Overview of common presenting signs and symptoms of childhood cancer

AUTHOR: Daniel S Wechsler, MD, PhD
SECTION EDITOR: Alberto S Pappo, MD
DEPUTY EDITOR: Sonali M Shah, MD

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INTRODUCTION

Childhood cancer often is difficult to detect in its early stages because the associated signs and symptoms are nonspecific, insidious in onset, and mimic other more common disorders.

The topic will provide an overview of common signs and symptoms that are suspicious for childhood cancer and outline the general principles of evaluation. The evaluation and diagnosis of specific pediatric malignancies are discussed separately:

- Acute leukemias (see "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children" and "Acute myeloid leukemia: Children and adolescents")
- Central nervous system tumors (see "Clinical manifestations and diagnosis of central nervous system tumors in children")
- Germ cell tumors (see "Ovarian germ cell tumors: Pathology, epidemiology, clinical manifestations, and diagnosis" and "Clinical presentation, diagnosis, and staging of testicular germ cell tumors")
- Lymphomas (see "Hodgkin lymphoma in children and adolescents" and "Overview of non-Hodgkin lymphoma in children and adolescents")
- Neuroblastoma (see "Epidemiology, pathogenesis, and pathology of neuroblastoma")
- Retinoblastoma (see "Retinoblastoma: Clinical presentation, evaluation, and diagnosis")
- Sarcomas (Ewing sarcoma, osteosarcoma, rhabdomyosarcoma) (see "Epidemiology, pathology, and molecular genetics of Ewing sarcoma" and "Osteosarcoma: Epidemiology, pathology, clinical presentation, and diagnosis" and "Rhabdomyosarcoma in childhood and adolescence: Clinical presentation, diagnostic evaluation, and staging")
- Thyroid cancer (see "Thyroid nodules and cancer in children")
- Wilms tumor (see "Clinical presentation, diagnosis, and staging of Wilms tumor")

BACKGROUND

Optimal management of childhood cancer requires a high level of suspicion by the primary care practitioner and early referral to a pediatric oncologist. Early detection and treatment may reduce disease-related morbidity and complications.

The following facts about childhood cancer set the stage for a discussion of issues surrounding clinical assessment of the child with suspected cancer:

- Although childhood cancers are rare, they are the leading cause of disease-related death in individuals between 1 and 19 years of age in the United States [1]. Mortality is higher among boys compared with girls and among adolescents compared with younger children [2,3].
- At least 85 percent of pediatric cancers are associated with the presenting signs and symptoms discussed in this topic review; the remaining 10 to 15 percent of tumors are associated with unusual signs and symptoms and are more difficult to diagnose in the early stages [4].
- Delays in diagnosis have been shown to be related to the child's age (older children are at a higher risk for delay), the specific type of cancer, presenting symptoms, tumor site, first medical specialty consulted, and access to health care [5-8]. The time from onset of symptoms to diagnosis of pediatric cancer is variable based on the type of malignancy. The reported average time to diagnosis ranges from 2 to 5 weeks for neuroblastoma, 3 to 5 weeks for acute leukemias, 7 to 10 weeks for lymphomas, 8 to 15 weeks for bone tumors, and 8 to >20 weeks for brain tumors [5].
- Common sites of childhood malignancies include blood and bone marrow, brain and nervous system, lymph nodes, kidneys, bone, and soft tissues [2,9]. The frequency of a particular cancer depends upon the age of the child (table 1). For example, neuroblastoma and Wilms tumor occur most commonly in children between birth and four years of age; leukemia occurs most often in children <10 years old; and Ewing sarcoma, Hodgkin lymphoma, and thyroid cancer are more common in children >10 years of age [10,11].
- Five-year survival rates vary by diagnosis but are approximately 80 to 85 percent when all cancer types are grouped together [12,13]. Survival has improved significantly over the past several decades [13-15].

WARNING SIGNS

Obtaining a detailed history is the first step in evaluating the child with suspected cancer. Emphasis should be placed on the chief complaint. Early warning signs of childhood cancer include [16]:

- Unexplained pallor and loss of energy
- A new lump, mass, or swelling
- Recent unexplained weight loss
- Unexplained fever or persistent constitutional symptoms
- Easy bruising or bleeding
- Prolonged or ongoing pain in one or more areas of the body
- Limping
- Frequent headaches, particularly if occurring in the morning and associated with vomiting

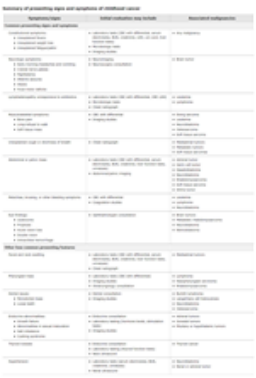
- Sudden eye or vision changes

PREDISPOSITION TO MALIGNANCY

Certain genetic conditions and immune deficiency syndromes are associated with an increased risk of developing cancer (table 2 and table 3) [17]. Survivors of certain types of childhood cancer (eg, retinoblastoma) are at risk for developing secondary malignancies [18,19]. The family history should include information about parents, siblings, and first cousins. Age, serious illnesses, congenital anomalies, and cause of death for deceased family members should also be elicited [20].

COMMON SIGNS AND SYMPTOMS

Childhood cancer may present with signs and symptoms that are shared by other childhood illnesses (table 4). Although a single finding in isolation does not always require evaluation for cancer, a combination of multiple findings (eg, weight loss, bone pain, and lymphadenopathy; easy bruising, abnormal blood counts, and hepatosplenomegaly) is worrisome and generally warrants evaluation for malignancy. In addition, certain findings are worrisome even as isolated findings (eg, abdominal or mediastinal masses, headaches associated with vomiting in the morning, blasts on the peripheral blood smear) and require prompt evaluation and consultation.



Summary of presenting signs and symptoms of childhood cancer

Table 4 - larger image below

Constitutional symptoms — Nonspecific constitutional symptoms including fever, weight loss, and fatigue are common findings in children with cancer.

Fever — Fever is a common complaint in children and is rarely attributable to malignancy.

- **When to suspect malignancy** – Suspicion for noninfectious causes should be raised when the febrile illness does not follow the usual course or fails to respond to seemingly appropriate therapy. However, even when fever is prolonged, infection remains the most common cause [21,22]. In published reports of children with prolonged fever, a small minority (approximately 5 percent) were found to have a malignancy, most commonly leukemia and lymphoma [21]. (See "Fever of unknown origin in children: Etiology" and "Fever of unknown origin in children: Evaluation", section on 'Causes'.)

  In the absence of infection, persistent or recurring fever may reflect an occult neoplasm, such as lymphoma; rarely, it may be secondary to tumor-related necrosis, such as with neuroblastoma or Wilms tumor. Persistent fever also may be the only complaint in children with leukemia, Ewing sarcoma, and Langerhans cell histiocytosis [20]. More than one-half of children with leukemia have fever at the time of presentation [23]. (See "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children" and "Clinical presentation, staging, and prognostic factors of Ewing sarcoma" and "Clinical manifestations, pathologic features, and diagnosis of Langerhans cell histiocytosis".)

A thorough physical examination may reveal additional worrisome findings such as lymphadenopathy or hepatosplenomegaly. (See 'Lymphadenopathy' below and "Approach to the child with an enlarged spleen".)

- **Evaluation** – The initial diagnostic evaluation for a child with a fever that does not respond to seemingly appropriate therapy should include (but is not limited to) a complete blood count (CBC) with differential, examination of the peripheral blood smear, blood culture, and chest radiography. Additional studies may be indicated for fever of unknown origin, as discussed separately. (See "Fever of unknown origin in children: Evaluation", section on 'Overview of evaluation'.)

  The white blood cell (WBC) differential and examination of the peripheral blood smear may help distinguish the underlying cause of fever. The presence of circulating blasts (picture 1A) or profound neutropenia or thrombocytopenia can suggest the diagnosis of leukemia, in which case, referral to a pediatric oncologist and bone marrow examination is generally warranted, particularly if two cell lines are affected (see 'Blood count abnormalities' below). On the other hand, the presence of atypical lymphocytes may suggest a nonmalignant etiology (eg, Epstein-Barr virus mononucleosis or other viral illnesses).

  Chest radiography may reveal an intrathoracic mass. (See 'Mediastinal masses' below.)

Weight loss — Most children who present with isolated weight loss have nonmalignant etiologies (eg, dehydration, infection, malnutrition). However, patients with continued, unintentional weight loss in the setting of anemia, pallor, bruising, body pains, lymphadenopathy, hepatosplenomegaly, unexplained fevers, or fatigue may have an underlying malignancy. The evaluation of children with weight loss is discussed separately. (See "Evaluation of weight loss in infants over six months of age, children, and adolescents".)

Fatigue and pallor — Decreased energy, fatigue, and pallor can occur in a wide range of diseases. Pallor is most often due to anemia but may also occur in nonhematologic conditions such as chronic infection, rheumatologic disorders, heart failure, arrhythmia, or metabolic disorders. Fatigue and pallor are most commonly due to nonmalignant causes; however, concern for malignancy may be raised if there are other concerning accompanying findings (petechiae, bruising, lymphadenopathy, hepatosplenomegaly, bone pain). Initial laboratory testing in children with pallor generally includes a CBC with differential and reticulocyte count. This can help to identify if there are other concerning hematologic findings (eg, other cell lines affected, peripheral blasts (picture 1A)), which should prompt hematology referral and bone marrow examination. (See 'Blood count abnormalities' below.)

The evaluation of pallor and anemia in children is discussed separately. (See "Evaluation of pallor in children" and "Approach to the child with anemia".)

Headache — Headache is another common symptom in general pediatric practice. Intracranial tumors are a rare cause of headache in children, but they must be included in the differential diagnosis when headaches are persistent or worsening in intensity, particularly if they are associated with vomiting, visual changes, asymmetric weakness, or coordination difficulties. (See "Clinical manifestations and diagnosis of central nervous system tumors in children", section on 'Common presenting signs and symptoms' and "Headache in children: Approach to evaluation and general management strategies", section on 'Additional evaluation for signs and symptoms consistent with secondary headache'.)

- **History and physical examination** – The history of headache for a child, particularly a child who is <10 years old, is best obtained with input from the caregiver (history) and physical examination (table 5A-B). The

approach to evaluating headache in childhood is discussed in detail separately. (See "Headache in children: Approach to evaluation and general management strategies", section on 'Physical examination'.)

Features of the history and physical examination that may raise concern for a brain tumor include (see "Clinical manifestations and diagnosis of central nervous system tumors in children", section on 'Headache'):

- Headaches that persist or recur frequently for more than three or four weeks
- Headaches that occur in a young child (ie, <4 years of age)
- Headaches that occur upon waking or that wake a child from sleep
- Headaches associated with vomiting upon waking
- Headaches associated with other concerning findings (eg, motor abnormalities, visual changes, papilledema, altered mental status, seizures)

- **Neuroimaging** – Neuroimaging is the major diagnostic modality in the evaluation for a possible brain tumor. Indications for neuroimaging and the choice of imaging modality in children with suspected brain tumors are reviewed separately. (See "Clinical manifestations and diagnosis of central nervous system tumors in children", section on 'Neuroimaging'.)

Lymphadenopathy — Lymphadenopathy is another common finding in children. The size of normal lymph nodes in children varies widely as children are exposed to new viruses and bacteria. Most children have palpable small cervical, axillary, or inguinal lymph nodes at some time during childhood. The size of a lymph node that is classified as abnormal varies depending upon the lymph node region and age of the child. The risk of malignancy is increased in lymph nodes that are >2 cm (0.8 inches) in diameter, although malignancy may occur in smaller nodes. This is discussed in greater detail separately. (See "Peripheral lymphadenopathy in children: Evaluation and diagnostic approach", section on 'Lymph nodes'.)

Most enlarged nodes are related to benign causes such as infection [24]. However, lymphadenopathy may be a presenting sign of leukemia, lymphoma and neuroblastoma. By contrast, lymphadenopathy is uncommon (although seen occasionally) with soft tissue, bone, and germ cell tumors. The site of the adenopathy and the child's age may help narrow the range of possible diagnoses. The most common cancers associated with lymphadenopathy of the head and neck are neuroblastoma, rhabdomyosarcoma, non-Hodgkin lymphoma, and leukemia in children <6 years old, whereas lymphomas (both Hodgkin and non-Hodgkin) predominate in children between 7 and 13 years of age; Hodgkin lymphoma is the most common histology in children older than 13 years.

- **Evaluation** – Clinical features that are worrisome for malignancy in children with lymphadenopathy are discussed in detail separately (table 6). (See "Peripheral lymphadenopathy in children: Evaluation and diagnostic approach", section on 'Worrisome features'.)

