Pediatric Oncologic Emergencies

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KEYWORDS
• Pediatrics • Oncology • Emergency • Prognosis

KEY POINTS
• Emergency providers who can identify and manage oncologic emergencies can contribute significantly to an improved prognosis.
• Effective care of pediatric malignancies requires an age-appropriate approach to patients and compassionate understanding of family dynamics.
• The overall prognosis for most pediatric cancers is good.

INTRODUCTION

Approximately 12,000 new cancers are diagnosed annually in children and adolescents. Cancer is second only to injury as a cause of death in children older than 3 months. Despite this, the overall prognosis for most pediatric cancers is good. Mortality for all childhood cancers combined is approximately half what it was in 1975, and the survival rates of many malignancies continue to improve. However, the incidence of childhood cancer is significant and the related emergencies that develop acutely carry significant morbidity and mortality.

Emergency providers who can identify and manage oncologic emergencies can contribute significantly to an improved prognosis. This article focuses on the recognition of oncologic processes, stabilization of the most common emergent situations, and pediatric-specific recommendations for the emergent care of childhood cancers.

EVALUATING PEDIATRIC PATIENTS FOR MALIGNANCY

Symptoms of pediatric cancer result from invasion of body cavities by abnormal cells (eg, marrow invasion resulting in pallor and bruising, space-occupying intracranial lesion resulting in vision changes and nausea, abdominal mass causing constipation). Practitioners must maintain a high index of suspicion when assessing such nonspecific symptoms.

Disclosures: None.

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When a potential malignancy is suspected, the initial management should focus on a complete and careful history and physical examination. Historical factors and physical examination findings that can suggest malignancy in pediatric patients are listed in Table 1.4 If malignancy is suspected, laboratory evaluation may include a complete blood count to evaluate for leukocytosis, leucopenia, anemia, or thrombocytopenia; peripheral blood smear to evaluate for abnormal cell proliferation; lactate dehydrogenase; uric acid; liver function tests; serum creatinine; and a full electrolyte panel including calcium, magnesium, and phosphorus.3 Multiple imaging modalities are used to evaluate pediatric patients with possible malignancy or associated malignancy-related emergencies (discussed later).

**DELIVERY OF A DIAGNOSIS OF PEDIATRIC ONCOLOGIC DISEASE**

The news of a childhood cancer diagnosis should be shared in as quiet and controlled an environment as possible. The information given should be compassionate,

### Table 1

<table>
<thead>
<tr>
<th>Historical factors concerning for cancer</th>
<th>Physical examination factors concerning for cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain without injury or out of proportion to reported mechanism</td>
<td>Diffuse lymphadenopathy, especially if supraclavicular, matted, immobile, nontender, or associated with hepatosplenomegaly</td>
</tr>
<tr>
<td>Unexplained weight loss</td>
<td>Palpable abdominal mass</td>
</tr>
<tr>
<td>Nausea and vomiting, especially if worse when waking or supine</td>
<td>Unexplained bruising with or without pallor</td>
</tr>
<tr>
<td>Headache associated with waking or supine position</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Balance issues or gait problems</td>
<td>Focal weakness</td>
</tr>
<tr>
<td>Unexplained fevers, especially if prolonged</td>
<td>Leukocoria</td>
</tr>
<tr>
<td>Intussusception in children older than 2 y</td>
<td>Painless unilateral testicular enlargement</td>
</tr>
</tbody>
</table>
concrete, and brief to allow for the disbelief, shock, and terror that are common after the receipt of tragic news.\textsuperscript{2,5} Data suggest that a child’s coping is linked to parental distress levels and the social supports available to them.\textsuperscript{6,7} For this reason, it is important that the family structure and any issues surrounding resources be considered early in treatment.

**Pediatric Cancers**

Some malignancies are found exclusively within the pediatric population and their presentations are unique. Although a discussion of all presentations of pediatric cancer is too lengthy for this article, a few sentinel examples are included to illustrate the approach to recognizing and managing malignancy in children.

**Retinoblastoma**

Retinoblastoma is a congenital malignant tumor of the retina. Leukocoria (white discoloration of the pupil), strabismus, or lack of a red reflex often brings children to medical attention. The median age at diagnosis is 2 years.\textsuperscript{8} Less often, children or infants may present with vitreous hemorrhage or orbital cellulitis.\textsuperscript{9} Practitioners play an important role in identifying patients with no red reflex or strabismus in the newborn nursery or at routine check-ups.\textsuperscript{10} Approximately 70% of cases of retinoblastoma are unilateral\textsuperscript{11}; in these cases, treatment is predominantly enucleation. When retinoblastoma is bilateral or extends beyond the orbit, radiation, chemotherapy, photocoagulation, and cryotherapy may be required to treat the tumor and preserve residual vision.\textsuperscript{8} Bilateral retinoblastoma also requires screening of patients for subsequent malignancies and careful examination of all first-degree family members, because their risk of malignancy is greater.\textsuperscript{10,12}

**Pediatric Abdominal Tumors**

The 2 most common malignant pediatric abdominal solid tumors, neuroblastoma and Wilms tumor, are discussed here. Other potential abdominal masses include non-Hodgkin lymphoma, hepatoma, rhabdomyosarcoma, germ cell tumor, and hepatoblastoma.

