Pediatric Hyperleukocytosis (PICU / Acute Care) Pathway

Pathway Purpose: Prompt notification of the multidisciplinary team involved in the care of children with hyperleukocytosis, to facilitate contingency plans, and minimize morbidity through expedited initiation of leukemia-directed treatment.

Inclusion Criteria
- Newly diagnosed or known acute leukemia

AND ONE OF THE FOLLOWING
- WBC ≥100K/microL
- WBC <100K/microL but with signs of leukostasis*

SIGNS OF LEUKOSTASIS
- Neuro: headaches, visual changes, seizures, altered mental status, focal deficits
- Resp: hypoxemia, shortness of breath, diffuse infiltrates
- Renal: Cr >2x baseline; Cr >1.5mg/dL, UOP <1cc/kg/hr

Prior to admission

- **Determine if patient needs PICU based on criteria below:**
  - Clinical concern and/or need for higher level of nursing care
  - WBC >200K/microL
  - Presence of mediastinal mass with airway or hemodynamic compromise (*see Anterior Mediastinal Mass Clinical Pathway*)
  - Signs of leukostasis*
- If going to PICU: PICU fellow to notify oncology fellow upon initial call
- Onc fellow to notify hematopathology and pharmacy of need for emergent diagnosis/therapy
- **If transfer from outside hospital (if possible, should not delay transfer):**
  - Request blood smear to be brought
  - Request 4 ml in EDTA to be brought (to send immediately for flow)

On admission

Lab studies

- CBCD and slide review, peripheral smear
  - *Repeat q4-6hr until WBC consistently declining*
  - *Onc and heme-path to review smear*
- CMP+Mg+Phos, uric acid, LDH
  - *Repeat q4-6hr*
- iSTAT K+ (*Leukocytolysis in lab samples can increase K+)*
- Venous blood gas and lactate with every CBC
- Coagulation panel, type and screen
- Peripheral blood flow cytometry
  - *Send STAT, onc to notify heme-path*

Imaging studies

- Chest x-ray AP and Lateral
- Head CT if symptomatic **OR** suspicion for acute myeloid leukemia (AML) (*Should not delay initiation of treatment)*

Additional measures

Team huddle (organized by oncology):
- If in PICU: ICU resident/APP, ICU attending, ICU fellow, onc attending, onc fellow, and ICU RN
- If on acute care: Onc resident/APP, onc attending, onc fellow, and onc RN
- If needed (e.g. mediastinal mass): anesthesia and Peds IR
- If concern for intracranial hemorrhage (ICH) by exam or CT scan: neurosurgery (fellow/attending)
- If concern for disseminated intravascular coagulation (DIC): hematology (fellow/attending)

Other
- Implement neuroprotective measures for all patients
- Begin hyperhydration with 2x maintenance IV fluids (NO K+ in fluid)
- Renal and cerebral NIRS monitoring

Contingency planning (discuss during huddle)

Does patient warrant initiation of empiric leukemia-directed therapy? → See next page for empiric treatment flowsheet

Should this patient receive blood products urgently prior to diagnosis and at what volume and rate? (Note: use cryoprecipitate to correct fibrinogen; use FFP to correct INR)

- For patients WITHOUT ICH, DIC, or bleeding transfuse if: Platelets ≤50K, INR >3.0. ONLY transfuse pRBC if evidence or inadequate oxygen delivery (and proceed with caution)
- For patients WITH ICH, DIC, or bleeding transfuse if: Platelets ≤100K, INR >2.0, fibrinogen <100. ONLY transfuse pRBC if evidence of inadequate oxygen delivery (and proceed with caution)

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Within 6 hours of admission

Leukostasis Risk Stratification

Huddle between oncology and hematopathology teams to review smear and determine morphology
Note: symptomatic leukostasis is a **TRUE MEDICAL EMERGENCY** and requires leukemia-directed therapy ASAP

Provisional Low Risk (all of the below):

- No signs of leukostasis* *(see first page)*
- Patient well-appearing
- Morphology favoring:
  - Acute lymphocytic leukemia (ALL)
  - Chronic myeloid leukemia (CML)

High Risk (any of the below):