  The evaluation of unexplained lymphadenopathy in children depends in part upon whether it is generalized or localized and, if localized, which lymph node region is involved. Asymmetric lymph node enlargement may also warrant further evaluation. In addition, the evaluation may vary depending upon whether there are other associated signs or symptoms. The diagnostic approach is summarized below and discussed in detail separately (see "Peripheral lymphadenopathy in children: Evaluation and diagnostic approach", section on 'Diagnostic approach'):

  - **Generalized lymphadenopathy** (table 7) – (See "Peripheral lymphadenopathy in children: Evaluation and diagnostic approach", section on 'Generalized lymphadenopathy'.)

- **Cervical lymphadenopathy** (table 8) – (See "Cervical lymphadenitis in children: Diagnostic approach and initial management", section on 'Diagnostic approach'.)
- **Supraclavicular (or lower cervical) lymphadenopathy** – (See "Peripheral lymphadenopathy in children: Evaluation and diagnostic approach", section on 'Supraclavicular lymphadenopathy'.)
- **Axillary adenopathy** (table 9) – (See "Peripheral lymphadenopathy in children: Evaluation and diagnostic approach", section on 'Axillary lymphadenopathy'.)
- **Epitrochlear lymphadenopathy** – (See "Peripheral lymphadenopathy in children: Evaluation and diagnostic approach", section on 'Epitrochlear lymphadenopathy'.)
- **Inguinal lymphadenopathy** (table 10) – (See "Peripheral lymphadenopathy in children: Evaluation and diagnostic approach", section on 'Inguinal lymphadenopathy'.)

- **Lymph node biopsy** – Excisional lymph node biopsy may be indicated in patients with worrisome features (table 6). This is discussed separately. (See "Peripheral lymphadenopathy in children: Evaluation and diagnostic approach", section on 'Lymph node biopsy'.)

Bone and joint pain — Bone and joint pain may be a presenting symptom for tumors that involve the bone or bone marrow (eg, primary or metastatic bone tumors, leukemias, neuroblastoma). (See "Evaluation of limp in children" and "Back pain in children and adolescents: Evaluation" and "Approach to hip pain in childhood".)

- **Malignant bone tumors** – Ewing sarcoma and osteosarcoma are the two most common malignant bone tumors in children. Most affected patients present with bone pain, typically for a duration of several weeks to months [25,26]. The pain associated with primary bone tumors typically begins as intermittent pain and increases in severity over time, though it may wax and wane [25,26]. An associated mass may be palpable on examination. (See "Clinical presentation, staging, and prognostic factors of Ewing sarcoma", section on 'Clinical presentation' and "Osteosarcoma: Epidemiology, pathology, clinical presentation, and diagnosis", section on 'Clinical presentation'.)

  Pathologic fractures occur in approximately 10 to 15 percent of cases of Ewing sarcoma or osteosarcoma [25]. Because fever may be present at diagnosis, particularly in patients with Ewing sarcoma, osteomyelitis must be included in the differential diagnosis of such cases. (See "Clinical presentation, staging, and prognostic factors of Ewing sarcoma" and "Hematogenous osteomyelitis in children: Evaluation and diagnosis", section on 'Differential diagnosis'.)

- **Acute leukemia** – Bone pain is a presenting symptom in approximately 20 to 30 percent of children with acute leukemia, and other musculoskeletal symptoms (including hip pain, limb pain, joint pain, and limp) occur in approximately 60 to 70 percent [23]. (See "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children", section on 'Presentation'.)

- **Differentiating leukemia from rheumatologic conditions** – The musculoskeletal pain associated with acute leukemia, particularly if it occurs in the joints, may be mistaken for rheumatologic pain [27-30]. A combination of clinical and laboratory findings may be helpful in making the distinction. Nocturnal pain and nonarticular bony pain are more commonly associated with leukemia, whereas morning stiffness and rash occur more commonly in rheumatologic conditions [31]. In addition, children with leukemia often (but not always) display more

significant abnormalities on CBC (ie, leukopenia, anemia, thrombocytopenia). (See 'Blood count abnormalities' below.)

Because the presenting features of childhood malignancy and rheumatologic disorders may overlap, bone marrow examination and/or peripheral blood flow cytometry [32,33] may be warranted if there is uncertainty about the diagnosis, particularly if **any** of the following are present [20,28,29,31,34,35]:

- Type and/or severity of pain are atypical for rheumatologic pain (table 11).
- Patient refuses to bear weight or has new-onset limping.
- Associated cytopenias (including mild leukopenia, anemia, or thrombocytopenia) (table 12 and table 13).
- Elevated serum lactate dehydrogenase.

It is important to perform a bone marrow or peripheral blood flow cytometry [32,33] evaluation **before** beginning treatment with glucocorticoids because glucocorticoids can induce a transient tumor response in some children with leukemia or lymphoma, which may interfere with the subsequent diagnostic evaluation [36]. (See "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children", section on 'Pretreatment evaluation'.)

- **Evaluation of bone and joint pain** – Findings that may raise concern for malignancy in children with bone and joint pain include:

  - Inability or refusal to walk
  - Nighttime pain that wakens a child from sleep
  - Pain at rest
  - Bone or hip pain in a child ≤3 years of age
  - Persistent (ie, >2 weeks) or recurring pain or limp
  - Limitation of joint movement on examination
  - Palpable mass on examination

  Patients with any of these findings should generally undergo evaluation including the following:

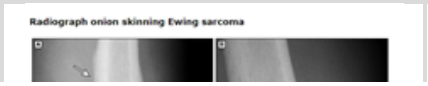
  - Plain radiographs
  - CBC with platelet count and differential
  - C-reactive protein and/or erythrocyte sedimentation rate
  - Alkaline phosphatase
  - Lactate dehydrogenase
  - Uric acid

  Plain radiographs are typically obtained as the initial imaging study; however, magnetic resonance imaging (MRI) is generally the preferred modality for definitive evaluation of bone and soft tissue lesions.

  The evaluation of children with bone pain or limp is discussed in greater detail separately. (See "Evaluation of limp in children" and "Approach to hip pain in childhood", section on 'Evaluation' and "Back pain in children and adolescents: Evaluation".)

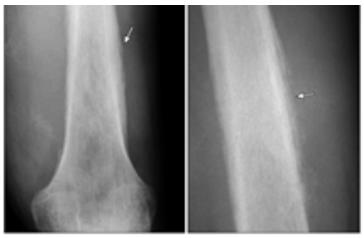
- **Radiographic findings** – Radiographic findings that are characteristic of malignant bone tumors include:

  - **Onion skinning** – "Onion skinning" is caused by repetitive periosteal reactions, each depositing a layer of calcium, as the tumor grows



beyond the periosteum (image 1). The onion skin periosteal reaction is most common in Ewing sarcoma but may occur in other conditions and may be absent in Ewing sarcoma. (See "Clinical presentation, staging, and prognostic factors of Ewing sarcoma", section on 'Radiographic studies'.)

- **Sunburst phenomenon** – "Sunburst" phenomenon is a periosteal reaction that occurs when malignant osteoblasts deposit new bone and blood vessels that radiate perpendicularly from the tumor [37,38]. This phenomenon is most commonly (but not necessarily) seen in osteosarcoma (image 2 and image 3). (See "Osteosarcoma: Epidemiology, pathology, clinical presentation, and diagnosis", section on 'Plain radiograph'.)



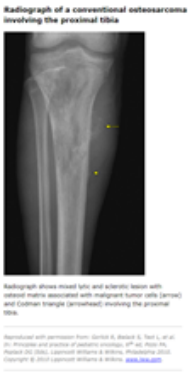
Radiograph onion skinning Ewing sarcoma

Image 1 - larger image below

A pathologic fracture should also raise suspicion for a bone tumor. Other nonmalignant causes of pathologic fractures in children are discussed separately. (See "General principles of fracture management: Fracture patterns and description in children", section on 'Pathologic fracture'.)

Radiographic features that suggest leukemia include osteopenia, lytic lesions, metaphyseal bands, periosteal new bone, and sclerotic lesions [39].

Although abnormal findings on diagnostic imaging can raise suspicion for malignancy, they generally do not obviate the need for obtaining a tissue biopsy. (See 'Obtaining tissue samples' below.)



Radiograph of a conventional osteosarcoma involving the proximal tibia

Image 2 - larger image below

Mediastinal masses — Mediastinal tumors may be asymptomatic or may be associated with symptoms such as cough, shortness of breath (often positional), hoarseness, wheezing, or facial or neck swelling [40]. When symptoms are present, they usually result from extrinsic compression or involvement of adjacent structures, such as the recurrent laryngeal nerve. Mediastinal masses are often incidentally discovered on chest radiographs obtained for other reasons.

- **Types of tumors according to location** – The mediastinum is divided into three anatomic compartments (figure 1). The compartment in which the mass is located can provide information about its likely etiology [41,42]:

  - **Anterior** – Masses commonly found in the anterior mediastinum include thymomas, teratomas, lymphomas, thyroid tumors, germ cell tumors, angiomas, and lipomas, [43]. The first four of these tumors are often referred to as the proverbial "four Ts": thymoma, teratoma, "terrible" (or T cell) lymphoma, and thyroid [44].

  - **Middle** – Masses commonly found in the middle mediastinum include lymphoma, metastatic cancer, infection-related lymphatic lesions, malignancies that extend directly from the abdomen, pericardial cysts, bronchogenic cysts, esophageal lesions, and hernias.

  - **Posterior** – Masses commonly found in the posterior mediastinum include neurogenic tumors such as neurofibromas; neuroblastomas; ganglioneuroblastomas; ganglioneuromas; enterogenous cysts; thoracic

meningoceles; and malignancies such as Ewing sarcoma (either osseous or extraosseous), lymphoma, and rhabdomyosarcoma.

In one study, children with malignant mediastinal masses were more likely to have tumors in the anterior mediastinum compared with patients with benign mediastinal masses [45]. In addition, children with malignant tumors more commonly presented with malaise, neck swelling, abnormal extrathoracic lymphadenopathy, and lymphopenia.

- **Evaluation** – Mediastinal masses that are discovered on chest radiography require further diagnostic imaging, which usually consists of contrast-enhanced computed tomography (CT) of the chest. This helps to delineate the precise location of the mass and provides additional anatomic detail that can help narrow the diagnostic possibilities. Other advanced imaging modalities may also be required (eg, MRI or 18-fluoro-2-deoxyglucose [FDG]-positron emission tomography [PET] scan [either as an integrated PET/CT or as a separate PET study]) [42,46-48].

  Children who are suspected to have malignancy based upon the imaging findings should be referred to pediatric oncology. Peripheral blood flow cytometry and/or bone marrow examination may be indicated. If these tests are nondiagnostic, it may be necessary to perform a more invasive procedure to obtain tissue from the mediastinal mass for definitive pathologic diagnosis. Patients with large anterior mediastinal masses are at increased risk of respiratory or cardiac arrest during general anesthesia or deep sedation. Therefore, this procedure should be undertaken with appropriate evaluation of the potential risks of anesthesia. Many centers of excellence in pediatric oncology have "mediastinal mass" evaluation teams that include clinicians from the pediatric intensive care unit, anesthesiology, and cardiology to address the potential need for extracorporeal membrane oxygenation (ECMO). (See "Approach to the adult patient with a mediastinal mass" and "Hodgkin lymphoma in children and adolescents", section on 'Diagnosis'.)

Abdominal masses — A palpable abdominal mass, which often is detected by a family member or primary care provider, is one of the most common presenting signs of malignant solid tumors in children [20]. The presenting symptom may be pain, vomiting, constipation, or, less commonly, intestinal obstruction. Although some abdominal masses are benign, all require early, thorough workup. Timely referral to an oncologist is critical to ensure that the proper diagnosis is be made and treatment is initiated promptly.

- **Common intraabdominal tumors** – Wilms tumor and neuroblastoma are the most common intraabdominal tumors; others include lymphoma, hepatic tumors, ovarian tumors, and soft tissue sarcomas. The age of the child helps in the differential diagnosis. Wilms tumor and neuroblastoma occur more commonly in infants and toddlers, whereas leukemic or lymphomatous involvement of the liver, spleen, or retroperitoneal lymph nodes occurs more commonly in older children [20]. (See "Clinical presentation, diagnosis, and staging of Wilms tumor" and "Clinical presentation, diagnosis, and staging evaluation of neuroblastoma".)

- **Evaluation** – When obtaining the history, it is important to determine whether the child has symptoms related to the mass and, if so, their duration and intensity. These features may help to determine how rapidly the mass is growing and/or to distinguish malignancy from another more chronic condition. Abdominal masses in infants and young children often originate in the kidney [20]. Thus, the history should include questions about genitourinary symptoms, including hematuria. Ovarian cysts and tumors are common causes of abdominal masses in girls. Thus, the history for adolescent females should include a menstrual and sexual history. (See "Evaluation of congenital anomalies of the kidney and urinary tract (CAKUT) in the neonate" and "Adnexal masses: Evaluation in infants, children, and adolescents".)

