Sign and Symptoms in Pediatric Hematological Diseases

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Pediatric Hematology- Diagnostic approach

- Although it seems that; we mostly deal with laboratory tests, mostly sophisticated
  - Complete Blood Count
  - Coagulation tests
    - INR, aPTT, PFA-100 ….
  - Peripheral and bone marrow smear
  - Flow cytometry
  - Genetic based tests
- But still anamnesis, phyical examination is the most important step for true diagnosis
- Recent year (18/02/2020) we have discussed role of '**Anamnesis and Physical Examination in Pediatric Hematology'**
- Now we will discuss **'Sign and Symptoms in Pediatric Hematological Diseases'**

Hospital Practice: Anamnesis and Physical Examination in Pediatric Hematology

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18/02/2020

Symptom and Sign- Definition

- ***Symptom***: subjective evidence of disease or physical disturbance observed *by the patient*
  - Headache
  - Rash
  - Visual disturbances may be a symptom of retinal atherosclerosis
- ***Sign***: an objective evidence of disease especially as observed and interpreted *by the physician* rather than by the patient or lay observer
  - Chvostek sign
  - Brudzinski sign
  - Hypertension
  - Narrow retinal vessels are a *sign* of arteriosclerosis

Meriam Webster Medical Dictionary

Signs and symptoms related to Hematologic Diseases

Symptoms

- Fatique
- Prolonged fever
- Recurrent infection
- Bruising
- Mucosal bleeding
  - Nose, mouth, GIS
- Pallor
- Jaundice
- Weight loss
- Bone pain

Signs

- Hematochesia
- Melena
- Petechia
- Purpura
- Hemarthrosis
- Hepatomegaly
- Splenomegaly
- Lymphadenopathy

A great number of hematologic disease or pathologies can present with multiple signs and symptoms

- **Hematologic problem** (primary or secondary);
  - **Complete blood count anormaly related**
    - Hemoglobin
      - Anemia
      - Polycythemia
    - Thrombocyte
      - Thrombocytopenia
      - Thrombocytosis
    - White blood cell
      - Neutropenia
      - Lymphopenia
      - Leucocytosis
  - **Bleeding diathesis**
  - **Thrombosis**
  - **Disease related**