**Neuroblastoma**

Neuroblastoma is the most common childhood solid tumor outside the central nervous system (CNS), and represents nearly 50% of malignancies seen in infancy.\textsuperscript{13} Neuroblastoma is a malignant tumor stemming from the neural crest cells and is found most commonly in the adrenal medulla or sympathetic chain. Its presentation depends on the location of the primary tumor and metastases, but typically an abdominal mass is one of the presenting signs. Associated symptoms from local mass effects may include bowel obstruction, scrotal or lower extremity edema, or hypertension as a result of compression of renal vasculature.\textsuperscript{14} Neuroblastoma should be considered whenever an abdominal mass is discovered, especially when hard, irregular, and crossing the midline.\textsuperscript{15} The median age at diagnosis is 2 years, and asymptomatic masses may be found during diapering or routine examination.\textsuperscript{2} More than half of children have metastases at the time of diagnosis, most commonly of bone or bone marrow.\textsuperscript{16} The frequency of neuroblastoma is higher in children with Beckwith-Wiedemann syndrome and neurofibromatosis.\textsuperscript{2}

Evaluation of suspected neuroblastoma should include a computed tomography (CT) scan of the chest, abdomen and pelvis to clearly delineate the area of origin and areas of metastasis. Head or spine involvement is better defined by magnetic resonance imaging (MRI). Urinalysis reveals increased catecholamine metabolites in nearly 90% of patients.\textsuperscript{17}
**Wilms tumor**

Wilms tumor (nephroblastoma), a malignancy of the developing kidney, is the most common renal tumor and accounts for approximately 6% of all childhood cancers.² The peak age at diagnosis is 2 to 3 years. Wilms is one of the few pediatric cancers with a higher incidence in African American patients.⁸

Typical presentation is an asymptomatic abdominal mass found incidentally during bathing or routine examination.¹⁸ Bleeding into the tumor is sometimes profound enough to cause anemia. Local stimulation of renin can result in hypertension.¹⁹ When present, hematuria is usually microscopic. Wilms tumor is, rarely, associated with congenital anomalies such as hemihypertrophy, aniridia, hypospadias, or malformed kidneys. Familial cases are more likely to be bilateral and occur at a younger age.²⁰

Ultrasonography is a noninvasive way to evaluate a potential renal mass, allowing identification of the organ of origin and assessment of local blood flow or vena caval involvement. CT is typically used to evaluate for lung metastases. Metastasis to the bones and brain are rare. Characteristics that can differentiate Wilms tumor from neuroblastoma are listed in Table 2.

**Intracranial Tumors**

Intracranial tumors are the most common solid tumor of childhood.¹ The specific tumors and their prognoses are different from those found commonly in adults, although the presenting symptoms can be similar. Possible symptoms are included in Table 3.²¹

The most common brain tumor in children is astrocytoma, which can be low grade or high grade.¹³,²² High-grade astrocytomas are the most malignant of all brain tumors. Brain stem gliomas occur almost exclusively in children, presenting most often in the school-aged population.²³ Signs of increased intracranial pressure (ICP) are rare with brain stem gliomas, and children typically present with facial or extremity palsies,

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Characteristics of neuroblastoma and Wilms tumor</th>
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<tbody>
<tr>
<td><strong>Neuroblastoma</strong></td>
<td><strong>Wilms Tumor</strong></td>
</tr>
<tr>
<td>Typical age of presentation</td>
<td>Median age 2 y</td>
</tr>
<tr>
<td>Typical location</td>
<td>Adrenal gland or paravertebral sympathetic ganglia; displaces rather than distorts the kidney; mass may cross midline</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Neural crest cells; fine calcifications common</td>
</tr>
<tr>
<td>Treatment</td>
<td>Chemotherapy, surgery, radiation</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Cure rate 85%–90% in low-stage disease, 15%–38% when more advanced</td>
</tr>
<tr>
<td>Possible associations</td>
<td>Beckwith-Wiedemann syndrome, neurofibromatosis, nesidioblastosis</td>
</tr>
</tbody>
</table>
double vision, or difficulties walking. Ependymomas tend to occur in or near the cerebellum, where they block the flow of cerebrospinal fluid. These gliomas are more common in children less than 10 years of age.24 Medulloblastomas are primitive neuroectodermal tumors found near the midline of the cerebellum. They are malignant and fast growing. Craniopharyngiomas are benign tumors diagnosed primarily in patients less than 20 years of age. They may disrupt hormonal cascades, leading to poor growth. Prognosis depends on type of tumor, proximity to vital structures, and presence of metastasis. Treatments vary by tumor type and location.

**Primary Bone Tumors**

The most common primary pediatric malignancies of the bone are Ewing sarcoma and osteosarcoma. They make up the third most common group of malignancies in adolescents, although only the seventh most common in children.2 The primary presenting symptom for each is pain that is characterized as intermittent, worse with activity, and often in severity out of proportion to the incidental minor injury that prompted evaluation.8,25 Characteristics of Ewing sarcoma and osteosarcoma are compared in Table 4.

**CARING FOR CHILDREN WITH KNOWN MALIGNANCY**

When caring for a pediatric patient with known malignancy, some special considerations must be taken. Fever is a worrisome symptom in patients who are potentially neutropenic. Given the probability of immunosuppression, temperatures should not be taken rectally. Every precaution should be taken to avoid exposure of immunosuppressed patients to infectious agents. Patients should be kept in so-called well waiting

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**Table 3**

| Signs of increased ICP | Headache  
Vomiting (especially early morning)  
Irritability  
Drowsiness  
Changes in personality |
|-----------------------|------------------|
| **Posterior fossa signs** | Signs of increased ICP  
Ataxia  
Imbalance  
Decreased muscle coordination |
| **Cerebral signs** | Signs of increased ICP  
Seizure  
Visual changes  
Weakness/paralysis  
Changes in personality  
Pupillary changes  
Speech problems  
Confusion |
| **Brain stem signs** | Signs of increased ICP  
Headache  
Seizures  
Visual changes  
Respiratory anomalies  
Facial palsies |

*Abbreviation: ICP, intracranial pressure.*
rooms or quickly ushered to an examination room rather than waiting in common areas. Emergency providers should use contact precautions and, during epidemics of illnesses transmitted by air or droplet (eg, influenza), masks and isolation should be used. When age-appropriate, patients can be encouraged to wear masks during