Physical examination should characterize the location and extent of the abdominal mass. Palpation is easier if the child is relaxed. The following structures are normally palpable in children and sometimes are mistaken for abdominal masses: liver edge, spleen, kidneys, aorta, sigmoid colon, and spine. (See "The pediatric physical examination: Chest and abdomen", section on 'Palpation'.)

If a mass is palpated on physical examination, the child should undergo additional evaluation including laboratory studies (a CBC, serum electrolytes, blood urea nitrogen, creatinine, and urinalysis) and abdominal imaging. Ultrasound is typically performed as the initial imaging study; however, depending on the findings, additional imaging with CT, PET scan, or MRI may be warranted. Details of the evaluation for common abdominal tumors in children are provided separately:

- Wilms tumor (see "Clinical presentation, diagnosis, and staging of Wilms tumor", section on 'Diagnostic evaluation')
- Neuroblastoma (see "Clinical presentation, diagnosis, and staging evaluation of neuroblastoma", section on 'Diagnostic and staging evaluation')
- Ovarian tumors (see "Adnexal masses: Evaluation in infants, children, and adolescents")
- Abdominal lymphomas (see "Hodgkin lymphoma in children and adolescents" and "Overview of non-Hodgkin lymphoma in children and adolescents")

Bleeding symptoms — When bleeding is the initial sign of childhood cancer, it is usually because of thrombocytopenia, which, in turn, is most often caused by neoplastic involvement of the bone marrow. This typically manifests as cutaneous bleeding (such as petechiae (picture 2) and ecchymoses) and/or mucosal bleeding (epistaxis, gingival bleeding, buccal bleeding). (See "Approach to the child with bleeding symptoms" and "Approach to the child with unexplained thrombocytopenia".)

Petechiae

Picture 2 - larger image below

Coagulopathy is less common but can accompany acute promyelocytic leukemia, a rare form of acute myeloid leukemia [49]. Coagulopathy also has been reported in patients with acute lymphoblastic leukemia (especially T cell acute lymphoblastic leukemia), lymphoma, and neuroblastoma [20]. Other disseminated malignancies may be associated with a coagulopathy, but signs or symptoms are rare findings unless disseminated intravascular coagulation supervenes. (See "Clinical manifestations, pathologic features, and diagnosis of acute promyelocytic leukemia in adults" and "Evaluation and management of disseminated intravascular coagulation (DIC) in adults" and "Disseminated intravascular coagulation in infants and children".)

- **Evaluation** – Important etiologies in the differential diagnosis for a child presenting with bleeding symptoms and thrombocytopenia include malignancy (particularly acute leukemia), infection, and immune thrombocytopenia (ITP) (table 14). Initial testing includes a CBC with differential, platelet count, coagulation studies (prothrombin time and activated partial thromboplastin time), and examination of the peripheral blood smear. Peripheral blood flow cytometry and bone marrow examination may be performed if there are concerning findings on initial testing (eg, peripheral blasts, multiple cytopenias) or if there are clinical findings

that are atypical for ITP (ie, if thrombocytopenia is associated with constitutional symptoms, bone pain, lymphadenopathy, or splenomegaly). The diagnostic approach is discussed in separate topics:

- Diagnostic approach to unexplained thrombocytopenia (see "Approach to the child with unexplained thrombocytopenia")
- Indications for bone marrow examination in children with suspected ITP (see "Immune thrombocytopenia (ITP) in children: Clinical features and diagnosis", section on 'Indications for bone marrow examination')
- Diagnostic approach to the child with suspected acute leukemia (see "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children", section on 'Laboratory evaluation')

Blood count abnormalities — Abnormal blood counts are a common presenting feature in childhood malignancies. These findings may be noted on a CBC obtained for evaluation of other concerning findings (eg, pallor, petechiae, lymphadenopathy, bone pain) or a CBC obtained for other reasons (eg, routine screening or evaluation of febrile illness). If the CBC was performed in an otherwise healthy patient and the results do not match the clinical picture (eg, marked thrombocytopenia in a child without bleeding symptoms), it should be confirmed with repeat testing.

- **Cytopenias** – Anemia, leukopenia, and thrombocytopenia often occur in combination or as isolated findings in acute leukemias and tumors that involve the bone marrow (eg, neuroblastoma, lymphoma, Ewing sarcoma, and rhabdomyosarcoma) [20]. Normal values for WBC counts and hemoglobin vary by age (table 13 and table 12). Thrombocytopenia is generally defined as platelet count <150,000/microL. The approach to evaluating cytopenias in children is discussed in separate topic reviews. (See "Approach to the child with anemia" and "Evaluation of neutropenia in children and adolescents" and "Approach to the child with unexplained thrombocytopenia".)
- **Abnormal WBCs** – Childhood leukemia can present with any of the following:
  - **Leukopenia** – Leukopenia, including neutropenia (absolute neutrophil count <1500/microL) and/or lymphopenia (absolute lymphocyte count <1500/microL), may be a presenting finding in childhood leukemia. Other causes include infections, drugs, primary immune disorders, hypersplenism, other bone marrow disorders (eg, aplastic anemia), and congenital neutropenias. (See "Evaluation of neutropenia in children and adolescents" and "Approach to the child with lymphocytosis or lymphocytopenia", section on 'Lymphocytopenia'.)
  - **Leukocytosis and lymphocytosis** – Leukocytosis, particularly lymphocytosis, is a common presenting feature of acute leukemia. Peripheral WBC counts >100,000/microL are almost always indicative of leukemia. Other causes of leukocytosis and lymphocytosis include infections (eg, bacterial infections, mononucleosis, pertussis), drugs (eg, glucocorticoids), stress, and asplenia. Usually, by the time the child has evidence of significant malignant lymphocytosis, there are other abnormal findings in the blood count that suggest the diagnosis of leukemia (eg, anemia, neutropenia, thrombocytopenia, peripheral blasts). (See "Approach to the child with lymphocytosis or lymphocytopenia", section on 'Evaluation of the child with lymphocytosis' and "Approach to the patient with neutrophilia".)
  - **Leukemoid reaction** – The term "leukemoid reaction" refers to the presence of a striking increase in leukocyte count (eg, >50,000 cells/microL) and/or immature cells (≥5 percent) in the peripheral blood. Immature WBCs, normally only present in the bone marrow, may be observed in the peripheral blood in a

variety of disorders including septicemia, sudden erythropoietic stimulation caused by hemolysis or hemorrhage, bone marrow recovery phase after bone marrow depression, and rheumatoid arthritis [20,50]. In a study of 603 pediatric patients with isolated leukemoid reaction, only 4 percent were ultimately found to have leukemia [50].

- **Abnormal WBCs (blasts)** – It is never normal to see blast forms (eg, lymphoblasts (picture 1A and picture 1B) or myeloblasts (picture 1C)) on the peripheral smear. Further evaluation of such patients (including hematology/oncology consultation, formal review of the peripheral smear, and bone marrow examination or peripheral blood flow cytometry) is warranted. (See "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children" and "Evaluation of the peripheral blood smear", section on 'Blasts or tumor cells'.)

- **Evaluation** – The evaluation of a patient with abnormal peripheral blood counts generally includes investigation for infectious and malignant causes. Referral to a hematologist/oncologist for further evaluation including bone marrow examination and peripheral blood flow cytometry is warranted if any of the following are present [20]:

  - Finding of atypical or blast cells on peripheral blood smears
  - Significant depression of two or more cell lines without obvious explanation
  - Association with unexplained lymphadenopathy or hepatosplenomegaly
  - Association with an abdominal or mediastinal mass
  - Absence of other explanation (eg, infectious cause) for the blood abnormality

Lymphoblasts in acute lymphoblastic leukemia

Picture 1a - larger image below

Peripheral blood smear of acute lymphoblastic leukemia

Picture 1b - larger image below

Myeloblasts with Auer rod in acute myeloid leukemia

GENERAL PRINCIPLES OF EVALUATION

Referral — The treatment for malignancy can begin only after the tumor has been accurately diagnosed and the extent of disease defined precisely. Thus, once initial evaluation shows a high likelihood of cancer, the child should be referred to a pediatric oncology center for a complete diagnostic workup. The subsequent evaluation and management of childhood cancer should be carried out in a pediatric oncology center where the necessary subspecialists and tests required for timely diagnosis and/or treatment protocols are available.

The importance of establishing the correct diagnosis and accurately determining the extent of disease before therapy begins must be emphasized to the parents and child (if of appropriate age) at the initial evaluation. Such care helps to ensure appropriate therapy and prevents

the need for performing repeat examinations and biopsies after the initiation of treatment [20].

Picture 1c - larger image below

Oncologic emergencies — In some cases, administration of emergency therapy is necessary at the time of presentation to stabilize the child's condition. Examples include:

- Mediastinal masses causing airway, cardiac, or major blood vessel compression. (See "Overview of non-Hodgkin lymphoma in children and adolescents", section on 'Oncologic emergencies'.)
- Brain tumors causing elevated intracranial pressure. (See "Overview of the management of central nervous system tumors in children", section on 'Elevated intracranial pressure'.)
- Hyperleukocytosis due to acute leukemia, which can cause neurologic morbidity, including intracranial hemorrhage or ischemic stroke. (See "Hyperleukocytosis and leukostasis in hematologic malignancies".)
- Hyperuricemia, electrolyte derangements (hyperkalemia, hyperphosphatemia, hypocalcemia), and acute kidney injury due to tumor lysis syndrome (TLS). TLS usually occurs after the initiation of cytotoxic therapy. However, TLS can occur prior to therapy in malignancies that have a high proliferative rate, such as some forms of lymphoma (eg, Burkitt lymphoma, T cell lymphoma) and acute leukemia. (See "Tumor lysis syndrome: Pathogenesis, clinical manifestations, definition, etiology and risk factors".)

In these cases, telephone consultation with a pediatric oncologist is critically important to ensure proper management and expedite the diagnostic workup. If the child is being evaluated in an outpatient clinic, appropriate arrangements should be made to transport the child to an emergency department.

Obtaining tissue samples — Noninvasive imaging techniques such as CT, diagnostic ultrasonography, MRI, positron emission tomographic (PET) scans, and nuclear medicine scans have improved the assessment and staging for cancer. However, for most malignancies, the diagnosis is primarily established by tissue biopsy. Whenever possible, this should be performed at a pediatric oncology center with appropriate coordination among pediatric oncologists, surgeons, and pathologists. A pediatric oncologist should be consulted prior to any biopsy to ensure that an appropriate biopsy approach is requested.

General principles for obtaining a biopsy are as follows:

- Enough tissue must be obtained so that additional biopsies are not necessary
- Obtaining tissue for diagnosis should not compromise future therapy
- Excisional biopsy is preferred when the malignancy involves an organ or lymph nodes
- Proper timing and handling of the biopsy material is essential

The specific approach to obtaining tissue depends on the suspected type of tumor/malignancy:

- **Suspected leukemia** – Bone marrow aspirate and biopsy are performed. This topic is discussed separately. (See "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children", section on 'Diagnosis' and "Acute myeloid leukemia: Children and adolescents".)
- **Suspected lymphoma** – The preferred approach is excisional biopsy of affected lymph node(s). Core needle biopsies are often not adequate for diagnostic studies, due to heterogeneity of the lymph nodes and rarity of cancer cells. This is discussed separately. (See "Peripheral lymphadenopathy in children: Evaluation and

diagnostic approach", section on 'Lymph node biopsy' and "Hodgkin lymphoma in children and adolescents", section on 'Diagnosis' and "Overview of non-Hodgkin lymphoma in children and adolescents".)

- **Suspected Wilms tumor** – Biopsies are not routinely performed unless the tumor is initially assessed to be inoperable. Surgical management varies. In some treatment protocols, surgical resection is performed prior to chemotherapy administration; other protocols use a primary chemotherapy approach followed by surgical resection and staging several weeks later. This is discussed separately. (See "Treatment and prognosis of Wilms tumor", section on 'Difference in approaches of COG and SIOP'.)

- **Suspected neuroblastoma** – Tissue is usually obtained by incisional or image-guided core needle biopsy of the primary tumor, or evaluation of the bone marrow by biopsy/aspirate in patients who are suspected to have metastatic disease in the marrow. This is discussed separately. (See "Clinical presentation, diagnosis, and staging evaluation of neuroblastoma", section on 'Biopsy'.)

- **Suspected hepatoblastoma** – The most common method of tissue sampling is image-guided percutaneous biopsy with fine-needle aspiration or core needle biopsy. This is discussed separately. (See "Overview of hepatoblastoma", section on 'Diagnosis and initial evaluation'.)