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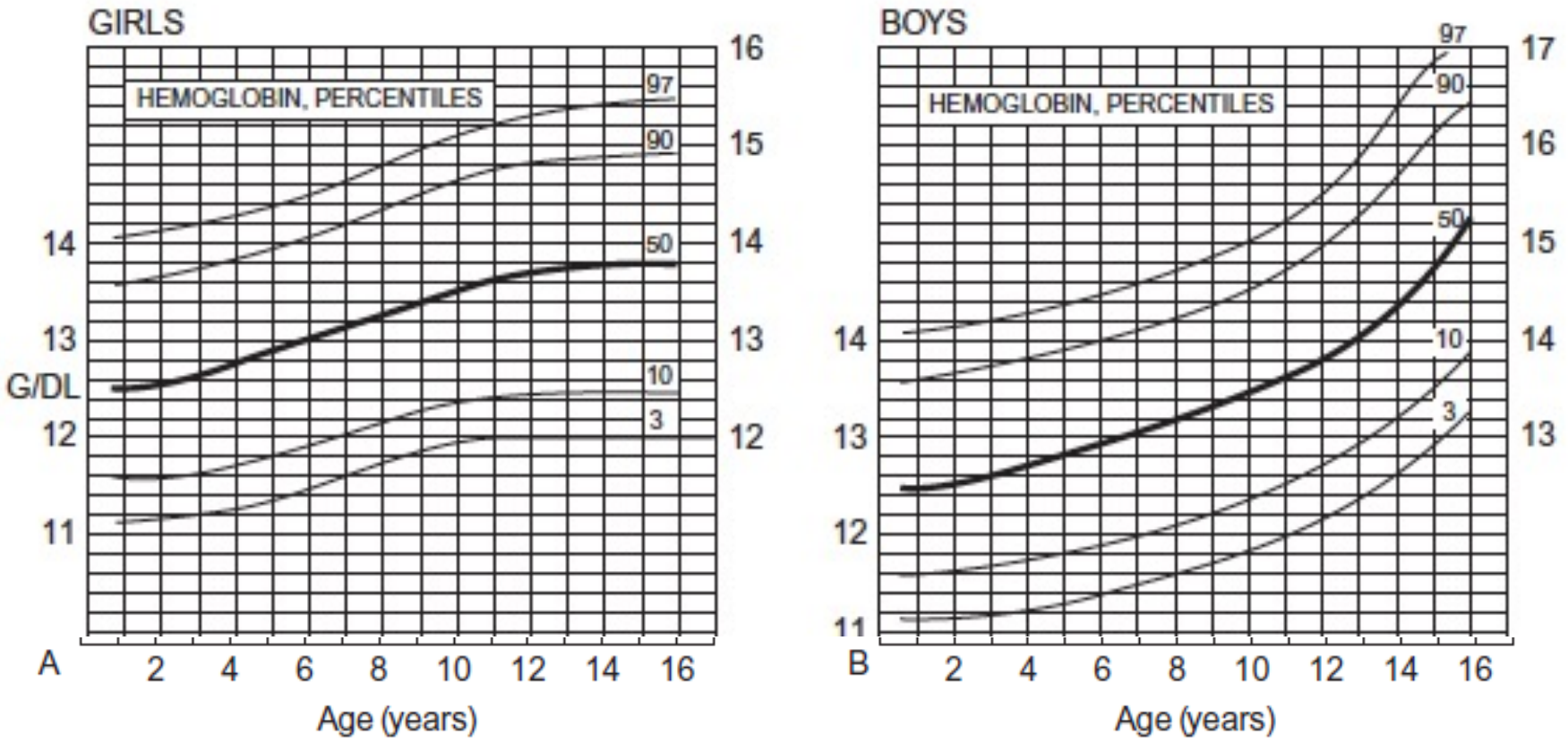
Anemia; Definitions

- Anemia;
  - Reduction of hemoglobin (Hb), RBC concentration or hematocrit concentration
  - Below -2SD, or 3p
- Normal ranges change with;
  - Age, gender and race

Yaşa göre Hb değerleri



Ref: Lanzkowsky P. Appendix-1 Hematologic reference values. Manual of Pediatric Hematology and Oncology. 5th ed. 2011. Page: 973. Source: From Dallman, P.R., Siimes, M.A., 1979. Percentile curves for hemoglobin and red cell volume in infancy and childhood. J. Pediatr. 94, 28.

Yaşa göre kırmızı küre değişkenleri

Table A1-4 Red Cell Values at Various Ages: Mean and Lower Limit of Normal (−2 SD)[a]

	Hemoglobin (g/dl)		Hematocrit (%)		Red Cell Count (10^{12}/l)		MCV (fl)		MCH (pg)		MCHC (g/dl)		Reticulocytes	
Age	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD	Mean	−2 SD
Birth (cord blood)	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30	3.2	1.8
1–3 days (capillary)	18.5	14.5	56	45	5.3	4.0	108	95	34	31	33	29	3.0	1.5
1 week	17.5	13.5	54	42	5.1	3.9	107	88	34	28	33	28	0.5	0.1
2 weeks	16.5	12.5	51	39	4.9	3.6	105	86	34	28	33	28	0.5	0.2
1 month	14.0	10.0	43	31	4.2	3.0	104	85	34	28	33	29	0.8	0.4
2 months	11.5	9.0	35	28	3.8	2.7	96	77	30	26	33	29	1.6	0.9
3–6 months	11.5	9.5	35	29	3.8	3.1	91	74	30	25	33	30	0.7	0.4
0.5–2 years	12.0	10.5	36	33	4.5	3.7	78	70	27	23	33	30	1.0	0.2
2–6 years	12.5	11.5	37	34	4.6	3.9	81	75	27	24	34	31	1.0	0.2
6–12 years	13.5	11.5	40	35	4.6	4.0	86	77	29	25	34	31	1.0	0.2
12–18 years														
Female	14.0	12.0	41	36	4.6	4.1	90	78	30	25	34	31	1.0	0.2
Male	14.5	13.0	43	37	4.9	4.5	88	78	30	25	34	31	1.0	0.2
18–49 years														
Female	14.0	12.0	41	36	4.6	4.0	90	80	30	26	34	31	1.0	0.2
Male	15.5	13.5	47	41	5.2	4.5	90	80	30	26	34	31	1.0	0.2