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Features of osteosarcoma and Ewing sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Peak incidence</td>
<td>Adolescence; 60% of malignant bone tumors in patients &lt;20 y old</td>
</tr>
<tr>
<td>Gender</td>
<td>Incidence equal in both sexes</td>
</tr>
<tr>
<td>Associations</td>
<td>Tall children; periods of rapid growth; retinoblastoma; ionizing radiation</td>
</tr>
<tr>
<td>Presentation</td>
<td>Pain waking patient at night; limp; systemic symptoms uncommon unless metastatic; often present secondary to incidental trauma</td>
</tr>
<tr>
<td>Common locations</td>
<td>Distal femur, proximal tibia, proximal humerus; 90% are metaphyseal</td>
</tr>
<tr>
<td>Physical examination findings</td>
<td>Palpable mass (60%); overlying local warmth</td>
</tr>
<tr>
<td>Metastases at Diagnosis</td>
<td>20%, primarily lung</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>80% have increased alkaline phosphatase, which predicts lung metastases</td>
</tr>
<tr>
<td>Common radiological findings</td>
<td>Codman triangle: cortical increase and diffuse cloudlike immature bone formation</td>
</tr>
<tr>
<td>Work-up after radiographs</td>
<td>MRI define extent of cortical and intermedullary spread and invasion of soft tissues; CT chest for lung metastases; open biopsy</td>
</tr>
<tr>
<td>Treatment</td>
<td>Neoadjuvant chemotherapy and amputation or limb salvage followed by chemotherapy</td>
</tr>
<tr>
<td>Prognosis</td>
<td>70% disease-free survival without metastases</td>
</tr>
<tr>
<td>Poor prognostic factors</td>
<td>Age &lt;10 y; involvement of axial skeleton; metastases</td>
</tr>
</tbody>
</table>
visits to clinics or emergency departments. Historical information that is pertinent to optimal management of patients with childhood cancer is listed in **Box 1**.

Emergency providers should specifically ask about pain, search for signs of pain, and investigate prior pain treatments used for the patient. Aggressive management of pain is often necessary. Pain can be a reason for presentation, a direct effect of cancer, or a side effect of treatment. In the pediatric population, it is also important to consider a patient’s possible fear of practitioners and procedures, because past experiences weigh heavily in children’s responses to the hospital or clinic environment. Prior painful procedures such as bone marrow biopsies or lumbar punctures can affect how a patient responds to even routine visits in the future.

Considerable progress has been made in assessing and reducing children’s distress during painful medical procedures, which are a routine part of pediatric cancer treatment. Age-appropriate pain scales are available, allowing more accurate self-report of discomfort by children of various developmental abilities or their caregivers. Better recognition of pain allows effective treatment with anesthetics, analgesics, anxiolytics, or procedural sedation.

**Mechanical Emergencies**

Mechanical emergencies in pediatric patients with malignancy can be similar in presentation to those in adults and result from direct compression, obstruction, or displacement of tissues by a neoplastic process. Discussion of cancer-associated mechanical emergencies can be found elsewhere in this issue. Some of these acute events and their management in pediatric patients are summarized here.

**Airway obstruction**

Airway obstruction frequently (60%) complicates pediatric mediastinal masses. Leukemia, lymphoma, rhabdomyosarcoma, and neuroblastoma are the most common diagnoses. Children are at increased risk because of their compressible tracheas and bronchi with smaller intraluminal diameters. Symptoms can be gradual or sudden, and depend on the level of obstruction. Stridor suggests extrathoracic involvement. Lower obstruction of the trachea or bronchi can cause wheezing, coughing, dyspnea, or

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**Box 1**

**Historical information optimizing management of children with cancer**

<table>
<thead>
<tr>
<th>Historical Information</th>
<th>Manner in Which Information Directs Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of cancer</td>
<td>Informs possible suspected symptoms or complications</td>
</tr>
<tr>
<td>Date of diagnosis, dates of any relapses</td>
<td>Informs phase of chemotherapy, offers some prognostic information if relapsed disease</td>
</tr>
<tr>
<td>Date of last chemotherapy</td>
<td>Informs likelihood of neutropenia and susceptibility to infection</td>
</tr>
<tr>
<td>Chemotherapeutics received</td>
<td>Directs search for common side effects or complications</td>
</tr>
<tr>
<td>Presence of indwelling catheters or ports</td>
<td>Directs blood draws, contributes to risk of sepsis</td>
</tr>
<tr>
<td>Sites of successful or preferred blood draws</td>
<td>Enhances therapeutic relationship, provides a sense of control during a painful procedure</td>
</tr>
<tr>
<td>Last blood counts, dates of last transfusions</td>
<td>Informs potential for cytopenias and need for transfusion</td>
</tr>
</tbody>
</table>
orthopnea. In children with palpable lymph nodes who are tachypneic, malignancy should be considered if symptoms worsen with bending or the supine position. Plain radiographs confirm a mediastinal mass in 97% of cases. CT scan further characterizes a mass, but can be difficult to obtain in children with positional compromise. Orthopnea is associated with increased risk of airway collapse with anesthesia. Patients in severe distress should be put in an upright or prone position. Preservation of at least 50% baseline tracheal diameter on CT scan of the chest suggests that the child may tolerate anesthesia; however, any intubation in a pediatric patient with an anterior mediastinal mass should be coordinated with specialists in pediatric anesthesia, otolaryngology, or intensive care.

Treatment is directed based on results of tissue biopsy, but symptoms may require emergent radiation, steroids, or chemotherapy. Local radiation is often effective, and adjunctive dexamethasone (0.5–2 mg/kg/d) or methylprednisolone (40 mg/m²/d) can reduce reflex edema. The decision to use emergency interventions must involve an oncologist, because the radiosensitivity and chemosensitivity of many pediatric malignancies can lead to diagnostic uncertainty after treatment.

