Leukostasis
Management to prevent crisis in acute leukemia

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BACKGROUND: Hyperleukocytosis, a peripheral white blood cell count greater than 100,000/mm³, is most commonly seen in patients with newly diagnosed or relapsed acute lymphoblastic leukemia and acute myeloid leukemia. Leukostasis is a reduction in blood flow related to hyperviscosity. Hyperleukocytosis, causing leukostasis, is an oncologic emergency and requires an exacting assessment and rapid response with appropriate intervention to prevent morbidity and mortality in the first week after diagnosis.

OBJECTIVES: The objectives of this article are to equip oncology nurse to identify patients with hyperleukocytosis and to provide nursing interventions that will ensure safe, quality care.

METHODS: A case study is used to demonstrate key concepts that are critical in early assessment, identification, and treatment of patients with leukostasis.

FINDINGS: Oncology nurses well versed in the pathophysiology, clinical presentation, and management of leukostasis can make a significant contribution to the safe management of patients with cancer.

KEYWORDS
hyperleukocytosis; leukostasis; acute leukemia; leukapheresis; hyperviscosity

DIGITAL OBJECT IDENTIFIER
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Leukostasis is a reduction in blood flow related to hyperviscosity from hyperleukocytosis. Two main theories have been proposed to explain the pathophysiology of leukostasis in acute leukemia. The first centers on the idea that with a higher than normal degree of viscosity, stasis can occur in microvasculature, resulting in organ damage (Ali, Mirrakhimov, Abboud, & Cashen, 2016; Jain, Bansal, & Marwaha, 2013; Ruggiero et al., 2016; Schiffer, 2016; Shiber & Fines, 2011; Stucki et al., 2001). If the leukocrit, or fractional volume of leukocytes, is greater than 12–15 ml/dl, a significant rise in blood viscosity can occur (Ali et al., 2016). The leukocrit is the volume percentage of leukocytes in whole blood, which is twice as high in leukemic myeloblasts than in the leukemic lymphoblasts. This may be one reason for a higher incidence of leukostasis in acute myeloid leukemia than in acute lymphoblastic leukemia (Ali et al., 2016; Ruggiero et al., 2016; Shiber & Fines, 2011). The large myeloblasts that create sludge in smaller vessels also lead to organ and vascular damage (Jain et al., 2013). Leukemic blasts are less deformable than mature leukocytes, which may account for the higher prevalence of leukostasis in acute leukemias compared to chronic leukemias (Ali et al., 2016).

The second theory involves the adhesion properties of cells. Under certain circumstances, leukemic cells can promote their own adhesion to endothelium. Stucki et al. (2001) discovered that when leukemic cells secrete cytokines, which change the adhesion molecule activation on the endothelial cells, the cells can regulate their own adhesion to endothelium. Blast-secreted cytokines can worsen leukostasis. Leukostasis can be a result of the adhesive interactions that occur when damaged endothelium is present in the blood vessel and leukemic blasts (Ali et al., 2016; Jain et al., 2013; Ruggiero et al., 2016; Stucki et al., 2001).

Clinical Presentation
Patients with leukemia and a WBC count of greater than 100,000/mm³ are diagnosed with hyperleukocytosis. Some of these patients will not develop leukostasis. Clinical symptoms associated with this laboratory value indicate
leukostasis (Ali et al., 2016). These patients are often very difficult to diagnose based on their symptoms at the initial clinical examination. Patients with leukostasis may present with different signs and symptoms, leaving little certainty as to the diagnosis. Leukostasis can be challenging to clinically distinguish between an infection or a hemorrhagic complication (Röllig & Ehninger, 2015). Research has shown that a classical presentation of leukostasis might include respiratory distress with renal and neurologic compromises, as well as gastrointestinal complications (Ali et al., 2016; Jain et al., 2013).

The most prominent and clinically evident symptoms of leukostasis involve the respiratory system. A patient may suddenly present with shortness of breath, cough, hypoxemia (often proven with an arterial blood gas test), or ventilation needs that stray from baseline (Ali et al., 2016). An accumulation of leukemic blasts in the intravascular system may be visible on a chest x-ray through a pattern of infiltrates (Ali et al., 2016). This may be visible through a simple oxygen demand greater than normal for that particular patient, increasing with time. An initial more obvious clinical presentation of dyspnea during leukostasis can rapidly lead to hypoxemia, diffuse alveolar hemorrhage, and respiratory failure (Röllig & Ehninger, 2015).

