Leukoreduction for Management of 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		

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

Evaluate degree of tumor lysis and coagulopathy
Start prompt supportive care

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

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

Yes

No

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

Is likely leukemia phenotype known?

Yes

No

Consider temporizing therapy with Hydroxyurea, steroid prophase, or low-dose cytarabine in discussion with Leukemia faculty member.
Continue surveillance for leukostasis symptoms and supportive care
In instances of diagnostic delay, suboptimal response to temporizing therapy, and symptoms of leukostasis, can consider red cell exchange
(See Clinical Management, Cytoreduction on Page 6)
*see Algorithm 2 for Apheresis Team coordination

Phenotype

Lymphoid

Myeloid

Start definitive chemotherapy (as directed by Oncology)
In instances of WBC greater than or equal to 400K, suboptimal response to chemotherapy, and symptoms of leukostasis, can consider red cell exchange (See Clinical Management, Cytoreduction on Page 6)
*See Algorithm 2 for Apheresis Team coordination

Start definitive chemotherapy (as directed by Oncology)
In instances of suboptimal response to chemotherapy and symptoms of leukostasis, can consider red cell exchange
(See Clinical Management, Cytoreduction on Page 6)
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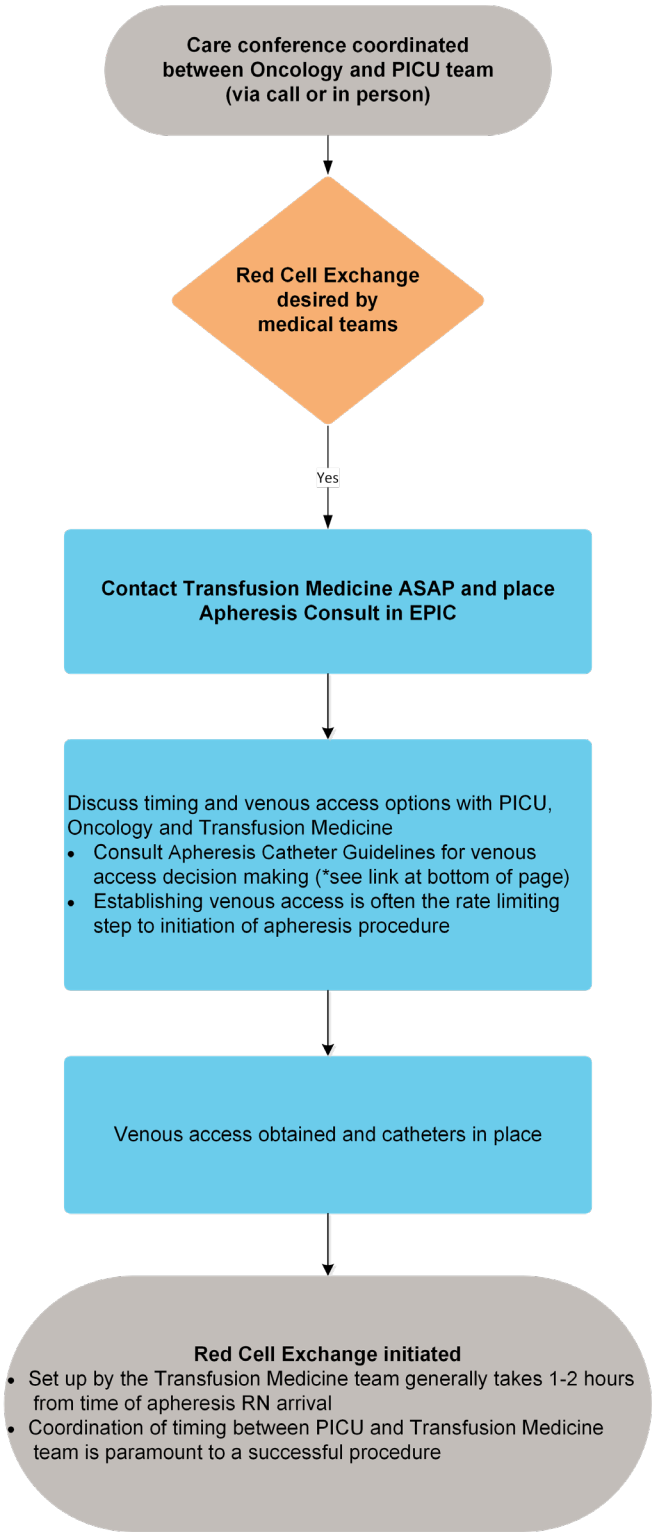
Apheresis Team Coordination