Superior vena cava syndrome
An anterior mediastinal mass can cause sudden or gradual symptoms of superior vena cava syndrome (SVCS). In children, the most common malignant causes of SVCS are leukemias and lymphomas. Initial manifestations may include facial edema, prominent superficial chest veins, cough, wheezing, shortness of breath, and stridor. Additional symptoms include plethora or cyanosis of the face, neck, or upper extremities. Compared with older children and adults, young children with SVCS are less likely to present with dizziness, syncope, confusion, or visual changes. In sudden cases of SVCS, which are more common in pediatric patients, the presentation can be shock caused by reduced ventricular volume from decreased venous return. Supine positioning can further exacerbate hemodynamic compromise because of decreased rib cage dimension or increased blood flow to the impinging mass. The increased use of implantable intravenous (IV) devices such as tunneled central venous catheters and port catheters has increased the prevalence of thrombosis-related SVCS in children.

Plain radiographs are the preferred initial diagnostic tool in children with SVCS, because the supine positioning and general anesthesia often required for CT scan carry the same risks as in adults with anterior mediastinal masses. Emergency treatment involves elevation of the head of the bed, keeping the child calm, supplemental oxygen, and occasionally moderate diuresis. Thrombosis-related SVCS is treated with removal of the intravascular device, anticoagulation, and stenting when necessary. SVCS related to compression may require temporizing radiation, chemotherapy, glucocorticoids, vascular stenting, or surgical resection. A complete blood count with differential may aid diagnosis, because two-thirds of children who present with SVCS have leukemia or lymphoma. Paracentesis of a pleural or pericardial effusion can be both therapeutic and diagnostic.

Spinal cord compression
Spinal cord compression is a medical emergency that can result in permanent neurologic impairment if treatment is delayed for even a few hours. In the pediatric oncology population, spinal cord compression can be the result of late metastasis, isolated recurrence, or a presenting symptom of malignancy. It is reported in up to 5% of pediatric patients with solid tumor. Most tumors causing spinal cord compression are extradural, especially neuroblastomas or soft tissue sarcomas such as
Ewing or rhabdomyosarcoma. The most common presenting symptom of spinal cord compression is back pain. Because a complaint of back pain is infrequent in the pediatric population, any child with cancer and back pain should be considered to have spinal cord compression until proved otherwise, even in the absence of neurologic findings. Other classic symptoms may be hard to elicit in the preambulatory or preverbal child, including pain that increases with percussion of the vertebral bodies, gait anomalies, sensory deficits, incontinence, and urinary retention. Any pediatric patient presenting with complaints or symptoms concerning for spinal cord compression should have a thorough neurologic examination and immediate imaging. When present, weakness tends to be symmetric. Sensory findings are less common. Plain films are poorly sensitive and are positive in only approximately 30% of patients with spinal cord compression. Plain films may show lytic or sclerotic changes in adjacent bone, widening of interpeduncular distances, enlargement of neural foramina, or calcifications within a mass surrounding the spine. MRI is the preferred modality for evaluating the spine, and generally the entire spine should be imaged to localize and characterize the cause. MRI can be challenging in pediatric patients, given the time required for spinal MRI and the typical exacerbation of pain with supine positioning. Analgesia and sedation may be required for optimal imaging.

Treatment of evolving neurologic symptoms must be immediate despite the need to maintain sufficient histologic information to make an accurate diagnosis and direct long-term management. IV dexamethasone 1 to 2 mg/kg may be administered when cord compression is strongly suspected clinically. However, if lymphoproliferative disease is the likely cause, local radiation may be preferable. Treatment should not be postponed for diagnostic certainty, because neuronal ischemia from compression causes irreversible loss of function.

Cerebral herniation
The presence of an expanding intracranial mass or obstruction of cerebrospinal fluid can result in increased ICP and eventual uncal herniation. This catastrophe can occur in pediatric oncology patients from tumor mass or as a result of therapy. CNS tumors are the second most common pediatric cancer and the most common pediatric solid malignancy. Primary malignancy and therapy-related intracranial complications include hemorrhage, infarction, thrombosis, and abscess. Nausea, emesis, and stiff neck are the most common presenting signs, but the potential symptoms are varied. Abnormal eye findings such as papilledema, gaze palsy, and pupillary anomalies can suggest increased ICP. The presenting symptom may be headache, altered consciousness, ataxia, or seizure. Cushing reflex of bradycardia, hypertension, and respiratory changes is a late and ominous sign.

CT can rapidly evaluate the presence of increased ICP or impending cerebral herniation, but has limited detail of the posterior fossa, where many primary pediatric CNS malignancies arise. Further characterization can be obtained with MRI. When progressive symptoms preclude further imaging, several treatment options are available. In some children with intracranial shunts, the shunt can be tapped, imaged, or externally adjusted to equalize pressure. These procedures are best performed by a neurosurgeon. Mannitol can be administered intravenously as a 25% solution at 0.5 to 2 g/kg over 20 minutes. IV dexamethasone 1 mg/kg can be particularly helpful when the cause is an intracranial mass. Intubation and hyperventilation to decrease the partial pressure of carbon dioxide to 30 to 35 mm Hg can decrease ICP via induced vasoconstriction and reduced cerebral blood volume. Neurosurgery staff should be aware of the patient because definitive treatment is often surgical.
Gastrointestinal Emergencies

Emergencies of the gastrointestinal (GI) tract in children with cancer can occur as a result of primary disease or treatment of their malignancy. GI obstruction and ileus are more common in adults with cancer, but direct tumor effects and postsurgical or postchemotherapeutic changes can contribute to obstruction in children.