Organ damage from tissue hypoxia related to leukemic vascular obstruction can greatly affect the renal system (Jain et al., 2013). Patients often present with an acute kidney injury accompanied by unexplained oliguria or anuria. The stasis from increased blood viscosity can lead to drastic changes in the central nervous system and neurologic compromises (Jain et al., 2013). A patient might present with an immediate history of tinnitus and dizziness or visual disturbances like blurry vision or diplopia, so complete assessments are imperative. Other signs or symptoms include confusion or altered mental status, headache, dilated blood vessels, retinal hemorrhages, unequal pupils, nystagmus, facial droop, tinnitus, or slurred speech (Ali et al., 2016; Blum & Porcu, 2007; Röllig & Ehninger, 2015). A computed tomography scan or magnetic resonance imaging might show ischemia, a mass, or even an intracranial hemorrhage from leukemia thrombi or ischemic tissue (Ichikawa et al., 2016). Although often subtle, these effects on the neurologic system are critical signs and symptoms in the clinical presentation and diagnosis of patients with leukostasis.

The gastrointestinal system may also be compromised during leukostasis, with the patient presenting with increased bleeding, hematemesis, or pain in the abdomen (Jain et al., 2013). Table 1 lists common presenting symptoms of leukostasis by organ or system. All of the manifestations of leukostasis convey their own warning signs in a clinical presentation that could quickly alter the patient’s plan of care. Only by complete and succinct assessments can an action plan be formulated to quickly and effectively treat leukostasis in patients with leukemia, thereby decreasing morbidity and mortality.

### Management

Management of patients with hyperleukocytosis requires quick, coordinated intervention to assess patient risk and prevent complications. The following measures should occur during the first 24 hours of patient admission to decrease morbidity and mortality until chemotherapy can be initiated.

Laboratory values must be checked immediately upon patient arrival to the hospital, even if he or she has had recent laboratory work at another facility. Nurses should forgo their usual routine of a full admission assessment and, instead, draw blood immediately. Necessary admission laboratory results are as follows:

- Coagulation study (prothrombin time, partial thromboplastin time, international normalized ratio, fibrinogen)
- Complete blood count with differential and platelets
- Chemistry panel
- Liver function test

### Table 1.

<table>
<thead>
<tr>
<th>ORGAN OR SYSTEM</th>
<th>SYMPTOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Confusion, somnolence, dizziness, headache, delirium, coma, local neurologic deficits</td>
</tr>
<tr>
<td>Ear</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Eye</td>
<td>Impaired vision, retinal hemorrhage</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Bleeding, hematemesis, pain in abdomen</td>
</tr>
<tr>
<td>Heart</td>
<td>Myocardial ischemia or infarction</td>
</tr>
<tr>
<td>Lung</td>
<td>Dyspnea, hypoxemia, diffuse alveolar hemorrhage, respiratory failure</td>
</tr>
<tr>
<td>Vascular</td>
<td>Limb ischemia, renal vein thrombosis, priapism</td>
</tr>
</tbody>
</table>

*Note. Based on information from Ali et al., 2016.*
Elevated WBC counts commonly cause a falsely elevated potassium level, so obtaining a whole blood potassium level is important. Potassium should not be replaced unless urgently needed because once treatment for leukemia begins, patients’ risk for hyperkalemia from tumor lysis syndrome (TLS) increases dramatically. A peripheral smear can help a provider or pathologist determine the cause of hyperleukocytosis. This provides critical information to assist in determining the next steps of treatment. The presence of blasts in the peripheral smear may indicate acute or chronic leukemia, and the appearance of myeloid, lymphoid, or promyelocytic characteristics further differentiates the diagnosis. The final diagnosis requires bone marrow aspiration and biopsy and peripheral blood for cytometry, but because results can take several days, a smear is recommended to give an initial impression for prompt treatment.