ALGORITHM 2



Apheresis Catheter Guidelines: Short Term Use

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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
    - Rationale:
        - Leukostasis is extremely rare in CML regardless of WBC
        - Apheresis procedures are contraindicated in APML due to high risk of worsening DIC

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

INITIAL EVALUATION

Assess for symptoms of leukostasis

Concerning symptoms should be discussed among all involved providers (Oncology/Leukemia, Transfusion Medicine, PICU, etc.)

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
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	"Pulmonary leukostasis syndrome": bilateral infiltrates, tachypnea, hypoxia		
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[a] Incidence of affected systems in hyperleukocytosis: 27% CNS, 39% respiratory, and 14% renal [7]

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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
- Phosphate binding medication (e.g. Amphogel, sevelamer) + 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 $\leq$ 4.5), administer small volumes ($\leq$ 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 team

Red Cell Exchange

- Rationale
  - Nationally, leukocyte reduction via leukapheresis is being performed less in favor of early chemotherapy initiation and aggressive supportive care measures, and the American Society of Apheresis reduced the recommendation for leukapheresis from Category II to Category III for symptomatic leukostasis in 2023 [9]. Given the rarity of need for leukapheresis procedure historically at CHCO, maintenance of competency is difficult and thus this procedure is not available.
  - Red cell exchange may be used in the setting of symptomatic leukostasis after the initiation of chemotherapy. Mack et al demonstrated feasibility of using red cell exchange and found it reduced the WBC similarly compared to leukodepletion alone [10]

- Apheresis procedure
  - Procedure basics
    - Age: Red cell exchange 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 [12]
    - Access: Requires a rigid, large diameter catheter to provide consistent flow and a minimally traumatic environment for removal of WBCs
      - CHCO Requirements: dual lumen HD catheter
      - 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

- Line-associated risk of bacteremia/sepsis, bleeding, or thrombosis
- Transfusion reaction (use of RBCs)
- Hypocalcemia secondary to citrate anticoagulant (calcium supplement routinely given and calcium levels monitored during procedure)

- 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 total blood volume and can reduce WBC by 20-60% [10]

Figure 1: American Society of Apheresis Recommendations for Use of Leukapheresis in Hyperleukocytosis [9]

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

RCT= Randomized controlled trial
CT= Controlled trial
CS= Case series
CR= Case report
Category III definition= Optimum role of apheresis therapy is not established. Decision-making should be individualized.
Grade 2B definition= Weak recommendation, moderate-quality evidence (best action may differ depending on circumstances or patients' or societal values)

Figure 2: Probability of Leukostasis Deduced from the Severity of Symptoms Attribute to Leukostasis (no obvious other causes) [11]

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 – 11/25/2024
Pharmacy & Therapeutics Committee – 12/5/2024

MANUAL/DEPARTMENT	Clinical Pathways/Quality
ORIGINATION DATE	November 22, 2021
LAST DATE OF REVIEW OR REVISION	12/19/2024
COLORADO SPRINGS REVIEW BY	N/A per Dr. DiStefano
APPROVED BY	 Leigh Anne Bakel, MD Medical Director Clinical Pathway Program
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REVIEW | REVISION SCHEDULE

Scheduled for full review on 11/25/2027

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