein distension</td>
<td></td>
<td></td>
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<tr>
<td>Tinnitus</td>
<td>Cranial nerve palsies</td>
<td></td>
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<tr>
<td>Ataxia</td>
<td>Intracranial ischemia or hemorrhage</td>
<td></td>
<td></td>
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<tr>
<td>Confusion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Somnolence/coma</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Respiratory:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Hypoxia/hypoxemia</td>
<td></td>
<td></td>
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<tr>
<td>Dyspnea at rest</td>
<td>Respiratory failure</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Bilateral infiltrates on radiographic evaluation of chest</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary hemorrhage</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>“Pulmonary leukostasis syndrome”**: bilateral infiltrates, tachypnea, hypoxia</td>
<td></td>
<td></td>
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<tr>
<td>Renal/Metabolic:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliguria</td>
<td>Acute kidney injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anuria</td>
<td>Tumor lysis syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIC</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Priapism</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arrhythmia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Peripheral vascular occlusion</td>
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</tr>
</tbody>
</table>

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* Incidence of affected systems in hyperleukocytosis: 27% CNS, 39% respiratory, and 14% renal [7]

* Severity of symptoms may indicate probability of relevant leukostasis, provided that other causes are not found. Grade 3+: severe, limiting self-care activities of daily living
Pulse ox may be unreliable due to increased methemoglobinemia and blood gas analysis can be altered by excessive oxygen consumption by leukocytes [8]. Concern for leukostasis should be highest for true respiratory failure requiring positive pressure or intubation without other clear identifiable causes, rather than mild hypoxia alone.

d The presence of tumor lysis syndrome alone would not indicate “symptomatic leukostasis” given ability to manage with supportive care measures in the vast majority of cases.

**Laboratory and Imaging Assessment**

**Recommended:**
- Complete blood count (CBC) with differential
- Peripheral blood smear
- Peripheral flow cytometry
- Comprehensive metabolic panel (CMP), uric acid
- DIC panel (PT/INR, PTT, D-dimer)
- Chest X-ray
  - Evaluate for presence of mediastinal mass

**Other considerations:**
- Blood cultures
  - If febrile, ill-appearing, or if starting antibiotics
- Computed tomography (CT) of chest
  - If concern for respiratory failure representing sequelae of leukostasis to evaluate for other potential causes (i.e., pneumonia)
- Head CT or brain magnetic resonance imaging (MRI) (may consider fast brain MRI/shunt series)
  - If concern for neurologic symptoms representing sequelae of leukostasis to evaluate for hemorrhage or embolic stroke, or to rule out other etiologies (Note: neuroimaging is not required for decision making for leukapheresis and clinical exam remains most important)

**CLINICAL MANAGEMENT**

**Supportive Care**

**Tumor lysis management**
- Hyperhydration with careful fluid management
- Rasburicase (see guideline) +/- allopurinol
- Amphogel + low phosphorus diet (if not NPO)
- Serial monitoring of potassium, phosphorus, uric acid, and calcium as well as overall renal function

*Please reference the departmental specific resource “Leukemia and Lymphoma Supportive Care Guidelines: General Management” for specifics regarding tumor lysis management.*

**Blood product support & optimization of coagulation**
- Conservative use of packed red blood cell (PRBC) transfusion due to risk of increased hyperviscosity; if necessary (in setting of developing heart failure, and would generally consider for hgb ≤ 4.5), administer small volumes (< 5 ml/kg), slowly with frequent re-assessment
- Liberal use of platelet transfusion due to risk of hemorrhage
  - Typically maintain platelets ≥ 50,000/µL until WBC showing significant improvement, or ≥ 100,000/µL if concern for stroke or CNS hemorrhage
- Serial monitoring for bleeding and DIC panel
If active bleeding or DIC:
  - Transfuse fresh frozen plasma (FFP) to maintain PT and PTT within normal limits
  - Transfuse cryoprecipitate to maintain fibrinogen > 100-150 mg/dL
  - Avoid routine use of heparin or anti-fibrinolytics

Prevention/treatment of infection
- If history of fevers or febrile at presentation, or ill-appearing at any time, start empiric antimicrobials
  - Cefepime recommended for broad coverage with consideration of adding Vancomycin if ill-appearing

Cytoreduction
Chemotherapy
- Prompt initiation of definitive versus temporizing (hydroxyurea, steroid, or low-dose cytarabine prophase) chemotherapy should be started based on patient’s likely leukemia phenotype and clinical status, as determined by Oncology/Leukemia team