Aggressive fluid infusion with solutions free of potassium and calcium should be initiated immediately to reduce blood viscosity and, therefore, reduce patient risk for leukostasis (Jain et al., 2013; Shiber & Fines, 2011). This decision must be mediated with knowledge of the patient’s comorbidities and clinical status (e.g., age, history of cardiac conditions). Hydration also helps with the renal excretion of blasts, as well as with the effects of TLS. Patients who present with hyperleukocytosis are at a greater risk for TLS once initial therapy has been started. TLS occurs when a patient with a large tumor burden, in this case, malignant WBCs, experiences rapid cell death on at the initiation of treatment. Although cell death is the goal, the speed at which the cancer cells rupture and empty their intracellular contents may exceed the ability of the kidneys to filtrate them, leading to acute kidney injury or kidney failure.

Allopurinol or rasburicase is usually started at admission to protect the kidneys from increased uric acid levels during TLS (Ruggiero et al., 2016). Efficient correction of metabolic abnormalities that commonly occur with TLS is necessary, so serum electrolytes should be monitored every six to eight hours until the threat for TLS has passed (Jain et al., 2013) (see Table 2). Hydroxyurea should also be initiated to rapidly decrease the excessive WBC population before deciding on a proper induction regimen (Röllig & Ehninger, 2015). Likewise, steroids can be used for quick cytoreduction if lymphoblastic leukemia is suspected. These agents should be given before the diagnosis is confirmed, because their benefits greatly outweigh the risks.

Leukapheresis is the process of rapidly removing harmful excess leukocytes by mechanical separation. This treatment should be considered after a patient’s diagnosis has been confirmed. Leukapheresis should not be considered in the treatment of acute promyelocytic leukemia or chronic leukemias because of patients’ heightened risk for bleeding (Röllig & Ehninger, 2015). Apheresis may be performed with large-bore peripheral IV cannulas, but this patient population does not usually have veins that can support these cannulas throughout treatment, so a central line is usually imperative. Once the line is in place, the apheresis team should be quickly mobilized. Laboratory results should be monitored closely.
Leukostasis during the apheresis process to determine the effect on counts. Typically, one apheresis session decreases circulating blasts by 20%–50% (Jain et al., 2013; Röllig & Ehninger, 2015; Ruggiero et al., 2016). Leukapheresis can be repeated daily until symptoms of leukostasis have disappeared or the patient’s WBC count has decreased to less than 100,000/mm³.

If the patient is hemodynamically stable, red cell transfusions are not indicated because they may increase the viscosity and serum oncotic pressure of the blood even more. Transfusions are considered only if the patient’s hemoglobin is less than 6 g/dl (Ruggiero et al., 2016; Shiber & Fines, 2011). However, platelets should be administered to patients with a platelet count less than 20,000/mm³ to decrease the risk for intracranial hemorrhage, particularly in patients with concurrent disseminated intravascular coagulation (Shiber & Fines, 2011). Platelet infusions do not affect blood viscosity like red blood cell transfusions. Fresh frozen plasma and cryoprecipitate should be given if needed, and oral vitamin K should be ordered for coagulopathy with an international normalized ratio greater than 1.5. Diuretics are almost never indicated in these patients because of the risk for increasing blood viscosity and renal injury (Ruggiero et al., 2016). Cardiac monitoring through telemetry should be initiated to closely monitor for the effects of TLS, such as cardiac arrhythmia associated with hyperkalemia.

Symptoms of leukostasis may mimic other emergencies that frequently occur in this patient population. Pneumonia, intracranial bleed, or other differential diagnoses must be ruled out. Leukapheresis and cytoreduction are not definitive therapy, and intensive chemotherapy is required to fully treat the underlying condition (Jain et al., 2013).

These measures should be initiated within the first 24 hours of admission to decrease morbidity and mortality until chemotherapy can be initiated. Figure 1 shows the flow of interventions needed for patients newly diagnosed with acute leukemia with hyperleukocytosis and leukostasis.

**Implications for Practice**

- Assess patients with hyperleukocytosis for subtle manifestations of early leukostasis in a detailed, systematic matter.
- Anticipate common complications of leukostasis to prevent and minimize associated morbidity and mortality.
- Improve clinical patient experience and related outcomes through anticipation and early assessment of patients with symptomatic hyperleukocytosis.