- Signs of leukostasis* *(see first page)*
- Patient ill-appearing
- Morphology favoring:
  - Acute myeloid leukemia (AML)
  - Acute promyelocytic leukemia (APML)
  - Ambiguous morphology

See **next page** for guidelines for empiric therapy based on morphology and symptomatology

- Leukemia-directed therapy to be initiated upon confirmation of diagnoses by flow cytometry

- If indicated, initiate chemotherapy ASAP (goal within 6 hours of admission)

***Note**: If patient is symptomatic and unable to initiate empiric leukemia-directed therapy within 6 hours, PICU to place a pheresis catheter*

Within 24 hours of admission

Additional diagnostic work-up

Managed by oncology:

- Blood flow cytometry review
- Bone marrow aspirate/biopsy
- Lumbar puncture +/- intrathecal chemo
- Initiation of leukemia-directed therapy (if not already done)

Managed by primary team (onc or PICU)

- Echocardiogram
- EKG
- Ophthalmologic evaluation (if eye/vision symptoms)
- Central line/PICC placement

Pathology contacts:

Flow Cytometry: 650-724-2250
Pathology: Flow Service (M-F daytime): 650-529-5634
Pathology: Marrow Service (M-F daytime): 650-529-5635
Hematopathology Fellow (after hours pager): 12005

Owner: Katherine Steffen, MD, Felice Su, MD, Agnes Reschke, MD, Michael Link, MD, Kathleen Sakamoto, MD, Tanja Gruber, MD, Sean Green, PharmD
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Empiric leukemia-directed therapy

This is to guide treatment and should not replace clinical judgement. Reassess based on risk of tumor lysis at each dose.

Morphology suggestive of ALL → **Symptomatic?**

- Yes → **Recommend initiation of:**
  - Prednisone 60mg/m^2/day divided into 2-3 doses/day (*recommended therapy for Total 17 – St. Jude's Study Protocol)*
  - If NPO consider: Methylprednisolone 48mg/m^2/day divided into 2-3 doses/day
  - Consider vincristine 1.5mg/m2 if WBC not dropping briskly despite steroids
  - Note: Hydroxyurea and cytarabine may be helpful, but makes patients ineligible for all active ALL studies
- No → Await confirmation by flow cytometry

Morphology suggestive of AML → **Regardless of symptomatology**

- Expedite flow cytometry

Recommend initiation of:

- Cytarabine 200mg/m^2/day divided BID
- Hydroxyurea 20mg/kg/day divided BID (max 1000mg PO BID)
- If WBC >200K: Daunorubicin 50mg/m^2 over 15 min ASAP *(prioritize over other meds)*
- If respiratory symptoms: methylprednisolone 1mg/kg BID

Morphology suggestive of APML → **Regardless of symptomatology**

- Send FISH for PML/RARA STAT

Recommend initiation of:

- ATRA 25mg/m^2/day divided BID

DO NOT perform lumbar puncture or leukapheresis if suspicious for APML

Morphology suggestive of CML → **Symptomatic?**

- Yes
  - Send FISH for BCL/ABL STAT

  Recommend initiation of:
  - Hydroxyurea 10-20mg/kg/day divided BID (max dose 1000mg PO BID)
- No → Await confirmation by flow cytometry

Ambiguous Morphology → **Symptomatic?**

- Yes → **Recommend initiation of:**
  - Cytarabine 200mg/m^2/day divided BID

  ALSO CONSIDER
  - Prednisone 40mg/m^2/day divided into 2-3 doses

  OR
  - Hydroxyurea 10-20mg/kg/day divided BID (max dose 1000mg PO BID)
- No → Await confirmation by flow cytometry. Low threshold for initiation of empiric therapy

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Definitions:

- Hyperleukocytosis: total white blood cell count >100K/microL. Particular attention should be given to AML patients.
- Problems caused by hyperleukocytosis:
  - Metabolic derangements: elevated K+/uric acid/phosphate
  - AKI: elevated BUN/creatinine, oliguria
  - Vision changes – consult ophtho
  - Hearing changes, tinnitus (CML)
  - Priapism (CML) – consult urology STAT
  - Pulmonary hemorrhage
  - Stroke (especially AML)
- Leukostasis: white blood cell sludging or plugging in the microvasculature leading to end organ damage. Due to poor deformability of myeloblasts. Rarely occurs in ALL and CML.
- Symptomatic leukostasis is a **true medical emergency** and requires emergent initiation of leukemia-directed therapy