- **Bone and soft tissue tumors** – Image-guided core needle biopsy is typically performed; however, an open biopsy may be required in some cases. Proper planning of the biopsy that takes into account the future definitive surgery is important so as not to jeopardize the subsequent treatment, particularly in the case of limb salvage procedure. This is discussed separately. (See "Bone tumors: Diagnosis and biopsy techniques" and "Clinical presentation, staging, and prognostic factors of Ewing sarcoma", section on 'Tumor biopsy' and "Rhabdomyosarcoma in childhood and adolescence: Clinical presentation, diagnostic evaluation, and staging", section on 'Diagnostic biopsy' and "Osteosarcoma: Epidemiology, pathology, clinical presentation, and diagnosis", section on 'Diagnostic biopsy'.)

- **Brain tumors** – Histologic examination is necessary for diagnosis of brain tumors. The surgical procedure varies and may involve complete resection of the tumor, tumor reduction surgery, or tumor biopsy. This is discussed separately. (See "Clinical manifestations and diagnosis of central nervous system tumors in children", section on 'Diagnosis' and "Overview of the management of central nervous system tumors in children", section on 'Surgery'.)

- **Germ cell tumors** – The approach varies. Details are provided separately. (See "Adnexal masses: Evaluation in infants, children, and adolescents", section on 'Indications for referral' and "Ovarian germ cell tumors: Pathology, epidemiology, clinical manifestations, and diagnosis", section on 'Staging and surgical treatment' and "Clinical presentation, diagnosis, and staging of testicular germ cell tumors", section on 'Diagnostic evaluation'.)

- **Thyroid nodules** – Fine-needle aspiration is performed if the nodule meets size criteria or has other concerning features. This is discussed separately. (See "Thyroid nodules and cancer in children", section on 'Fine-needle aspiration'.)

- **Retinoblastoma** – The diagnosis is made based upon the dilated retinal examination and imaging findings. There is no role for direct tumor biopsy for tissue diagnosis, given the risk of extraocular spread of disease. Tissue samples are obtained only if the child undergoes enucleation as part of treatment. (See "Retinoblastoma: Clinical presentation, evaluation, and diagnosis", section on 'Diagnosis'.)

Proper timing and handling of tissue from biopsy or tumor resection is essential. Prior to biopsy, it is essential to involve a pathologist, ideally with pediatric oncology expertise, to ensure appropriate initial specimen processing. Biopsy specimens should be placed in normal saline and then transported immediately on ice to the surgical pathology laboratory. Gross examination of the tissue by the pathologist before processing helps to ensure that the specimen is adequate. Intraoperative frozen sections may be necessary to ensure diagnostic material, particularly if an immediate diagnosis will alter the planned operation. Definitive, specific diagnoses are rarely made from frozen sections, and it is **critical** to wait for final pathology results to ensure an accurate treatment plan. When appropriate, other procedures (eg, central venous catheter placement, bone marrow aspirate/biopsy) may be performed at the time of biopsy.

SUMMARY AND RECOMMENDATIONS

- **Importance of early diagnosis** – Optimal management of childhood cancer requires a high level of suspicion by the primary care practitioner and early referral to a pediatric oncologist. Early detection and treatment may reduce disease-related morbidity and complications. (See 'General principles of evaluation' above.)
- **Common sites and types of cancer in childhood** – Common sites of malignancies in childhood include blood and bone marrow, brain and nervous system, lymph nodes, kidneys, bone, and soft tissues. The frequency of particular types of cancer varies depending upon the age of the child (table 1). (See 'Background' above.)
- **Presenting signs and symptoms** – Childhood cancer may present with signs and symptoms that are shared by other childhood illnesses (table 4).
  - Although a single finding in isolation does not always require an evaluation for cancer, a combination of multiple findings (eg, weight loss, bone pain, and lymphadenopathy; easy bruising, abnormal blood counts, and hepatosplenomegaly) is worrisome and warrants prompt referral to a pediatric oncologist and evaluation for malignancy. (See 'Common signs and symptoms' above.)
  - In addition, certain isolated findings are worrisome (eg, abdominal or mediastinal masses (figure 1), headaches associated with vomiting in the morning, blasts on the peripheral blood smear (picture 1A-C)). These symptoms also require prompt evaluation and consultation. (See 'Abdominal masses' above and 'Headache' above and 'Blood count abnormalities' above.)
- **Warning signs** – Early warning signs of childhood cancer include (see 'Warning signs' above and 'Common signs and symptoms' above):
  - Unexplained pallor and loss of energy (see 'Fatigue and pallor' above and "Evaluation of pallor in children")
  - Unusual lump, mass, or swelling (see 'Lymphadenopathy' above and 'Abdominal masses' above)
  - Sudden unexplained weight loss (see 'Weight loss' above and "Evaluation of weight loss in infants over six months of age, children, and adolescents")
  - Unexplained persistent fever or illness (see 'Fever' above and "Fever of unknown origin in children: Etiology")
  - Easy bruising or bleeding (see 'Bleeding symptoms' above and "Approach to the child with bleeding symptoms")

- Prolonged or ongoing pain in one or more areas of the body (see 'Bone and joint pain' above)
- Limping (see 'Bone and joint pain' above and "Evaluation of limp in children")
- Frequent headaches, particularly if occurring in the morning and associated with vomiting (see 'Headache' above and "Clinical manifestations and diagnosis of central nervous system tumors in children", section on 'Headache')
- Sudden eye or vision changes (see "Evaluation of the child with leukocoria" and "Diagnostic approach to acute vision loss in children")

- **Referral** – If malignancy is suspected based upon initial clinical, laboratory, and imaging studies, the child should be referred to a pediatric oncology center. The subsequent diagnostic workup and management of childhood cancer should be carried out in a pediatric oncology center where the necessary subspecialists and tests required for diagnosis and/or treatment protocols are available. (See 'Referral' above.)

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Topic 6243 Version 37.0

GRAPHICS

Table 1: **The most common malignancies in infants, children, and adolescents**

Cancer type	Age <1 year	Age 1 to 4 years	Age 5 to 9 years	Age 10 to 14 years	Age 15 to 19 years	All pediatric ages
	Percentage of all cancers					
Leukemias	18	40	33	23	35	26
Central nervous system tumors	12	19	26	18	22	16
Lymphoma	7	8	14	19	22	16
Germ cell tumors	7	1	2	5	11	6
Soft tissue sarcomas	7	5	7	8	7	7
Bone tumors	0.2	0.7	5	9	6	5
Neuroblastoma	23	10	4	1	0.5	5
Wilms and other kidney cancers	5	8	5	1	0.8	4
Melanoma and skin cancers	2	0.7	3	14	27	12
Retinoblastoma	11	4	0.3	<0.1	0	2
Liver tumors	6	3	1	0.7	0.6	2
Other tumors	1	0.4	0.4	0.3	0.5	0.5

The most common causes of pediatric cancer in the United States (2017 to 2021). The percentages for each age group correspond to the age at diagnosis. Data obtained by Data from Cancer in North America (CiNA) and the Surveillance, Epidemiology and End Results (SEER) Registries of the National Cancer Institute, submitted December 2023.

*Data from: Statistics NCCR*Explorer. National Cancer Institute. https://nccrexplorer.ccdi.cancer.gov (Accessed February 4, 2025).*

Graphic 99680 Version 6.0

Table 2: **Common hereditary disorders associated with childhood cancer**

Disorder	Type of malignancy
Chromosomal disorders	
Down syndrome	Leukemia, testicular, retinoblastoma
Turner syndrome	Neurogenic, gonadal, endometrial
Klinefelter syndrome	Leukemia, germ cell tumors
Other sex aneuploidy	Retinoblastoma
XY gonadal dysgenesis	Gonadoblastoma, dysgerminoma
Trisomy 13	Teratoma, leukemia, neurogenic
Trisomy 18	Neurogenic, Wilms tumor
XYY, XYY mosaic	Osteosarcoma, medulloblastoma
Other genetic disorders	
Xeroderma pigmentosum	Basal, squamous cell carcinoma, melanoma
Bloom syndrome	Leukemia, lymphoma, gastrointestinal
Fanconi anemia	Leukemia, hepatoma, squamous cell carcinoma
Ataxia-telangiectasia	Lymphoma, leukemia, Hodgkin disease, brain, gastric, ovarian, other epithelial
Neurofibromatosis type 1	Gliomas, malignant peripheral nerve sheath tumors
Tuberous sclerosis	Brain tumors, rhabdomyosarcomas
Von Hippel-Lindau disease	Renal cell carcinoma, pheochromocytoma

Graphic 68833 Version 2.0

Table 3: **Immune deficiency diseases predisposing to neoplastic disease**

X-linked lymphoproliferative disease
Bruton agammaglobulinemia
Severe combined immunodeficiency
Wiskott-Aldrich syndrome
IgA deficiency
Common variable immunodeficiency
DiGeorge syndrome
Ataxia-telangiectasia
Chediak-Higashi syndrome

IgG: immunoglobulin G.

Graphic 58449 Version 2.0

Table 4: **Summary of presenting signs and symptoms of childhood cancer**

Symptoms/signs	Initial evaluation may include	Associated malignancies
Common presenting signs and symptoms		
Constitutional symptoms: ▪ Unexplained fevers ▪ Unexplained weight loss ▪ Unexplained fatigue/pallor	▪ Laboratory tests (CBC with differential, serum electrolytes, BUN, creatinine, LDH, uric acid, liver function tests) ▪ Microbiologic tests ▪ Imaging studies	▪ Any malignancy
Neurologic symptoms: ▪ Early morning headaches and vomiting ▪ Cranial nerve palsies ▪ Papilledema ▪ Afebrile seizures ▪ Ataxia ▪ Focal motor deficits	▪ Neuroimaging ▪ Neurosurgery consultation	▪ Brain tumor
Lymphadenopathy unresponsive to antibiotics	▪ Laboratory tests (CBC with differential, CRP, LDH) ▪ Microbiologic tests ▪ Chest radiograph	▪ Leukemia ▪ Lymphoma
Musculoskeletal symptoms: ▪ Bone pain ▪ Limp/refusal to walk ▪ Soft tissue mass	▪ CBC with differential ▪ Imaging studies	▪ Ewing sarcoma ▪ Leukemia ▪ Neuroblastoma ▪ Osteosarcoma ▪ Soft tissue sarcoma
Unexplained cough or shortness of breath	▪ Chest radiograph	▪ Mediastinal tumors ▪ Metastatic tumors ▪ Soft tissue sarcomas
Abdominal or pelvic mass	▪ Laboratory tests (CBC with differential, serum electrolytes, BUN, creatinine, liver function tests, urinalysis) ▪ Abdominal/pelvic imaging	▪ Adrenal tumor ▪ Germ cell tumor ▪ Hepatoblastoma ▪ Neuroblastoma ▪ Rhabdomyosarcoma ▪ Soft tissue sarcoma ▪ Wilms tumor
Petechiae, bruising, or other bleeding symptoms	▪ CBC with differential ▪ Coagulation studies	▪ Leukemia ▪ Lymphoma ▪ Neuroblastoma
Eye findings: ▪ Leukocoria ▪ Proptosis ▪ Acute vision loss	▪ Ophthalmologist consultation	▪ Brain tumors ▪ Metastatic rhabdomyosarcoma ▪ Neuroblastoma ▪ Retinoblastoma

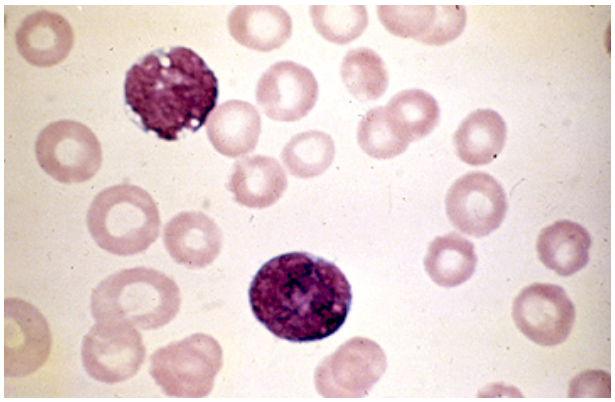
▪ Double vision ▪ Intraorbital hemorrhage		
Other less common presenting features		
Facial and neck swelling	▪ Laboratory tests (CBC with differential, serum electrolytes, BUN, creatinine, liver function tests, urinalysis) ▪ Chest radiograph	▪ Mediastinal tumors
Pharyngeal mass	▪ Laboratory tests (CBC with differential) ▪ Imaging studies ▪ Otolaryngology consultation	▪ Lymphoma ▪ Nasopharyngeal carcinoma ▪ Rhabdomyosarcoma
Dental issues: ▪ Periodontal mass ▪ Loose teeth	▪ Dental consultation ▪ Imaging studies	▪ Burkitt lymphoma ▪ Langerhans cell histiocytosis ▪ Neuroblastoma ▪ Osteosarcoma
Endocrine abnormalities: ▪ Growth failure ▪ Abnormalities in sexual maturation ▪ Salt imbalance ▪ Cushing syndrome	▪ Endocrine consultation ▪ Laboratory testing (hormone levels, stimulation tests) ▪ Imaging studies	▪ Adrenal tumors ▪ Gonadal tumors ▪ Pituitary or hypothalamic tumors
Thyroid nodules	▪ Endocrine consultation ▪ Laboratory testing (thyroid function tests) ▪ Neck ultrasound	▪ Thyroid cancer
Hypertension	▪ Laboratory tests (serum electrolytes, BUN, creatinine, urinalysis) ▪ Renal ultrasound	▪ Neuroblastoma ▪ Renal or adrenal tumor

This table summarizes some of the presenting signs and symptoms associated with childhood cancer. Childhood cancer may present with signs and symptoms that are shared by other childhood illnesses. Although a single finding in isolation does not always require evaluation for cancer, a combination of multiple findings (eg, unexplained weight loss, bone pain, and lymphadenopathy; easy bruising, abnormal blood counts, and hepatosplenomegaly) is worrisome and generally warrants evaluation for malignancy. In addition, certain findings are worrisome even as isolated findings (eg, abdominal or mediastinal masses, headaches associated with vomiting in the morning, blasts on the peripheral blood smear) and require prompt evaluation and consultation. For additional details, refer to UpToDate's topic on the presenting signs and symptoms of childhood cancer and topics on specific malignancies.