**FIGURE 2. CASE STUDY FROM A NURSE’S PERSPECTIVE**

A 68-year-old man with a potential diagnosis of leukemia arrived on the acute leukemia unit as a transport from out of state. A report from an outside hospital related that he had stable vital signs, was on 2 L per nasal cannula of oxygen, and had a medical history of type 2 diabetes and hypertension. His laboratory work demonstrated a high white blood cell (WBC) count of 110,000/mm³ with elevated transaminase and a potential acute kidney injury with a creatinine level of 2.5 mg/dl. The nurse assigned to this admission prepared for the patient, who could present as much sicker than was reported or who could rapidly deteriorate. The nurse had immediate access to telemetry and pulse oximetry at the bedside.

The patient had no history of hospitalization and had been experiencing fatigue, dyspnea on exertion, sore throat, blurry and double vision, sinus pain, and frontal headaches for two weeks. He had left eyelid droop but an otherwise normal neurologic assessment.

The patient became tachypneic, and the oxygen was quickly titrated to 3 L per nasal cannula, with the highest resulting oxygen saturation at 92%. The patient’s respiratory assessment revealed coarse sounds with inspiratory crackles at the bases.

The admitting nurse was concerned about the patient’s respiratory decline. Using critical thinking in assessment, the nurse evaluated the patient’s overall appearance and oxygen demands, lung assessment, and high WBC count. In addition, the patient reported new onset of numbness and tingling that started in his right jaw and traveled up his cheek. These new symptoms increased the nurse’s concern for central nervous system compromise from leukostasis. The nurse quickly drew peripheral laboratory tests as ordered, knowing that hyperleukocytosis could rapidly worsen, even within a few hours. Orders were obtained for telemetry, pulse oximetry, a stat portable chest x-ray, and progressive care unit status. The nurse started the patient’s maintenance IV fluids, as ordered, because hydration is imperative to adequately control the symptoms associated with leukostasis. The fluids could lead to a decrease in serum uric acid and could prevent potential acute kidney injury.

The redraw of the patient’s WBC showed that the count increased to 152,000/mm³. The patient’s chest x-ray showed diffuse interstitial infiltrates, and his arterial blood gases reflected hypoxemia. His oxygen was increased to 5 L per nasal cannula, which brought his oxygen saturation to 94% with continued tachypnea.

A brain magnetic resonance imaging was ordered to check for neurologic complications of leukostasis. Immediate central line placement was arranged to prepare for possible leukapheresis. The patient was transferred to the intensive care unit, because he had great potential to decline rapidly.

**Implications for Nursing**

Patients who present with hyperleukostasis may have few, if any, accompanying symptoms. As a result, healthcare practitioners may view these patients as stable. Practitioners who are familiar with the pathophysiology and clinical presentation of leukostasis in patients know how quickly the disease can progress to clinically critical situations. Thorough, prioritized assessments can help oncology nurses identify symptoms that might be easy to miss. Once they identify these symptoms, the healthcare team can take quick, coordinated action to ensure the safest management of patients with leukostasis to prevent morbidity and mortality.

The case study presented in Figure 2 illustrates an example of a patient with hyperleukocytosis who seems fairly stable on
admission, but then deteriorates quickly. The nurse’s strong knowledge base and experience identifying leukapheresis allows her to anticipate necessary actions and interventions prior to the patient’s arrival on the unit. A thorough assessment helps her to identify rapidly progressing symptoms related to leukapheresis. Critical thinking allows the healthcare team to prioritize treatment for the patient with leukapheresis. The nurse can coordinate beside care and delegate care as needed to ensure a swift, coordinated effort in the implementation of ordered interventions. Oncology nurses who understand the pathophysiology, clinical presentation, and management of leukostasis can make significant contributions to the safe management of patients with cancer.

Conclusion
Although not the most common presentation of patients with newly diagnosed acute leukemia, hyperleukocytosis can lead to leukostasis and, therefore, morbidity and mortality. Because the potential outcome for these patients is so dire, oncology nurses who work with these patients must be well versed in the subtle presentation symptoms and ready to act with interventions to prevent crisis. Patient outcomes may be directly related to the knowledge, expertise, and coordination of the entire healthcare team shortly after a diagnosis of acute leukemia.

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