[a]These data have been compiled from several sources. Emphasis is given to studies employing electronic counters and to the selection of populations that are likely to exclude individuals with iron deficiency. The mean ±2 SD can be expected to include 95% of the observations in a normal population.
From: Dallman PR. Blood and blood-forming tissue. In: Rudolph A, editor. Pediatrics. 16th ed. E. Norwalk, CT: Appleton-Cernuary-Croles, 1977, with permission.

Ref: Lanzkowsky P. Appendix-1 Hematologic reference values. Manual of Pediatric Hematology and Oncology. 5th ed. 2011. Page: 973.

Anemia related sign and symptoms

Severity changes with degree of anemia and effectiveness of compansatory mechanisms

- Pallor
- Lethargy
- Poor feeding
- Tachycardia
- Hearth murmur
- Dyspnea on exercise
- Hearth failure
- Shock

- Compansatory mechanisms of body against anemia
  - Symptoms related to anemia is mostly correlated to the severity and the chronicity of the condition
  - Severe anemia that develops weeks and months can be well tolerated
  - Symptoms are generally more pronounced in patients with limited cardiopulmonary reserve or in whom the anemia developed very rapidly

Pallor

A *perceptual reduction* in usual *color* and *tone* of the *skin and mucosa*

Highly nonspecific

Underlying etiology may be severe

May be non-disease related

TABLE 37.1 Causes of Pallor in Children Based on Etiologic Mechanism

I. Anemia
II. Decreased Tendency of the Skin to Pigment
  A. Physiologic (fair-skinned individuals)
  B. Limited sun exposure
III. Alteration of the Consistency of the Subcutaneous Tissue
  A. Edematous states, increased intravascular hydrostatic pressure (e.g., congestive heart failure), decreased intravascular oncotic pressure (hypoproteinemia), increased vascular permeability (e.g., vasculitis)
  B. Hypothyroidism
IV. Decreased Perfusion of the Cutaneous/Mucosal Vasculature
  A. Hypotension, cardiogenic shock (pump failure or rhythm disturbance), hypovolemia (blood loss, dehydration), anaphylaxis, sepsis, acute adrenal insufficiency, vasovagal syncope
  B. Vasoconstriction, increased sympathetic activity (hypoglycemia, pheochromocytoma), neurologic complications (head trauma, seizures, migraine)
V. Chronic Medical Conditions
  A. Malignant disease
  B. Atopy
  C. Chronic inflammatory disease, juvenile idiopathic arthritis, inflammatory bowel disease
  D. Cardiopulmonary disease (including cystic fibrosis)
  E. Diabetes mellitus
  F. Congenital and acquired immunodeficiencies

From Reece RM. *Manual of Emergency Pediatrics*. 4th ed. Philadelphia: WB Saunders; 1992.