CBC: complete blood count; BUN: blood urea nitrogen; LDH: lactate dehydrogenase; CRP: C-reactive protein.

Graphic 131813 Version 1.0

Picture 1A: **Lymphoblasts in acute lymphoblastic leukemia**



Blood smear showing small lymphoblasts with rare nucleoli and vacuoles, as seen in acute lymphocytic leukemia.

Courtesy of Robert Baehner, MD.

Graphic 57831 Version 5.0

Table 5A: **Important components of the headache history for children and adolescents**

Historical feature	Possible significance
Headache history	
Age at onset	▪ Migraines frequently begin in the first decade of life. ▪ Chronic nonprogressive headaches begin in adolescence.
Mode of onset	▪ Abrupt onset of severe headache ("thunderclap headache" or "worst headache of my life") may indicate intracranial hemorrhage.
What is the headache pattern: acute, acute recurrent, chronic progressive, nonprogressive daily, or mixed?	▪ Helps to determine the cause (refer to the UpToDate topic on evaluation of headache in children).
How often does the headache occur?	▪ Migraines typically occur 2 to 4 times per month; almost never daily. ▪ Chronic nonprogressive headaches may occur 5 to 7 days per week. ▪ Cluster headaches typically occur 2 to 3 times per day for several months.
How long does the headache last?	▪ Migraines typically last 2 to 3 hours in young children and may last longer (48 to 72 hours) in adolescents. ▪ The duration of tension headaches is variable; they may last all day. ▪ Cluster headaches usually last 5 to 15 minutes but may last for 60 minutes.
Is there an aura or prodrome?	▪ Aura or prodrome is suggestive of migraine; if the warning symptoms are focal and repeatedly located to the same side of the body, a seizure or vascular or structural cause should be suspected.
When do the headaches occur?	▪ Headaches that wake the child from sleep or occur on waking may indicate increased intracranial pressure/space-occupying lesion. ▪ Tension-type headaches typically occur late in the day.
What is the headache quality (throbbing/pulsating, dull aching, squeezing, etc)?	▪ Migraines have a throbbing/pulsating quality. ▪ Chronic nonprogressive headaches have a squeezing pressure or tightness that waxes and wanes. ▪ Cluster headaches have a deep continuous pain.
Where is the pain?	▪ Occipital location may indicate posterior fossa neoplasms but also may occur in basilar migraine. ▪ Cluster headaches are usually temporal or retro-orbital. ▪ Localized pain may suggest a specific secondary etiology (eg, sinusitis, otitis, dental abscess).
What brings the headache on or makes it worse?	▪ Headache in the recumbent position or with straining/Valsalva may indicate an intracranial process. ▪ Migraines may be triggered by certain foods, odors, bright lights, noise, lack of sleep, menses (in females), and strenuous activity. ▪ Tension-type headaches may worsen with stress, bright lights, noise, strenuous activity. ▪ Cluster headaches may worsen with lying down or resting.
What makes the headache go away?	▪ Migraines typically respond to analgesic medications; dark, quiet room; cool compress; or sleep.

	▪ Chronic tension-type headaches may respond to sleep (but not to analgesic medications).
Are there associated symptoms?	▪ Neurologic deficits (eg, ataxia, altered mental status, binocular horizontal diplopia) may indicate increased intracranial pressure and/or a space-occupying lesion. ▪ Fever may indicate infection, or rarely intracranial hemorrhage. ▪ Stiff neck may indicate meningitis, complicated pharyngitis, or intracranial hemorrhage. ▪ Localized pain may indicate localized infection (eg, otitis media, pharyngitis, sinusitis, dental abscess). ▪ Autonomic symptoms (eg, nausea, vomiting, pallor, chills, fever, dizziness, syncope, etc) may indicate migraine or cluster headache. ▪ Dizziness, numbness, and/or weakness may occur with idiopathic intracranial hypertension.
Do symptoms continue between headaches?	▪ Persistence of symptoms (neurologic symptoms or nausea/vomiting) between headache episodes is suggestive of increased intracranial pressure and/or mass lesions. ▪ Resolution of symptoms between episodes is characteristic of migraine headaches.
Headache burden	
Do the headaches impair normal functioning (eg, school attendance, activity) and quality of life?	▪ Children with chronic nonprogressive headaches have frequent school absences; impaired function may warrant referral.
Additional information	
Past medical history	▪ Certain underlying conditions increase the likelihood of intracranial pathology (eg, sickle cell disease, immune deficiency, malignancy or history of malignancy, coagulopathy, cardiac disease with right-to-left intracardiac shunt, head trauma, neurofibromatosis type 1, tuberous sclerosis complex).
Medications and vitamins	▪ Medications that may cause headache include oral contraceptives, glucocorticoids, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors, among others. Medications associated with idiopathic intracranial hypertension include growth hormone, tetracyclines, vitamin A (in excessive doses), and withdrawal of glucocorticoids.
Recent change in weight or vision	▪ May be associated with intracranial process (eg, pituitary tumor, craniopharyngioma, idiopathic intracranial hypertension).
Recent changes in sleep, exercise, or diet	▪ May precipitate headaches; may be associated with mood disorder.
Change in school or home environment	▪ May be a source of psychosocial stress.
Family history of headache or neurologic disorder	▪ Migraine and some tumors and vascular malformations are heritable.
What do child and parents think is causing the pain?	▪ Indicates their levels of anxiety about the headache.
Mental health history/symptoms, psychosocial stressors	▪ Chronic nonprogressive headaches may be associated with depression or anxiety.

Information compiled from:

1. *Lewis DW, Koch T. Headache evaluation in children and adolescents: When to worry? When to scan? Pediatr Ann 2010; 39:399.*
2. *Rothner AD. The evaluation of headaches in children and adolescents. Semin Pediatr Neurol 1995; 2:109.*
3. *Strasburger VC, Brown RT, Braverman PK, et al. Headache. In: Adolescent Medicine: A Handbook for Primary Care, Lippincott Williams & Wilkins, Philadelphia 2006. p.25.*

Graphic 71717 Version 11.0

Table 5B: **Important aspects of the examination of a child with headache**

Examination feature	Possible significance
General appearance	Altered mental status may indicate meningitis, encephalitis, intracranial hemorrhage, elevated intracranial pressure, hypertensive encephalopathy.
Vital signs	▪ Hypertension may cause headache or be a response to increased intracranial pressure ▪ Fever suggests infection (most commonly upper respiratory infection) but may occur with intracranial hemorrhage or central nervous system malignancy
Head circumference	Macrocephaly may indicate slowly progressive increases in intracranial pressure.
Height and weight trajectories	Abnormal or altered trajectories may indicate intracranial pathology.
Auscultation of the neck, eyes, and head for bruit	Bruit may indicate arteriovenous malformation.
Palpation of the head and neck	▪ Localized scalp tenderness may occur in migraine and tension-type headaches ▪ Scalp swelling may indicate head trauma ▪ Sinus tenderness may indicate sinusitis ▪ Temporomandibular joint (TMJ) and/or masseter tenderness suggests TMJ dysfunction ▪ Nuchal rigidity may indicate meningitis ▪ Posterior neck pain may indicate an anatomic abnormality (eg, Chiari malformation) ▪ Thyromegaly may indicate thyroid dysfunction
Visual fields	Visual field abnormalities may indicate increased intracranial pressure and/or a space-occupying lesion.
Funduscopy	▪ Papilledema may indicate increased intracranial pressure ▪ Funduscopic examination is normal in primary headache
Otoscopy	May demonstrate otitis media; hemotympanum may indicate trauma.
Oropharynx	Signs of pharyngitis? Dental decay or abscess?
Neurologic examination (see text for details)	Abnormal neurologic examination (particularly mental status, eye movements, papilledema, asymmetry, coordination disturbance, abnormal deep tendon reflexes) may indicate intracranial pathology but also may occur with migraine headache.
Skin examination	Signs of neurocutaneous disorders (eg, neurofibromatosis, tuberous sclerosis complex, which are associated with intracranial neoplasms) or trauma (bruises, abrasions, etc).
Spine	Signs of occult spinal dysraphism (eg, midline vascular of pigment changes), which may be associated with structural abnormalities (eg, Chiari malformation).

Data from:

1. *Great Ormond Street Hospital for Children Clinical Guideline. Headache. www.gosh.nhs.uk/clinical_information/clinical_guidelines/cmg_guideline_00045. Accessed on March 29, 2011.*
2. *Lewis DW, Koch T. Headache evaluation in children and adolescents: When to worry? When to scan? Pediatr Ann 2010; 39:399.*
3. *Newton RW. Childhood headache. Arch Dis Child Educ Pract Ed 2008; 93:105.*

Graphic 59967 Version 8.0

Table 6: **Clinical features worrisome for malignancy or granulomatous disease in children with peripheral lymphadenopathy**

Systemic symptoms (fever >1 week, night sweats, weight loss [>10% of body weight])
Supraclavicular (lower cervical) nodes
Generalized lymphadenopathy
Fixed nontender nodes in the absence of other symptoms; matted nodes
Nontender lymph nodes >1 cm with onset in the neonatal period
Nontender lymph nodes ≥2 cm in diameter that increase in size from baseline or do not respond to 2 weeks of antibiotic therapy
Abnormal chest radiograph (particularly mediastinal mass or hilar adenopathy)
Abnormal complete blood count (eg, lymphoblasts, cytopenias in more than 1 cell line)
Elevated lactate dehydrogenase
Absence of symptoms in the ear, nose, and throat regions
Persistently elevated ESR/CRP or rising ESR/CRP despite antibiotic therapy

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

References:

1. *Lake AM, Oski FA. Peripheral lymphadenopathy in childhood. Ten-year experience with excisional biopsy. Am J Dis Child 1978; 132:357.*
2. *Niedzielska G, Kotowski M, Niedzielski A, et al. Cervical lymphadenopathy in children--incidence and diagnostic management. Int J Pediatr Otorhinolaryngol 2007; 71:51.*
3. *Oguz A, Karadeniz C, Temel EA, et al. Evaluation of peripheral lymphadenopathy in children. Pediatr Hematol Oncol 2006; 23:549.*
4. *Slap GB, Brooks JS, Schwartz JS. When to perform biopsies of enlarged peripheral lymph nodes in young patients. JAMA 1984; 252:1321.*
5. *Soldes OS, Younger JG, Hirschl RB. Predictors of malignancy in childhood peripheral lymphadenopathy. J Pediatr Surg 1999; 34:1447.*

Graphic 106127 Version 5.0

Table 7: **Our step-wise approach to the evaluation and initial management of generalized lymphadenopathy in children**

1. History and examination to look for obvious causes
2. Early biopsy* of most abnormal node for children with: ▪ Supraclavicular nodes ▪ Massively enlarged nodes (ie, >4 cm [1.6 inches]) ▪ Group of nodes with a total diameter >3 cm (1.2 inches)
3. Initial testing typically includes: ▪ CBC with differential, ESR/CRP ▪ LDH ▪ Serology for CMV and EBV ▪ Serology for other viral illnesses as warranted by the history and examination¶ ▪ TST ▪ Chest radiograph
4. Provide treatment or additional evaluation as indicated for conditions that are identified through initial history, examination, and testing
5. When the cause remains uncertain after the initial evaluation, obtain the following second-tier tests **if there are indications based on the initial evaluation**¶: ▪ Serology for *Bartonella henselae*, toxoplasmosis, histoplasmosis, coccidiomycosis, brucellosis, syphilis, HIV, and other viruses ▪ ANA
5. Obtain biopsy* of the most abnormal node within 4 weeks of initial evaluation if: ▪ Any lymph nodes increase in size ▪ There is a lymph node ≥2 cm (0.8 inches) in diameter and **either** of the following: • The diagnosis remains uncertain after 4 weeks • There is no response to therapy as indicated by the findings of initial or second-tier tests

CBC: complete blood count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LDH: lactate dehydrogenase; CMV: cytomegalovirus; EBV: Epstein-Barr virus; TST: tuberculin skin test; ANA: antinuclear antibody.
* Excisional biopsy is preferred; fine needle aspirate biopsies usually are inadequate for evaluation of pediatric malignancies or infiltrative diseases.
¶ Refer to UpToDate topic on evaluation of peripheral lymphadenopathy in children for details.