Intussusception

Intussusception, an invagination of the proximal intestine into a more distal portion, is concerning for malignancy in children more than 2 years of age. Neoplasm is often the lead point of the intussusception. Causes can include acute lymphoblastic leukemia (ALL), Burkitt lymphoma, and hamartomas. Emergency providers need to maintain a high index of suspicion for malignancy in patients with a nonreducible intussusception or an intussusception occurring outside the expected age range (ie, less than 2 years). Diagnosis can be suggested when plain radiographs show obstruction. Ultrasonography is diagnostic and can identify a lead point, if one exists. In children with known malignancy, especially those with neutropenia or recent radiation therapy, the common management with air or contrast enema should be discussed with a pediatric oncologist and pediatric surgeon because of the risk of infection or rupture of thinned intestinal mucosa. In addition, management of partial or intermittent obstruction must be carefully considered in neutropenic or acutely ill patients who are at risk for poor wound healing.

Bowel perforation

Bowel wall perforation can cause significant hemorrhage, especially in children with coagulopathy. Wall erosion can result from tumor infiltration, chronic use of ulcer-promoting medications such as prednisone, or necrosis caused by thrombosis or vascular insufficiency. Early symptoms may include abdominal pain or altered stool patterns, both nonspecific and common symptoms in the pediatric population. Perforation is suspected in patients with abdominal tenderness, distention, and decreased bowel sounds, especially when associated with hematemesis, melena, or altered vital signs. Plain films may show free air, and abdominal ultrasonography or CT may reveal free fluid. Perforation is managed surgically, but temporizing and supportive measures include IV hydration, broad-spectrum antibiotics, frequent vital signs, and a complete blood count to direct the use of blood products.

Altered stool patterns

Many GI symptoms in patients with childhood cancer are nonspecific. Primary malignancies need to be distinguished from the functional obstruction that can result from constipation or obstipation induced by chemotherapeutics or narcotic management of pain. Neuroblastoma can present with severe secretory diarrhea. However, diarrhea, severe dehydration, vomiting and decreased oral intake can also be results of chemotherapy. Oral ulcers and thrush can be consequences of chemotheraphy and significantly affect oral intake. Treatments include analgesia, IV fluids, antiemetics, and antidiarrheals. Pancreatitis in the child with cancer is typically the result of L-asparaginase, 6-mercaptopurine, or sustained glucocorticoids. It should be considered in any child with epigastric pain and vomiting who has received L-asparaginase.

GI infection

Infection of the GI tract in pediatric patients with cancer can be grave. Diagnosis is often delayed because of the generalized pain that is common in immunosuppressed patients who do not localize infectious processes or produce reliable inflammatory responses. Mucositis and esophagitis are painful diseases that can contribute
significantly to dehydration or malnutrition. Treatment is focused on pain control and oral, nasogastric, or parenteral hydration and nutrition. Mouthwashes or rinses containing topical anesthetics can be used safely in children of all ages. Antifungal swish-and-swallow treatments containing nystatin are effective for thrush. Early recognition of oropharyngeal and esophageal inflammation can help prevent dehydration and malnutrition.46

Typhlitis is a necrotizing neutropenic enterocolitis caused by bacterial or fungal invasion of the bowel wall. It is a serious disease process seen most commonly during induction therapy in pediatric leukemias or after aggressive chemotherapy for pediatric tumors.47 Management involves broad-spectrum antibiotics and surgical consultation.48,49 Perirectal cellulitis and abscess can have delayed presentations in patients who are neutropenic as a result of slow inflammatory responses and age-related reticence to have the area examined. Although diapered children are more likely to present early in the disease course, they are also at increased risk for this surgical emergency given the potential for perineal irritation in patients not yet toilet trained.

Hematologic Emergencies

Hematologic emergencies can be classified as abnormalities of hematopoiesis or coagulopathy. Abnormal hematopoiesis is typically underproduction of various cell lines as a result of marrow infiltration or therapy-associated toxicity of hematopoietic tissues. Underproduction can result in anemia, neutropenia, and thrombocytopenia. Leukocytosis and its associated effects can be presenting symptoms of leukemias. Coagulopathy can result in hemorrhage or thrombosis and may be the consequence of treatment of disease, increased viscosity related to leukemia, or local effects of solid tumors.

Treatment of hematologic complications in pediatric patients is largely supportive and may include transfusions, treatments to support marrow production, and vigilance in searching for potential infectious disorders. Judicious use of blood products reduces the risk of blood-borne illness and a heightened immune response to future transfusions. Immunosuppressed patients with cancer should receive only irradiated blood products to prevent graft-versus-host disease. Children should be assumed to be nonimmune to cytomegalovirus (CMV) and receive only CMV-negative blood products until their CMV immunity status is known. Leukocyte-reduced blood and platelets can reduce CMV contamination and decrease the risk of febrile transfusion reactions or alloimmunization.40 Alloimmunization is particularly concerning in children because the underlying malignancy may be best managed with bone marrow transplantation (BMT). Alloimmunization limits the chance of successful transplantation. In particular, intrafamilial donation of blood products should be avoided in patients who may need BMT in an effort to restrict exposure to familial human leukocyte antigens and subsequent graft rejection.50 More detailed information on the use of blood products and transfusion reactions can be found elsewhere in this issue.