Leukapheresis
- Rationale
  - Provides prompt leukoreduction to be used as an adjunct, or bridge, to starting definitive therapy
  - Historically, was also used to control or prevent metabolic complications (tumor lysis), though this is less applicable now with the consistent use of rasburicase and other aggressive supportive care measures [3]
  - Use in hyperleukocytosis
    - There are no definitive conclusions for the efficacy of leukapheresis in hyperleukocytosis. Evaluation of published literature is difficult due to: retrospective studies, lack of consistency in decision to treat and subsequent selection bias (majority of studies use physician discretion as indication for leukapheresis), variability in treatment (+/- concomitant chemotherapy) and outcome measures, and the routine use of historical controls for comparison
    - In pediatric ALL, Nguyen et al showed there was no significant difference in the rate of early complications between leukapheresed (n=9) and non-leukapheresed (n=44) patients [9]
    - In AML, there is conflicting data regarding effect of leukapheresis on the risk of early death
      - A reduction in early death following leukapheresis is reported in several adult AML studies, but with no associated difference in remission rate or long-term survival [10-12]
      - No difference in early death following leukapheresis was seen in pediatric AML [3] and adult AML [13, 14] studies, or in meta-analyses [15, 16]
    - American Society of Apheresis Guidelines [17] (Figure 1)
      - Leukapheresis has a category II indication (accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment) for the treatment of symptomatic leukostasis
      - No well-accepted criteria for defining symptomatic leukostasis
      - To better define symptoms, Novotny et al introduced a grading system for an individual patient’s risk of leukostasis [18] (Figure 2), with the high probability group showing higher risk of early death in a secondary analysis [19]
      - “Chemotherapy should not be postponed and is required to prevent rapid re-accumulation of circulating blasts” [18]
- Leukapheresis has a category III indication (role not well established so decision making should be individualized) for prophylaxis in high-risk patients (AML with WBC ≥100,000/µL, especially monocytic AML, or ALL with WBC ≥ 400,000/µL)

- Leukapheresis procedure
  - Procedure basics
    - **Age**: Leukapheresis has been performed on even very young patients, but in these patients, one could also consider use of manual exchange transfusion for leukoreduction as well [20]
    - **Access**: Requires a rigid, large diameter catheter to provide consistent flow and a minimally traumatic environment for removal of WBCs
      - **CHCO Requirements**: dual lumen, each at least 4 French diameter for turbo flow
      - See most updated Apheresis Catheter Guidelines available at: Apheresis Catheter Guidelines: Short Term Use
    - **Timing**:
      - Apheresis is available at CHCO at any time if deemed clinically indicated
      - Typically requires 1-2 hours of transfusion medicine preparation before procedure can start, assuming appropriate access obtained, and takes approximately 2-6 hours to complete procedure
  - **Risks**: Overall well tolerated and safe at experienced institutions
    - Delay in starting definitive chemotherapy [3,4,14]
    - Line-associated risk of bacteremia/sepsis, bleeding, or thrombosis
    - Transfusion reaction (priming performed with PRBCs)
    - Hypocalcemia secondary to citrate anticoagulant (calcium supplement routinely given and calcium levels monitored during procedure)
    - Blood loss (mean reductions of 45% and 16% in platelet count and hemoglobin, respectively) [21]
  - **Goal**
    - No universally accepted criteria, but general goal is for resolution of leukostasis symptoms and WBC < 100,000/µL (AML) or < 400,000/µL (ALL)
    - One procedure typically processes 1-2 total blood volumes and can reduce WBC by 30-60% [17]; thus, most patients require only one procedure
Figure 1: American Society of Apheresis Recommendations for Use of Leukapheresis in Hyperleukocytosis [17]

**HYPERLEUKOCYTOSIS**

<table>
<thead>
<tr>
<th>Incidence: AML: WBC &gt;100x10⁹/L; 5-13% adults; ALL: WBC &gt;400x10⁹/L; 10-30% adults</th>
<th>Indication</th>
<th>Procedure</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic</td>
<td>Leukocytopheresis</td>
<td>Grade 2B</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Prophylactic or secondary</td>
<td>Leukocytopheresis</td>
<td>Grade 2C</td>
<td>III</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># reported patients: &gt;300</th>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>0</td>
<td>14(2400)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ALL</td>
<td>0</td>
<td>6578</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia

Figure 2: Probability of Leukostasis Deduced from the Severity of Symptoms Attribute to Leukostasis (no obvious other causes) [18]

<table>
<thead>
<tr>
<th>Group</th>
<th>Probability of leukostasis syndrome</th>
<th>Severity of symptoms</th>
<th>Pulmonary symptoms</th>
<th>Neurologic symptoms</th>
<th>Other organ systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not present</td>
<td>No limitations</td>
<td>No symptoms and no limitations in ordinary activities</td>
<td>No neurologic symptoms</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Possible</td>
<td>Slight limitations</td>
<td>Mild symptoms and slight limitation during ordinary activity, comfortable at rest</td>
<td>Mild tinnitus, headache, dizziness</td>
<td>Moderate fatigue</td>
</tr>
<tr>
<td>2</td>
<td>Probable</td>
<td>Marked limitations</td>
<td>Marked limitation in activity because of symptoms, even during less than ordinary activity, comfortable only at rest</td>
<td>Severe visual disturbances¹, severe tinnitus, headache, dizziness</td>
<td>Severe fatigue</td>
</tr>
<tr>
<td>3</td>
<td>Highly probable</td>
<td>Severe limitations</td>
<td>Dyspnoea at rest, oxygen or respirator required</td>
<td>Severe visual disturbances¹, acute inability to read, confusion, delirium, somnolence, intracranial haemorrhage</td>
<td>Myocardial infarction, priapism, ischaemic necrosis</td>
</tr>
</tbody>
</table>

¹Blurred vision, diplopia, hemianopia.
REFERENCES

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