Graphic 106345 Version 3.0

Table 8: **Our step-wise approach to the evaluation and initial management of cervical lymphadenopathy in children that does not appear to be caused by an infection**

1. History and examination to look for obvious causes or worrisome features*
2. Refer children with worrisome features for early biopsy¶
3. Evaluate and treat causes that appear obvious based on initial evaluation
4. When the cause remains uncertain after the initial evaluation: ▪ Lymph node <2 cm (0.8 inches) in longest diameter: • Observe for 10 to 14 days: ○ Regression in size – No additional evaluation or therapy ○ No regression in size: ▪ Obtain CBC/differential; ESR/CRP; serology for EBV, CMV, and HIV; evaluate for Kawasaki disease and other uncommon causes of cervical lymphadenopathy as indicated by the history and examinationΔ ▪ Provide referral or treatment as indicated based upon results ▪ Lymph node ≥2 cm (0.8 inches) in longest diameter • Obtain CBC, ESR/CRP, and chest radiograph ○ Worrisome features* – Refer for biopsy ○ No worrisome features and cause remains uncertain (including possible occult infection) – Perform TST and provide 10- to 14-day trial of antibiotics◇ ▪ TST positive – Additional testing may be necessary to establish diagnosis of tuberculosis or nontuberculous mycobacteria ▪ TST negative and lymph node regresses in size – No additional evaluation or therapy ▪ TST negative and lymph node does not regress: • Obtain serology for EBV, CMV, and HIV; evaluate for Kawasaki disease and other uncommon causes of cervical lymphadenopathy as indicated by the history and examinationΔ • Provide referral or treatment as indicated based upon results
5. Obtain biopsy¶ after 4 weeks if the diagnosis remains uncertain and the lymph node has not regressed in size or there is no response to antimicrobial therapy/broadened antimicrobial therapy§

CBC: complete blood count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; EBV: Epstein-Barr virus; CMV: cytomegalovirus; TST: tuberculin skin test; CA-MRSA: community-associated methicillin-resistant *Staphylococcus aureus*.
* Worrisome features include: systemic symptoms (fever >1 week, night sweats, weight loss [>10% of body weight]), fixed nontender nodes in the absence of other symptoms; abnormal chest radiograph (eg, mediastinal mass or hilar adenopathy), abnormal CBC/differential, lack of upper respiratory tract symptoms, lymph nodes >2 cm in diameter that have increased in size from baseline or have not responded to 2 weeks of antibiotic therapy, and persistently elevated ESR/CRP or rising ESR/CRP despite antibiotic therapy.
¶ Excisional biopsy is preferred; fine-needle aspirate biopsies usually are inadequate for evaluation of pediatric malignancies or infiltrative diseases.
Δ Refer to UpToDate topic on evaluation of peripheral lymphadenopathy in children for details.
◇ Empiric antibiotic therapy should include coverage for common pathogens such as group A *Streptococcus* and *Staphylococcus aureus* (eg, clindamycin in areas with a high prevalence of CA-MRSA or a first-generation cephalosporin [eg, cephalexin] or amoxicillin-clavulanate in areas with a low prevalence of CA-MRSA). If the patient's systemic symptoms (eg, fever) do not improve within 72 hours or the lymph node increases in size (at any point during treatment), we broaden the antimicrobial coverage to include coverage for common pathogens that were not included initially (eg, CA-MRSA, *Bartonella henselae* [for children with exposure to cats or kittens]). Refer to UpToDate topic on evaluation of peripheral lymphadenopathy in children for details.
§ For lymph nodes <2 cm (0.8 inches) in diameter, continued observation may be reasonable if there are no worrisome features.

Graphic 106347 Version 4.0

Table 9: **Our step-wise approach to the evaluation and initial management of axillary lymphadenopathy in children**

1. History and examination to look for obvious causes or worrisome features*
2. Refer children with worrisome features for early biopsy[¶]
3. Evaluate and treat causes that appear obvious based on initial evaluation
4. When the cause remains uncertain after the initial evaluation:
▪ Lymph node ≥2 cm (0.8 inches) in longest diameter:
a. Obtain CBC/differential, ESR/CRP, LDH, CXR ▪ Worrisome features*: Proceed to biopsy[¶] ▪ No worrisome features*: • Signs of infection in lymph node or distal to lymph node: ○ Obtain cultures and other microbiologic studies as indicated[Δ] ○ Provide 10 to 14 day trial of antibiotic therapy, broadened as indicated[◇] • No signs of infection: ○ Observe for two to three weeks
b. Response to antibiotic therapy/broadened antibiotic therapy[Δ] or observation ▪ Regression in size: No additional evaluation or therapy ▪ No regression or increase: Biopsy[¶]
▪ Lymph node <2 cm (0.8 inches) in longest diameter:
a. Initial management according to symptoms/signs of infection within or distal to node: ▪ Symptoms or signs of infection: • Obtain cultures and other microbiologic studies as indicated[Δ] • Initiate a 10 to 14 day trial of antibiotic therapy, broadened as indicated[◇] ▪ No symptoms or signs of infection: • Observe for two to three weeks
b. Response to antibiotic therapy/broadened antibiotic therapy[◇] or observation: ▪ Regression in size: No additional evaluation or therapy ▪ No regression or increase: Obtain a CBC/differential, perform TST, and initiate or broaden antimicrobial therapy • CBC/differential concerning for malignancy (eg, lymphoblasts, cytopenias in more than one cell line): Biopsy[¶] • TST positive: Additional evaluation as indicated for tuberculosis or nontuberculous mycobacteria • TST negative and lymphadenopathy regresses in size: No additional evaluation or therapy • TST negative and lymphadenopathy does not regress in size: Obtain ESR/CRP and serology for EBV, CMV, HIV, and *Bartonella henselae* (for children with exposure to cats or kittens); evaluate other conditions as indicated by the history and examination[Δ]
5. Obtain biopsy[¶] after four weeks if the diagnosis remains uncertain and the lymph node has not regressed in size or there is no response to antimicrobial therapy/broadened antimicrobial therapy

CBC: complete blood count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LDH: lactate dehydrogenase; CXR: chest radiograph; TST: tuberculin skin test; EBV: Epstein-Barr virus; CMV: cytomegalovirus; CA-MRSA: community-associated methicillin-resistant *Staphylococcus aureus*.

* Worrisome features include systemic symptoms (fever >1 week, night sweats, weight loss [>10% of body weight]); fixed nontender nodes in the absence of other symptoms; abnormal chest radiograph (eg, mediastinal mass or hilar adenopathy); abnormal CBC/differential; lack of upper respiratory tract symptoms; lymph nodes >2 cm in diameter that have increased in size from baseline or have not responded to two weeks of antibiotic therapy; and persistently elevated ESR/CRP or rising ESR/CRP despite antibiotic therapy. Refer to UpToDate topic on evaluation of peripheral lymphadenopathy in children for

details.
¶ Excisional biopsy is preferred; fine needle aspirate biopsies usually are inadequate for evaluation of pediatric malignancies or infiltrative diseases.
Δ Refer to UpToDate topic on evaluation of peripheral lymphadenopathy in children for details.
◇ Empiric antibiotic therapy should include coverage for common pathogens such as group A *Streptococcus* and *S. aureus* (eg, clindamycin in areas with a high prevalence of CA-MRSA or a first-generation cephalosporin [eg, cephalexin] or amoxicillin-clavulanate in areas with a low prevalence of CA-MRSA). If the patient's systemic symptoms (eg, fever) do not improve within 72 hours or the lymph node increases in size (at any point during treatment), we broaden the antimicrobial coverage to include coverage for common pathogens that were not included initially (eg, CA-MRSA, *B. henselae* [for children with exposure to cats or kittens]). Refer to UpToDate topic on evaluation of peripheral lymphadenopathy in children for details.

Graphic 106346 Version 5.0

Table 10: **Our step-wise approach to the evaluation and initial management of inguinal lymphadenopathy in children**

1. History and examination to look for obvious causes or worrisome features*
2. Refer children with worrisome features for early biopsy¶
3. Evaluate and treat causes that appear obvious based on initial evaluation
4. When the cause remains uncertain after the initial evaluation: ▪ Lymph node ≥2 cm (0.8 inches) in longest diameter and tender: • Initiate 10 to 14 day trial of antibiotic therapy, broadened as indicatedΔ ○ Regression in size: No additional evaluation or therapy ○ No regression in size: Obtain CBC/differential, ESR/CRP, CXR, TST, *Bartonella henselae* serology and provide referral or treatment based on the results ▪ Lymph node ≥2 cm (0.8 inches) in longest diameter, nontender, with symptoms/signs of infection within or distal to node • Obtain bacterial and fungal cultures or other fungal studies as indicated by the initial evaluation◇, *B. henselae* serology, and provide a 10 to 14 day trial of antibiotic therapy, broadened as indicatedΔ ○ Regression in size: No additional evaluation or therapy ○ No regression in size: Obtain CBC, ESR/CRP, and CXR to evaluate worrisome features* ▪ Lymph node ≥2 cm (0.8 inches) in longest diameter, nontender, no symptoms/signs of infection within or distal to node • Obtain CBC/differential, ESR/CRP, LDH, CXR and abdominal ultrasonography ○ Worrisome features*, abdominal mass, or abdominal lymphadenopathy: Proceed to biopsy¶ ○ No worrisome features*, no abdominal mass or lymphadenopathy, and cause remains uncertain: Perform TST and provide a 10 to 14 day trial of antibiotic therapy broadened as indicatedΔ ▪ TST positive: Additional testing may be necessary to establish diagnosis of tuberculosis or NTM ▪ TST negative and lymph node regresses in size: No additional evaluation or therapy ▪ TST negative, lymph node does not regress: Obtain additional microbiologic studies as indicated by the history and examination◇ and provide referral or treatment based on the results ▪ Lymph node <2 cm (0.8 inches) in longest diameter: • Worrisome features*: Proceed to biopsy¶ • No worrisome features*: Continue to observe, even if the lymph node does not regress after four weeks
5. For lymph nodes ≥2 cm (0.8 inches), obtain biopsy¶ after four weeks if the diagnosis remains uncertain and the lymph node has not regressed in size or there is no response to antimicrobial therapy/broadened antimicrobial therapy

CBC: complete blood count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CXR: chest radiograph; TST: tuberculin skin test; LDH: lactate dehydrogenase; NTM: nontuberculous mycobacteria; CA-MRSA: community-associated methicillin-resistant *Staphylococcus aureus*.

* Worrisome features include systemic symptoms (fever >1 week, night sweats, weight loss [>10% of body weight]); fixed nontender nodes in the absence of other symptoms; abnormal chest radiograph (eg, mediastinal mass or hilar adenopathy); abnormal CBC/differential; lack of upper respiratory tract symptoms; lymph nodes >2 cm in diameter that have increased in size from baseline or have not responded to two weeks of antibiotic therapy; and persistently elevated ESR/CRP or rising ESR/CRP despite antibiotic therapy.

¶ Excisional biopsy is preferred; fine needle aspirate biopsies usually are inadequate for evaluation of pediatric malignancies or infiltrative diseases.

Δ Empiric antibiotic therapy should include coverage for common pathogens such as group A *Streptococcus* and *S. aureus* (eg, clindamycin in areas with a high prevalence of CA-MRSA or a first-generation cephalosporin [eg, cephalexin] or amoxicillin-clavulanate in areas with a low prevalence of CA-MRSA). If the patient's systemic symptoms (eg, fever) do not improve within 72 hours or the lymph node increases in size (at any point during treatment), we broaden the antimicrobial coverage to include coverage for common pathogens that were not included initially (eg, CA-MRSA, *B. henselae*). Refer to

UpToDate topic on diagnostic approach to peripheral lymphadenopathy in children for details.
◇ Refer to UpToDate topic on evaluation of peripheral lymphadenopathy in children for details.