Anemia

Anemia can be the result of marrow infiltration by malignant cells or marrow toxicity from cancer treatments. Children generally tolerate hemoglobin (Hb) levels of 7 to 8 g/dL unless they are critically ill.50 Hb levels less than 7 to 8 g/dL may be an indication for transfusion, especially if the patient is symptomatic. Transfusion should be considered with prolonged bone marrow dysfunction and for the purpose of maintaining intravascular volume or oxygen-carrying capacity in patients with severe illness or hemorrhage. Packed red blood cells (pRBCs) are transfused in 10-mL/kg aliquots over 2 to 4 hours, or aliquots of 3 mL/kg in patients with prolonged severe anemia, Hb levels
less than 5 g/dL, or symptoms of heart failure. A 10-mL/kg transfusion raises Hb levels by approximately 2 to 3 g/dL. Total necessary volume can be calculated as follows:

\[
\text{Volume of pRBCs} = \frac{\text{Weight in kg} \times 70 \text{ mL/kg}}{(\text{desired hematocrit} - \text{current hematocrit})^{51} \times \text{Hematocrit of pRBCs}}
\]

A single unit of blood typically contains 250 to 300 mL. When multiple transfusions are necessary in small children, it is optimal to maximize the number or transfusions that can be given from a single unit to limit blood-borne pathogen exposure and alloimmunization. Further information regarding the pathology and management of anemia can be found elsewhere in this issue. When children are mildly symptomatic and their anemia is related to marrow suppression, recovery can be aided with the use of recombinant erythropoietin.

**Thrombocytopenia**

Thrombocytopenia can result from marrow infiltration by malignant cells, marrow toxicity from cancer treatments, or increased consumption of platelets. New thrombocytopenia should raise concern for acute leukemia in children. Platelet transfusions remain the primary treatment in children with cancer for both prophylaxis and treatment of bleeding related to thrombocytopenia. This treatment differs from the preferred treatments for other pediatric acquired thrombocytopenias, most notably steroid use in idiopathic thrombocytopenic purpura. A single dose of steroids can cause remission of aggressive hematologic malignancies, rendering bone marrow biopsy less sensitive for diagnosis. For this reason, steroids should not be used to treat any undiagnosed thrombocytopenia until hematology has been consulted. In the absence of bleeding, transfusion should not be used to treat thrombocytopenia resulting from increased platelet consumption. In the treatment of leukemia-associated thrombocytopenia, guidelines are based on underlying illness. Consider empiric transfusion of platelets in patients with:

- Acute nonlymphocytic leukemia (ANLL) receiving chemotherapy and platelets less than 15 to 20 \(\times\) \(10^9\)/L
- ANLL with platelets less than 20 \(\times\) \(10^9\)/L and leukocytes less than 100 \(\times\) \(10^9\)/L
- ALL with platelets less than 20 \(\times\) \(10^9\)/L and leukocytes less than 300 to 400 \(\times\) \(10^9\)/L
- Any cancer with overt bleeding, normal coagulations studies, and platelets less than 50 \(\times\) \(10^9\)/L\[^{52}\]

Single-donor platelet units contain approximately the same number of platelets as 6 random donor units. Use of single-donor platelets reduces exposure to infection and alloimmunization.

All platelet products should be irradiated, leukocyte filtered, and CMV negative when transfused in pediatric patients with cancer. In patients with known alloimmunization to blood products, the rate of platelet infusion should be reduced. A platelet transfusion of 0.1 to 0.2 U/kg of random donor platelets should raise platelets by 50 to 100 \(\times\) \(10^9\)/L\[^{51}\]. Failure of platelet counts to increase as expected after 2 consecutive platelet transfusions suggests alloimmunization and the need for crossmatching of future transfusions. Further information regarding the pathology and management of thrombocytopenia can be found elsewhere in this issue.

Children with cancer often have to undergo invasive procedures despite thrombocytopenia. In such circumstances, the risks of transfusion should be weighed against
those of procedure-related bleeding. Lumbar puncture has been studied in patients with platelet counts as low as $10 \times 10^9/L$ and is generally considered safe with platelet counts greater than $50 \times 10^9/L$.\textsuperscript{53}

**Thrombosis**
Cancer-related thrombosis is less common in children than in adults and, when present, is most often related to therapy. The risk factors for thrombosis include central venous catheters, malignancies associated with hyperleukocytosis, and the use of L-asparaginase, which has been reported to cause severe thromboembolism, primarily of the cerebral venous sinus, in up to 11.5\% of patients.\textsuperscript{54} Presentation of venous sinus thrombosis can include headache, seizure, motor deficits, cognitive deficits, or obtundation. Other thrombosis-related presentations are specific to the location of thrombosis.

**Disseminated intravascular coagulation**
Disseminated intravascular coagulation (DIC) is characterized by excessive activation of blood coagulation and resultant consumption of clotting factors. DIC results in hemorrhage, thrombosis, and microangiopathic hemolytic anemia.\textsuperscript{55} A detailed discussion of DIC is found elsewhere in this issue. In children with cancer, DIC can be found in patients with sepsis, widely disseminated metastases, and as a result of leukemic blast cell destruction during induction chemotherapy for ANLL. Treatment is focused on the underlying cause and supportive care. Unfractionated heparin at 7.5 U/kg/h can be used to treat thrombosis. PRBCs and platelets may be required if hemorrhage is the primary clinical problem. Cryoprecipitate can replenish fibrinogen, whereas fresh frozen plasma can replace coagulation factors in the setting of prolonged prothrombin time and partial thromboplastin time.\textsuperscript{55}

**Hyperleukocytosis**
Hyperleukocytosis is defined as a white blood cell (WBC) count greater than $100 \times 10^9/L$. It occurs in up to 20\% of childhood leukemias and is present at diagnosis in up to 15\% of pediatric patients with ALL, up to 22\% of those with ANLL, and almost all with chronic myelogenous leukemia.

Although WBC counts can be significantly higher in ALL, the blasts of ANLL tend to cause more clinical complications such as sludging and thrombi of the microcirculation.\textsuperscript{45} Associated symptoms are shown in Box 2.