Management of hyperleukocytosis:

- Arrive at prompt diagnosis - time is of the essence!
- **Begin definitive leukemia-directed therapy immediately (best way to rapidly reduce WBC)**
- **Do not delay initiation of definitive therapy for additional workup or other interventions**

Who should undergo leukapheresis?

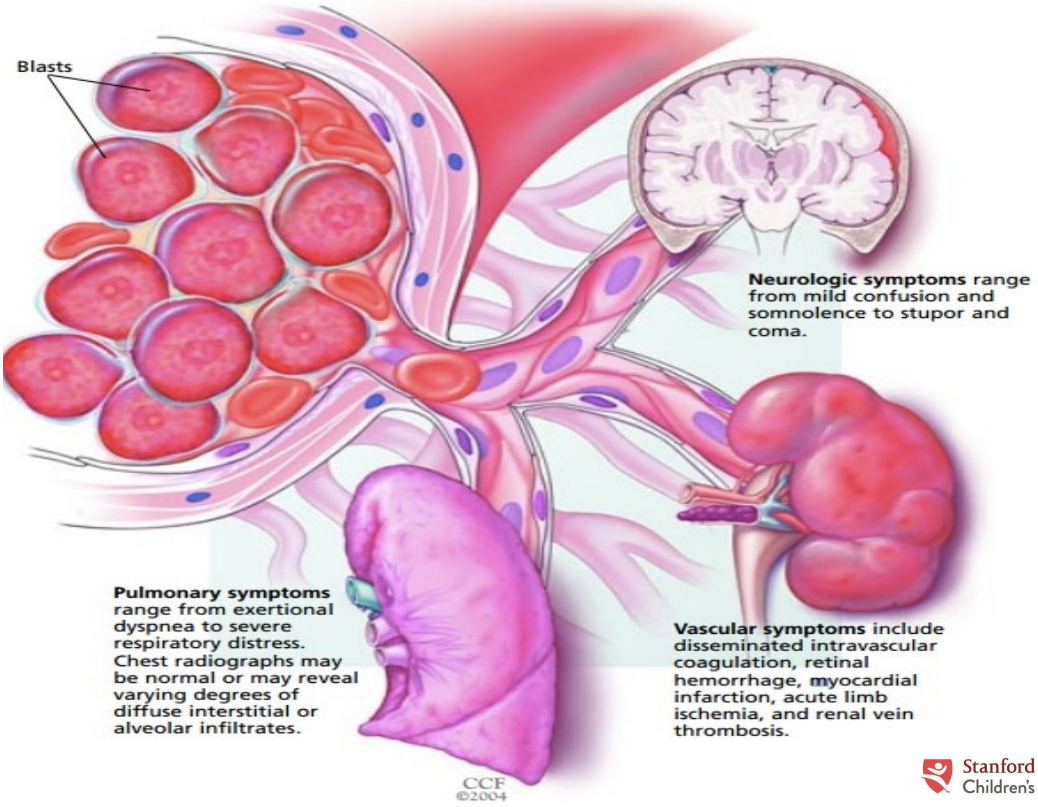
- Leukapheresis is **very rarely** indicated
- There are no data to suggest that there is any evidence for prophylactic leukapheresis
- Leukapheresis should **only** be considered in AML patients with ongoing leukostasis as an adjunct to initiation of chemotherapy OR CML patients with priapism or hearing loss
- Symptoms warranting leukapheresis include altered mental status, focal neuro deficits, hypoxemia, pulmonary infiltrates on CXR, signs of coronary ischemia, renal failure

References:

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Hyperleukocytosis, leukostasis, and sludging

Symptoms of hyperleukocytosis are mainly due to leukostasis, a clinicopathologic syndrome caused by the sludging of circulating leukemic blasts in tissue microvasculature.



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