Graphic 106348 Version 3.0

Table 11: **Atypical features of juvenile idiopathic arthritis that should prompt consideration of leukemia***

Nocturnal pain that may cause waking
Severe pain, requiring opiate analgesia
Pain out of proportion to severity of arthritis
Systemic symptoms out of proportion to severity of arthritis
Nonarticular bone pain

* Particularly before the initiation of corticosteroid or cytotoxic therapy.

Adapted from Murray, MJ, Tang, T, Ryder, C, et al. BMJ 2004; 329:959.

Graphic 57459 Version 2.0

Table 12: **Normal values for hematologic parameters in children**

Age	Hemoglobin (g/dL)		Hematocrit (%)		MCV (fL)		RDW (%)	
	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit
6 months to <2 years*	11.0¶	13.5	31	42	73	85	12.3	15.6
2 to 6 years	11.0¶	13.7	34	44	75	86	12.0	14.6
6 to 12 years	11.2	14.5	35	44	78	90	11.9	13.8
12 to <18 years								
Female	11.4	14.7	36	46	80	96	11.9	14.6
Male	12.4	16.4	40	51	80	96	11.9	13.7

This table summarizes lower and upper limits (defined as the 2.5th and 97.5th percentile, respectively) for hematologic parameters in children according to age and sex, based upon normative data from healthy populations in the United States. Previous reports have described lower values for hemoglobin in Black Americans compared with White Americans (approximately 0.5 to 1 g/dL lower for Black Americans). However, those differences likely reflect health disparities related to social determinants of health. We recommend using the same hemoglobin and hematocrit thresholds for evaluating anemia in all racial and ethnic groups (ie, we do not assume that a slightly lower value in a Black individual is normal). Reference ranges may differ slightly from 1 laboratory to another. For more specific guidance, clinicians should refer to the reference ranges at the laboratory performing the testing.

MCV: mean corpuscular volume; RDW: red cell distribution width.

* Normal values for hemoglobin, hematocrit, and MCV change dramatically during the first 6 months after birth. Refer to UpToDate topic on the approach to the child with anemia for a discussion of normal values in young infants.

¶ The lower limit of normal (ie, 2.5th percentile) for hemoglobin at these ages is slightly less than 11 g/dL. However, for the purposes of screening for iron deficiency anemia in infants and young children, many experts use a cutoff of hemoglobin <11 g/dL to define an abnormal screen.

References:

1. *Brugnara C, Oski FA, Nathan DG. Diagnostic approach to the anemic patient. In: Nathan and Oski's Hematology and Oncology of Infancy and Childhood, 8th ed, Orkin S, Nathan D, Ginsburg D, et al (Eds), Elsevier 2015. p.293.*
2. *Cembrowski GS, Chan J, Cheng C. NHANES 1999-2000 data used to create comprehensive health-associated race-, sex- and age-stratified pediatric reference intervals for the Coulter MAXM. Laboratory Hematol 2004; 10:245.*
3. *Baker RD, Greer FR, Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency andiron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics 2010; 126:1040.*
4. *Staffa SJ, Joerger JD, Henry E, et al. Pediatric hematology normal ranges derived from pediatric primary care patients. Am J Hematol 2020; 95:e255.*
5. *Higgins V, Tahmasebi H, Bohn MK, et al. CALIPER Hematology Reference Standards (II). Am J Clin Pathol 2020; 154:342.*

Graphic 101544 Version 12.0

Table 13: **Normal values for white blood count and absolute neutrophil count in neonates and children**

Age	WBC (cells/microL)	ANC (cells/microL)	Percent neutrophils (approximate)
Fetus >30 weeks	7710 (range 2720 to 12,700)		23% of nucleated cells including nucleated RBCs
Birth	18,100 (range 9000 to 30,000)	11,000 (range 6000 to 26,000)	61% of WBCs
24 hours	18,900 (range 9000 to 34,000)	11,500 (range 5000 to 21,000)	61% of WBCs
1 week	12,200 (range 5000 to 21,000)	5500 (range 1500 to 10,000)	45% of WBCs
1 month	10,800 (range 5000 to 19,500)	3800 (range 1000 to 9000)	35% of WBCs
1 year	11,400 (range 6000 to 17,500)	3500 (range 1500 to 8500)	31% of WBCs
10 years	8100 (range 4500 to 13,500)	4400 (range 1800 to 8000)	54% of WBCs

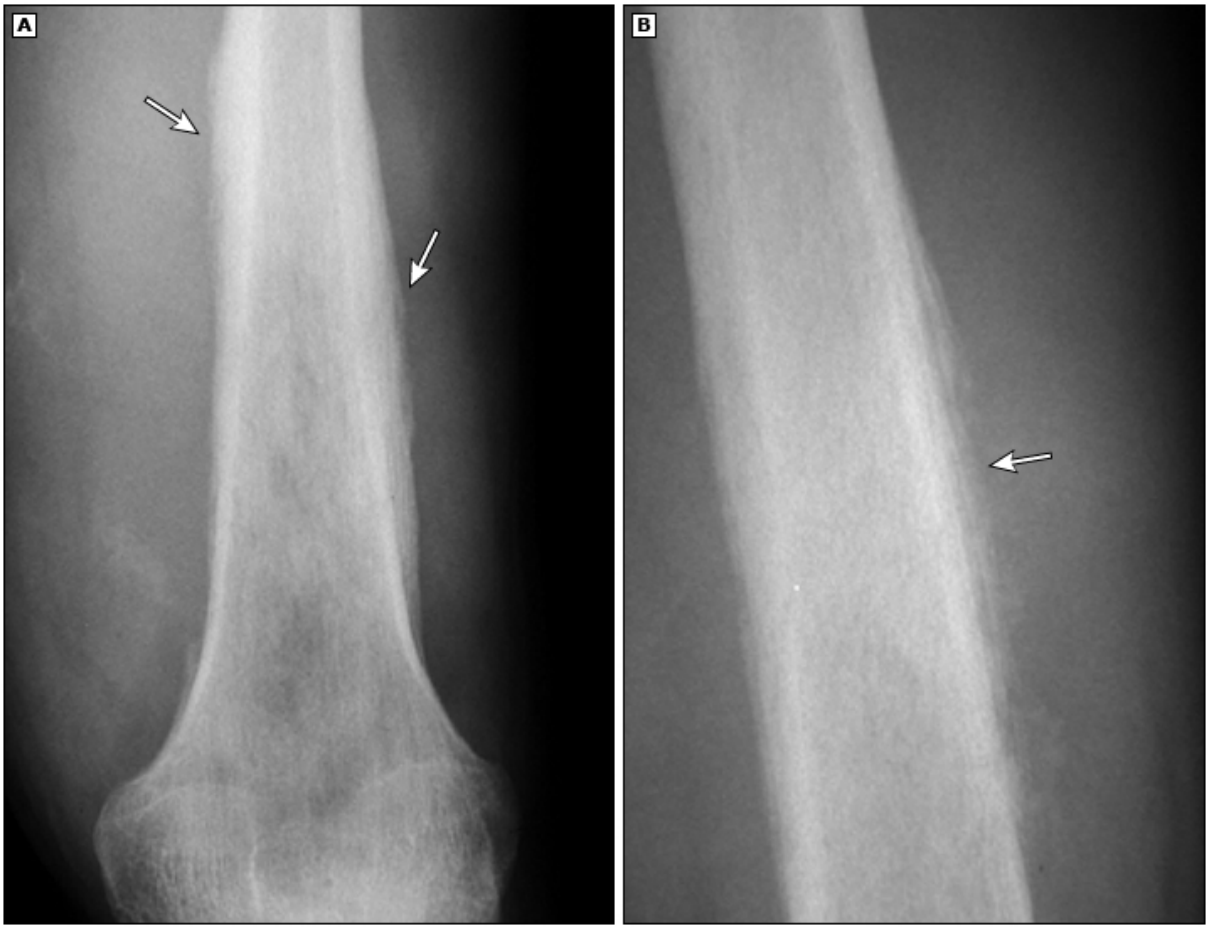
Refer to UpToDate content on neutropenia in children for information about causes of neutropenia and appropriate interventions, and an ANC calculator. Percent neutrophils depends on the percentages of other cells, and ANC should always be used when evaluating neutropenia; this value is presented only as a guide.

WBC: white blood cell count; ANC: absolute neutrophil count; RBCs: red blood cells.

Adapted from Orkin SH, Nathan DG, Ginsburg D, et al. Nathan and Oski's Hematology of Infancy and Childhood, 7th Edition, Saunders, Philadelphia 2009.

Graphic 105415 Version 1.0

Image 1: **Radiograph onion skinning Ewing sarcoma**

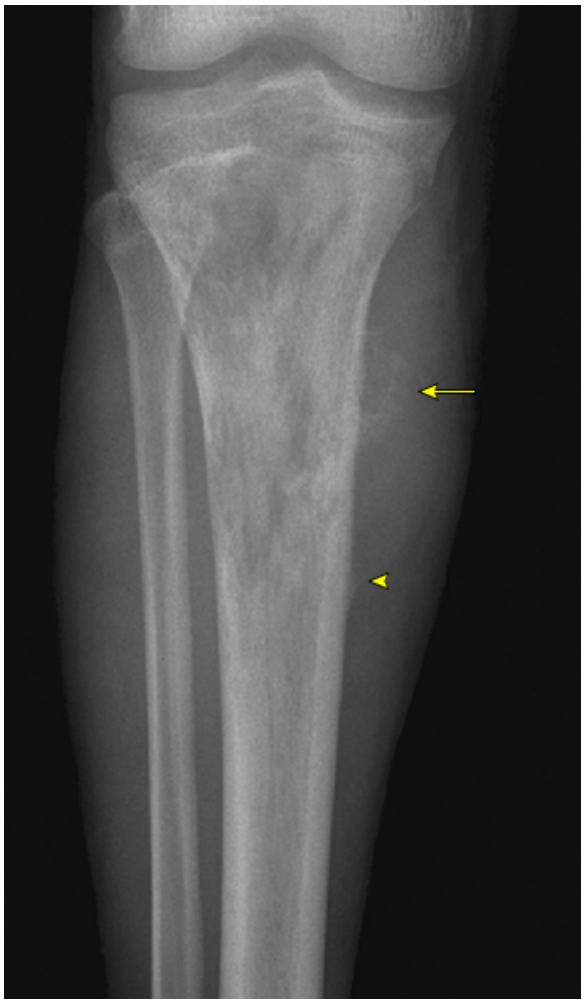


"Onion skin" periosteal reaction AP (A) and lateral (B) view of the distal femur (arrows) in a 15-year-old female child with Ewing sarcoma. Multiple layers of periosteal reaction simulate the appearance of the layers of an onion's skin. Note the disruption of the outermost layer and the soft tissue mass, suggestive of a malignant process.

AP: anteroposterior.

Graphic 61818 Version 7.0

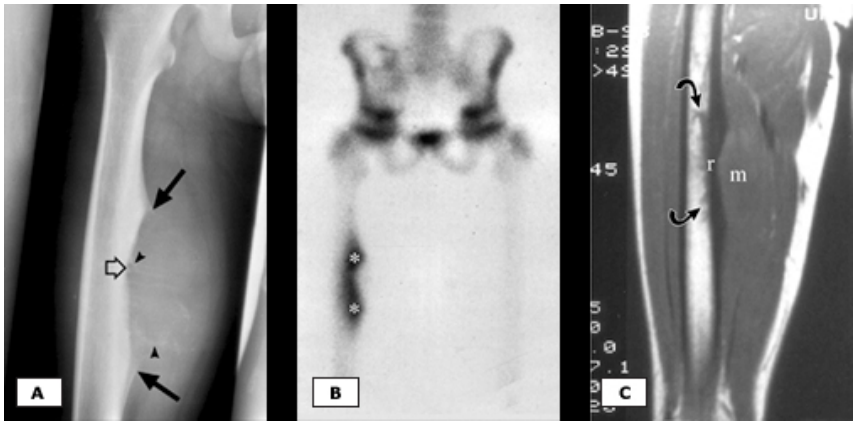
Image 2: **Radiograph of a conventional osteosarcoma involving the proximal tibia**



Radiograph shows mixed lytic and sclerotic lesion with osteoid matrix associated with malignant tumor cells (arrow) and Codman triangle (arrowhead) involving the proximal tibia.