Hyperleukocytosis is a poor prognostic factor in acute pediatric leukemias because it increases risk of tumor lysis syndrome (TLS) and hemorrhagic complications.\textsuperscript{50}

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**Box 2**

**Symptoms associated with hyperleukocytosis**

- Respiratory symptoms: dyspnea, tachypnea, hypoxia, acute respiratory distress syndrome, respiratory failure
- Neurologic symptoms: focal deficits, headache, confusion, delirium, ataxia, stroke, seizure
- Genitourinary symptoms: priapism, renal failure
- Cardiac symptoms: cardiac ischemia, pulmonary edema
- Ocular symptoms: papilledema, renal artery or vein distention
- Skin symptoms: cyanosis, plethora
Treatment is directed toward reducing the peripheral WBC count and controlling risks of metabolic derangements and bleeding. IV hydration and prophylaxis for TLS should be initiated. Hydroxyurea can prevent further leukocyte production. Cytapheresis can be used to reduce cell counts, but must be performed with careful assessment of the risks of anticoagulation and central venous catheterization. Partial-exchange transfusion can reduce WBC counts and can be used even in infants less than 12 kg who may be too small for safe leukopheresis. Hyperleukocytosis is associated with increased risk of bleeding caused by the fibrinolytic proteases released from blast cells and decreased coagulation factors associated with consumption or severe systemic illness. Transfusion of pRBCs and use of diuretics can increase blood viscosity and should be avoided. Platelet transfusions have less effect on viscosity and may be used when indicated. Definitive treatment involves cancerspecific therapy, and thus involvement of a pediatric oncologist is imperative.

**Metabolic Emergencies**

**TLS**

In children, TLS is seen in ALL, high-grade non-Hodgkin lymphoma such as Burkitt lymphoma, and occasionally in other malignancies with high tumor burden. Rapid tumor cell death releases intracellular contents that accumulate faster than they can be cleared by the kidneys. Symptoms include nausea, anorexia, cardiac arrhythmias, seizures, muscles cramps and tetany, decrease or lack of urine output, and altered mental status. TLS can be the presenting feature of malignancy or the result of initiating chemotherapy. Diagnosis of TLS in children is based on laboratory values and clinical status similar to adults. Patients are at highest risk for TLS within 12 to 72 hours of initiating chemotherapy but remain susceptible for at least 7 days.

Prevention and treatment of TLS primarily involves adequate IV hydration, laboratory monitoring, and use of supportive medications. Aggressive IV hydration should be initiated early at 2 to 4 times maintenance. Hydration goals include urine output of 3 mL/kg/h and specific gravity less than 1.010. First-line medications for hyperuricemia include rasburicase and allopurinol. These medications should not be

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![Fig. 2. Metabolic imbalances associated with TLS.](image-url)
### Table 5
**Features of TLS and suggested management in pediatric patients**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms/Causes</th>
<th>Laboratory Values</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLS</td>
<td>Nausea/anorexia, Seizures, Cramps/tetany, Altered mental status, Oliguria/anuria</td>
<td>Monitor Q 4–8 h: urine pH, uric acid, electrolytes, BUN, creatinine, ionized calcium, magnesium, phosphorus, lactate, dehydrogenase</td>
<td>D5 1/2 NS + 40 mEq NaHCO₃ at 2–4 times maintenance rate Avoid K/Phos/Ca in IV fluids Goal urine pH: 7.0–8.0 Furosemide 0.5–1.0 mg/kg or mannitol 0.5 g/kg if oliguric or anuric and not hypovolemic</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>Caused by release of intracellular phosphate from malignant cells, which can contain up to 4× more phosphate than somatic cells</td>
<td>Moderate: &gt;5.0 mg/dL Severe: associated with hypocalcemia</td>
<td>Aluminum hydroxide Severe: dialysis, CVVH, CVAH</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Caused by calcium phosphate crystal precipitation</td>
<td>&lt;6 mg/dL</td>
<td>Avoid treatment if no symptoms to avoid precipitation of calcium phosphate</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Caused by rapid release of intracellular contents from malignant cells; worsened by renal insufficiency and acidosis</td>
<td>Moderate: &gt;6.0 mmol/L Severe: &gt;7.0 mmol/L or symptomatic</td>
<td>ECG, cardiorespiratory monitor Avoid IV or oral potassium Kayexalate Nebulized albuterol Insulin/dextrose Calcium gluconate Dialysis</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>Caused by breakdown of intracellular components such as DNA</td>
<td>Serum creatinine &gt;1.5 ULN Or Uric acid &gt;7 mg/dL</td>
<td>Rasburicase: 0.15–0.2 mg/kg/d IV daily up to 5 d (avoid bicarbonate) Allopurinol: PO: 300 mg/m2/d or 10 mg/kg/d IV: 200 mg/m2/d (maximum 600 mg/d)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>SIADH</td>
<td>Na &lt;130 mEq/L Serum osmolality &lt;280 mOsm/L Urine osmolality &gt;500 mOsm/L</td>
<td>Furosemide 1 mg/kg Fluid restriction</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>—</td>
<td>Mild: &gt;10.5–11.9 mg/dL Moderate: &gt;12–13.9 mg/dL Severe: &gt;14 mg/dL</td>
<td>Monitor ionized calcium, serum pH, phosphorus, magnesium, and potassium Obtain ECG IVF Pamidronate or zoledronate</td>
</tr>
</tbody>
</table>

**Abbreviations:** BUN, blood urea nitrogen; CVAH, congenital virilizing adrenal hyperplasia; CVVH, continuous venovenous hemofiltration; D5, 5% dextrose in water; ECG, electrocardiogram; IVF, idiopathic ventricular fibrillation; NS, normal saline; Phos, phosphate; PO, by mouth; Q, every; SIADH, syndrome of inappropriate antidiuretic hormone secretion; ULN, upper limit of normal.
used concurrently and rasburicase is contraindicated in patients with glucose-6-phosphatase deficiency.57

**Syndrome of inappropriate antidiuretic hormone secretion**

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in pediatric patients with cancer is usually caused by chemotherapeutic side effects (Box 3),62 injury to brain tissue from surgery or radiation, or in rare cases is the result of ADH-secreting tumors. This syndrome is less common in pediatric patients. Patients presenting with SIADH generally have nonspecific symptoms such as weight gain, nausea, fatigue, oliguria, and headache, but symptoms can progress to hallucinations, seizures, coma, and death if left untreated.41,62 SIADH is usually recognized on laboratory investigation. Low serum osmolality (<280 mOsm/L) in the presence of high urine osmolality (>500 mOsm/L) and moderate (125–130 mEq/L) to severe (<120) hyponatremia are virtually diagnostic of SIADH.

