Leukapheresis for Hyperleukocytosis in Acute Leukemia

ALGORITHM 1

Assess for symptoms of leukostasis

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

Affected System[a]	Symptoms[b]	Signs	Imaging findings
Central nervous system (CNS):	Headache Dizziness Vision disturbance Tinnitus Ataxia Confusion Somnolence/coma	Papilledema Retinal hemorrhage Retinal vein distension Cranial nerve palsies	Intracranial ischemia or hemorrhage
Respiratory:	Tachypnea Dyspnea at rest	Hypoxia/hypoxemia[c] Respiratory failure	Bilateral infiltrates on radiographic evaluation of chest Pulmonary hemorrhage
	"Pulmonary leukostasis syndrome": bilateral infiltrates, tachypnea, hypoxia		
Renal/Metabolic:	Oliguria Anuria	Acute kidney injury Tumor lysis syndrome[d]	
Other:	DIC Priaprism Myocardial infarction Arrhythmia Peripheral vascular occlusion		

Evaluate patient degree of tumor lysis and coagulopathy
Start prompt supportive care

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

Review smear, obtain peripheral flow, and coordinate diagnostic procedures ASAP

Any symptoms of leukostasis present?
*Presence of concerning symptoms should be discussed among Oncology/Leukemia. PICU, and Apheresis teams involved.
(See inset table and on page 4)

Yes

Is likely leukemia phenotype known?

Yes

Phenotype

Lymphoid

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

Myeloid

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

No

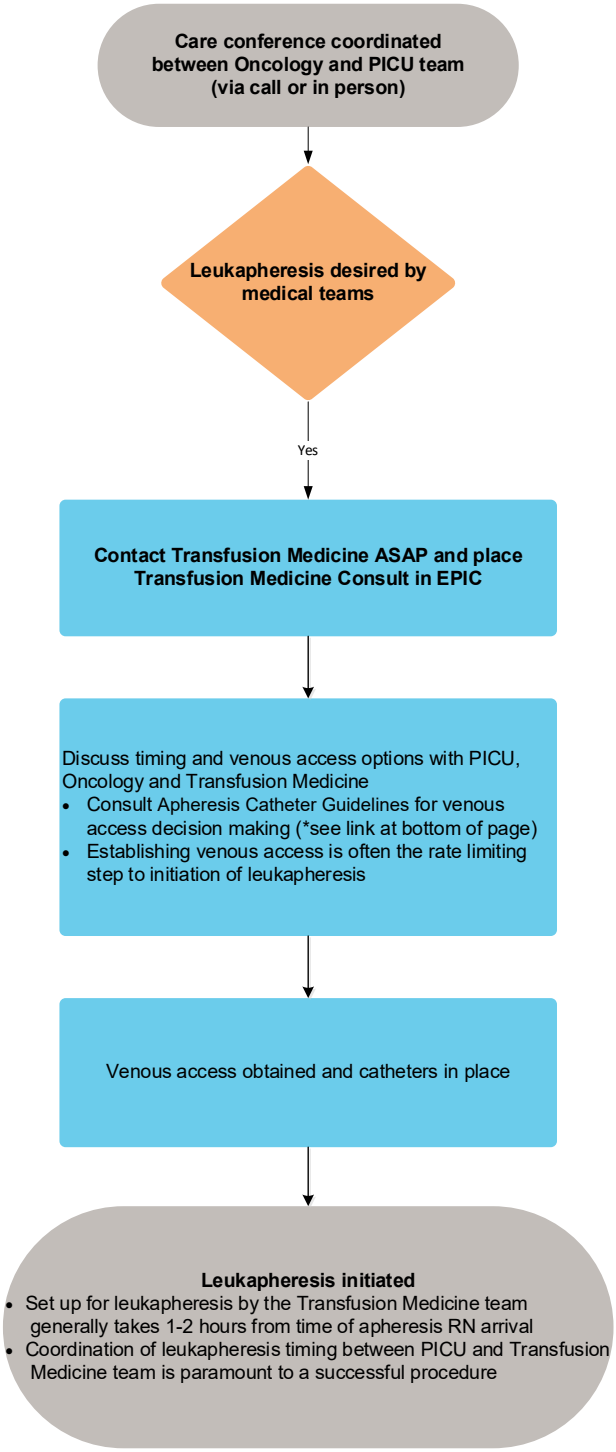
Consider:
- Hydroxyurea or steroid prophase in discussion with Leukemia faculty member.
- Leukapheresis as bridge to definitive chemo therapy (as directed by Oncology)

No

Continue surveillance for leukostasis symptoms, supportive care and diagnostic work-up to start definitive chemotherapy (as directed by Oncology).

Leukapheresis Coordination

ALGORITHM 2



Apheresis Catheter Guidelines: Short Term Use

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TARGET POPULATION

Inclusion Criteria

- New diagnosis or relapse of acute leukemia
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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

Affected System[a]	Symptoms[b]	Signs	Imaging findings
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	"Pulmonary leukostasis syndrome": bilateral infiltrates, tachypnea, hypoxia		
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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 <u>symptomatic leukostasis</u>
      - 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

Incidence: AML: WBC >100×10^9/L; 5-13% adults; ALL: WBC >400×10^9/L; 10-30% adults	**Indication**	**Procedure**	**Recommendation**	**Category**
	Symptomatic	Leukocytapheresis	Grade 2B	II
	Prophylactic or secondary	Leukocytapheresis	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
AML	0	14(2400)	NA	NA
ALL	0	6(578)	NA	NA

AML = acute myeloid leukemia; ALL = acute lympoblastic leukemia

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

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

[1]Blurred vision, diplopia, hemianopia.

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APPROVED BY

Clinical Pathways and Measures Review Committee – November 22, 2021
Pharmacy & Therapeutics Committee – November 4, 2021

MANUAL/DEPARTMENT	Clinical Pathways/Quality
ORIGINATION DATE	November 22, 2021
LAST DATE OF REVIEW OR REVISION	November 22, 2021
COLORADO SPRINGS REVIEW BY	N/A per Dr. DiStefano
APPROVED BY	 Lalit Bajaj, MD, MPH Chief Quality Outcomes Officer

REVIEW | REVISION SCHEDULE

Scheduled for full review on November 22, 2025

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