Graphic 70494 Version 18.0

Image 3: **Periosteal osteosarcoma involving femoral diaphysis in 14-year-old boy who presented with painful thigh mass**

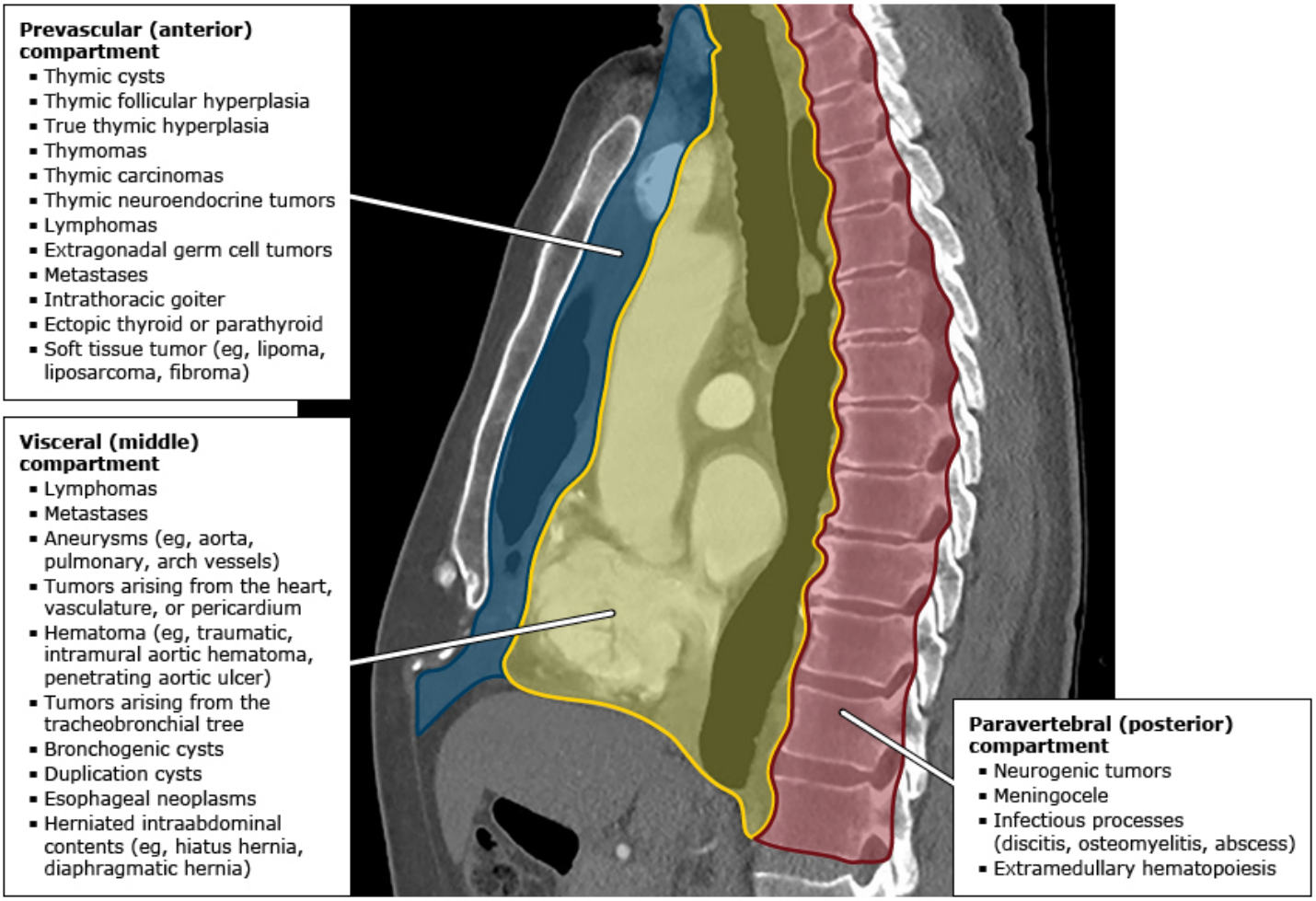


(A) Anteroposterior radiograph of femur shows cortical thickening (with Codman triangles [solid arrows] superiorly and inferiorly) that is eroded by a broad-based soft-tissue mass, with involvement of the underlying preexisting cortex (open arrow). Perpendicular periosteal reaction extends into the soft-tissue mass (arrowheads).
(B) Bone scintigram (anterior projection) shows marked and eccentric increased radionuclide uptake (*).
(C) Coronal T1-weighted MR image (650/17) also shows thickened cortex, which is extrinsically eroded centrally (r) by the broad-based intermediate-signal-intensity soft-tissue mass (m). The marrow shows focal areas of decreased signal intensity (arrows) that are separated from the soft-tissue mass by normal intervening cortex.

MR: magnetic resonance.

Graphic 68702 Version 4.0

Figure 1: **Common diagnostic possibilities of mediastinal masses**



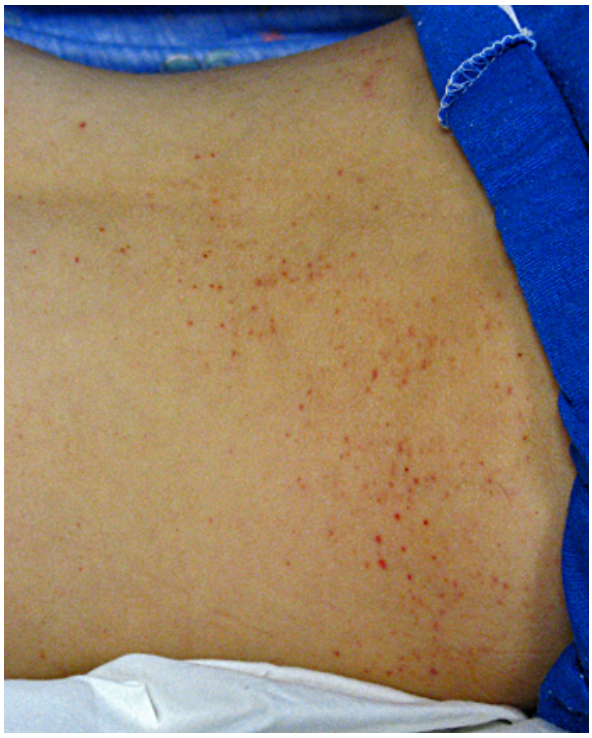
The differential diagnosis of a mediastinal mass depends upon the anatomic compartment in which it arises.

Reference:

1. *Carter BW, Benveniste MF, Madan R, et al. ITMIG classification of mediastinal compartments and multidisciplinary approach to mediastinal masses. Radiographics 2017; 37:413.*

Graphic 56637 Version 8.0

Picture 2: **Petechiae**



Courtesy of Leslie Raffini, MD.

Graphic 73905 Version 2.0

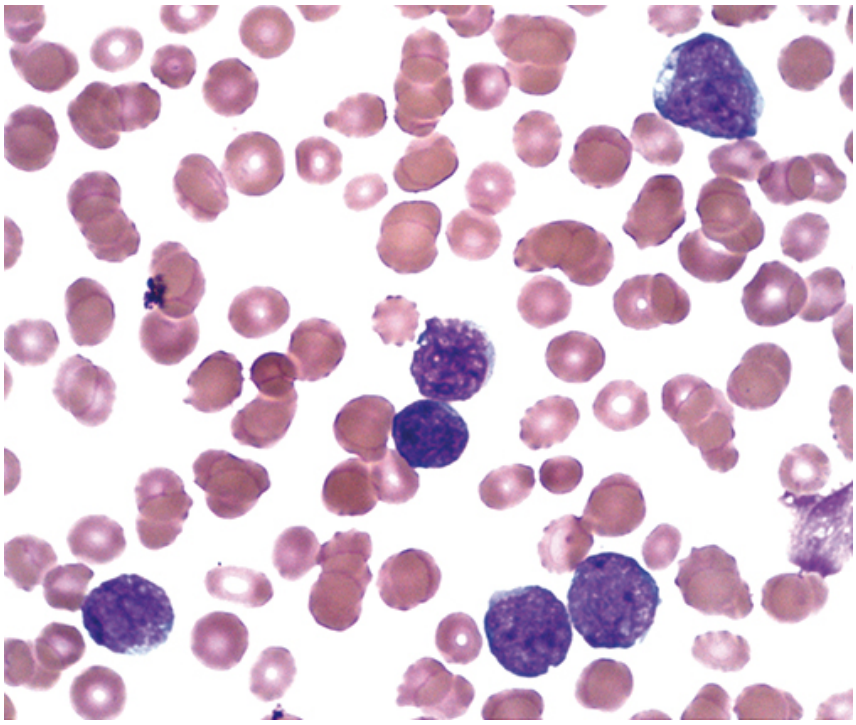
Table 14: **Major causes of thrombocytopenia in infants and children**

Decreased platelet production	Increased platelet destruction
Infection ▪ Epstein-Barr virus ▪ Cytomegalovirus ▪ Bacterial sepsis ▪ Parvovirus ▪ Varicella ▪ Rickettsia ▪ Dengue virus **Nutritional deficiencies** ▪ Folate ▪ B12 ▪ Iron **Acquired bone marrow failure** ▪ Aplastic anemia ▪ Myelodysplastic syndromes ▪ Myelosuppressive/myeloablative therapies (eg, chemotherapy, radiation) **Infiltrative bone marrow diseases** ▪ Leukemia or lymphoma ▪ Metastatic cancer ▪ Infectious granuloma ▪ Storage disease **Genetic causes of impaired thrombopoiesis*** ▪ Wiskott-Aldrich syndrome/X-linked thrombocytopenia ▪ Inherited bone marrow failure syndromes • Fanconi anemia • Dyskeratosis congenita • Shwachman-Diamond syndrome • Congenital amegakaryocytic thrombocytopenia ▪ Thrombocytopenia with absent radii syndrome ▪ Amegakaryocytic thrombocytopenia with radioulnar synostosis ▪ Familial platelet disorder with predisposition to hematologic malignancy ▪ Bernard-Soulier syndrome ▪ *MYH9*-related disorders ▪ Paris-Trousseau syndrome ▪ X-linked thrombocytopenia with dyserythropoiesis	**Immune-mediated** ▪ Immune thrombocytopenia (ITP) ▪ Neonatal alloimmune thrombocytopenia ▪ Drug-induced thrombocytopenia ▪ Systemic autoimmune disorders and immune dysregulation syndromes (secondary ITP) • Systemic lupus erythematosus • Autoimmune lymphoproliferative syndrome • Antiphospholipid antibody syndrome • Common variable immunodeficiency • DiGeorge (22q11.2 deletion) syndrome **Platelet activation and consumption** ▪ Microangiopathic disorders • Hemolytic-uremic syndrome • Thrombotic thrombocytopenic purpura • Disseminated intravascular coagulation ▪ Major surgery or trauma ▪ Type 2B or platelet-type (pseudo) von Willebrand disease ▪ Heparin-induced thrombocytopenia ▪ Vascular anomalies, including Kasabach-Merritt syndrome **Mechanical destruction** ▪ Extracorporeal therapies (eg, cardiopulmonary bypass)
	Sequestration
	▪ Hypersplenism
	Dilutional thrombocytopenia
	▪ Massive transfusion ▪ Large intravenous fluid resuscitation

MYH9: nonmuscle myosin heavy chain gene.

* This is a partial list. For further details, refer to UpToDate topics on causes of thrombocytopenia in children and disorders of platelet function.

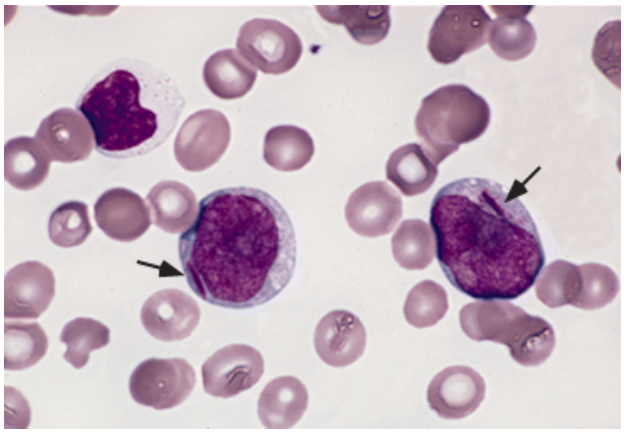
Picture 1B: **Peripheral blood smear of acute lymphoblastic leukemia**



Peripheral blood smear shows small, uniform blasts with scant cytoplasm and inconspicuous nucleoli. Wright-Giemsa, 100x magnification.

Graphic 83240 Version 7.0

Picture 1C: **Myeloblasts with Auer rod in acute myeloid leukemia**



Peripheral smear from a patient with acute myeloid leukemia. There are two myeloblasts, which are large cells with high nuclear-to-cytoplasmic ratio and nucleoli. Each myeloblast has a pink/red rod-like structure (Auer rod) in the cytoplasm (arrows).

From Brunning RD, McKenna RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.

Graphic 78291 Version 4.0

Contributor Disclosures

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