Treatment of SIADH in healthy children is fluid restriction, careful hydration with IV fluids, and diuretic administration.59 In patients receiving chemotherapy, management can be challenging and is complicated by the need to maintain hydration status. Careful and judicious fluid restriction in conjunction with IV fluid replacement of ongoing and insensible losses (normal saline at 500 mL/m²/24 h) is the optimum strategy. In cases that have progressed to seizure or coma, cautious use of 3% saline to increase serum sodium concentration should be started (Box 4).

**Infectious Emergencies**

**Infection**

Patients with cancer are at increased risk for infection because of several factors including chemotherapy-induced immunosuppression, neutropenia, hypogammaglobulinemia, and breakdown of normal physiologic barriers. These patients have increased risk of bacterial, viral, fungal, and parasitic infections. In general, pediatric patients with cancer are susceptible to complications or dissemination of common pediatric pathogens, but they are also at risk from normal flora overgrowth, opportunistic pathogens, or dormant viral infections.

**Febrile neutropenia**

Febrile neutropenia is an oncologic emergency and is defined as fever (temperature ≥38°C twice in 24 hours) in the presence of neutropenia (absolute neutrophil count<500 cells/μL). A thorough review of febrile neutropenia is provided elsewhere in this issue. Management of febrile neutropenia in the pediatric patient includes prompt assessment, early IV or port access, pan cultures, and the administration of

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**Box 3**

**Antineoplastic drugs associated with SIADH in children**

- Vincristine
- Cyclophosphamide
- Ifosfamide
- Cisplatin
- Melphalan
broad-spectrum antibiotics (Box 5). Patients with neutropenia are at increased risk for both bacterial and viral illness.

Studies have shown a direct correlation between mortality and time to antibiotic administration in patients who are hypotensive because of septic shock. Hypotension is an ominous sign in pediatric patients, who typically manifest shock initially as tachycardia and decreased perfusion. Although no studies have effectively shown similar outcome benefits (compared with septic shock) for patients with fever and neutropenia, there should be no delay in antibiotic administration for patients with confirmed or suspected neutropenia. Standard goal times to antibiotic administration at pediatric emergency departments range from 30 to 60 minutes. Antibiotics should be given within this time frame and should not be withheld because of difficulty obtaining laboratory results (eg, blood cultures). Commonly used antibiotics in neutropenic pediatric patients include ceftriaxone (50 mg/kg/dose) and cefepime (50 mg/kg/dose).

**Neurologic Emergencies**

**Seizures**
Seizures in the pediatric patient with cancer can be the presenting sign of an intracranial mass, TLS, SIADH, or hyperleukocytosis, or can be seen following the administration of febrile neutropenia (Box 5).
intrathecal chemotherapy. Management of the seizing patient should be directed at stopping seizure activity (Table 6) and then eliciting the cause of the seizure.

Cerebrovascular accidents

Cerebrovascular accidents (CVAs) are uncommon in the pediatric population, but patients with a cancer diagnosis are at higher risk for experiencing a CVA caused by either the disease or its treatment. Causes of CVA include hyperleukocytosis, hypercoagulability, thrombocytopenia, hemorrhage, and radiation-induced vasculopathy. When a CVA is suspected, immediate care includes stabilization of airway, breathing, and circulation; cessation of all potentially causative medications (eg, L-asparaginase); and emergent imaging (CT head followed by MRI/magnetic resonance angiography). Platelets may be indicated if the patient is thrombocytopenic (especially in the presence of hemorrhage) or initiation of chemotherapy may be warranted if hyperleukocytosis is the cause of the CVA.

SUMMARY

Early recognition is an important contributor to a good overall prognosis for pediatric cancers. Effective care of pediatric malignancies requires an age-appropriate approach to patients and compassionate understanding of family dynamics. Some of the sentinel factors that differentiate pediatric from adult malignancies are summarized in Box 6.

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Seizure ablation medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg IV at 2 mg/min up to 4 mg</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>20 mg/kg IV at 50 mg/min</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>20 mg/kg PE at 150 mg PE/min</td>
</tr>
</tbody>
</table>

Abbreviation: PE, phenytoin equivalents.

Box 6

Pearls for recognition and care of pediatric malignancies

- Leukemia can cause bone pain. Pain out of proportion to injury may indicate a primary bone tumor, with peak incidence in adolescence. Clinicians should maintain a high index of suspicion for malignancy in children with persistent, unremitting pain that limits movement.
- Findings concerning for malignancy include diffuse lymphadenopathy, unexplained bruising, or intussusception in children older than 2 years.
- Children should receive leukocyte-reduced, CMV-negative blood products. Alloimmunization is a particular concern in the pediatric malignancies best treated by BMT, and is a primary reason to not use familial directed-donor blood products.
- Steroids should not be used to treat thrombocytopenia or anemia without hematology consultation because a single dose can cause remission of aggressive hematologic malignancies, rendering bone marrow biopsy less sensitive and potentially delaying diagnosis or expedited treatment.
- Intracranial tumors are the most common solid tumors of childhood. Early morning vomiting, increasing head circumference, and ataxia are common presenting signs.
REFERENCES


48. Song LW, Marcon NE. Typhlitis (neutropenic enterocolitis). In: UpToDate, Marr KA, Thorner AR, editors. Waltham (MA): UpToDate; 2012.