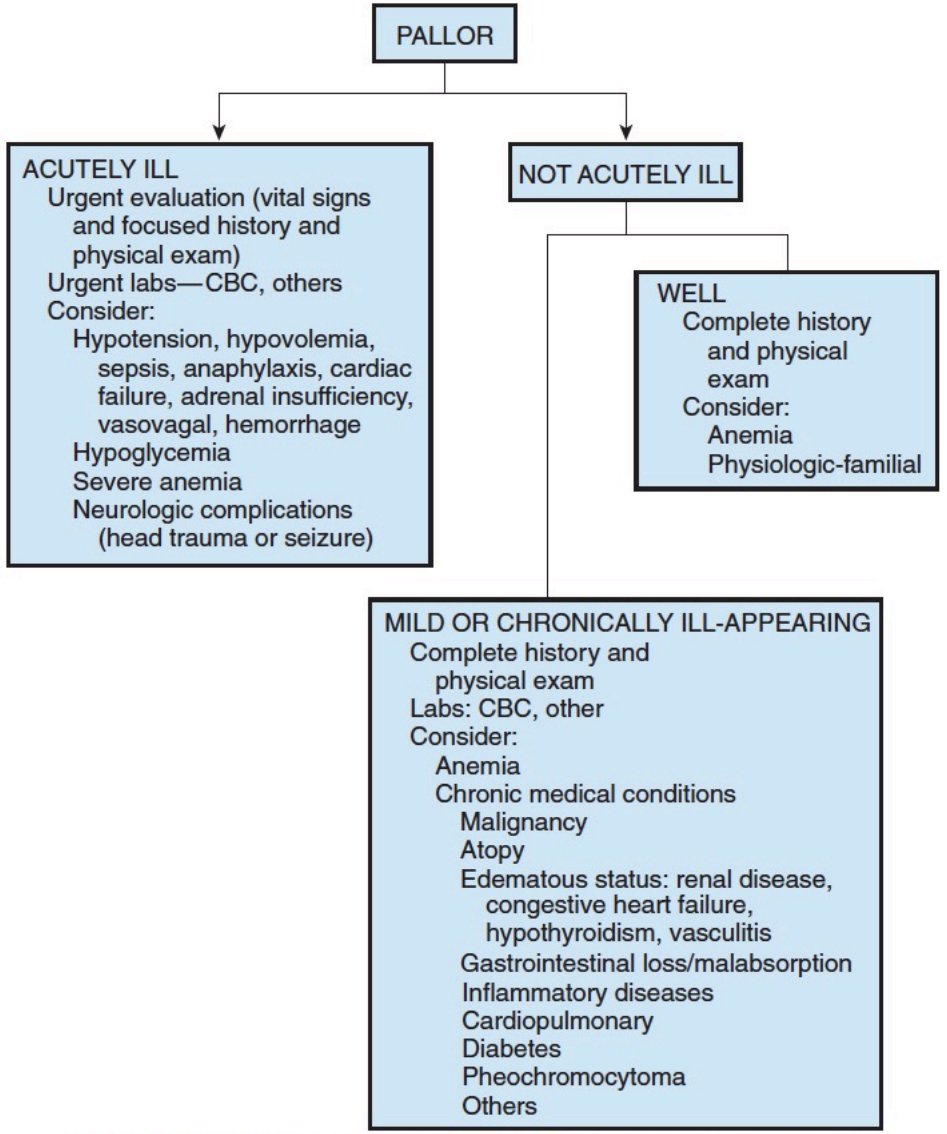


FIGURE 37.3 Approach to the pale child. CBC, complete blood count.

Brandow A. Pallor and Anemia, Section 8: Hematologic Diseases in book, Nelson Pediatric Symptom Based Diagnosis, Elsevier, 2018.

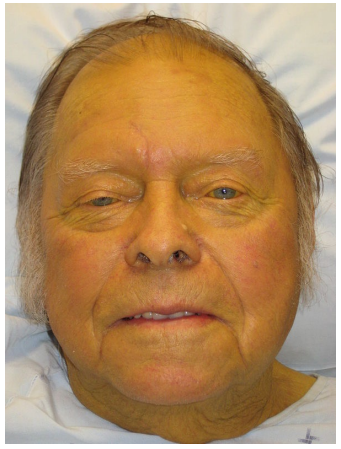
Symptoms or signs related to etiology of anemia

- **Hemolytic anemias**
  - Urine color changes:
    - Red to Black urine: Hemolysis
      - Presence of myoglobin in the urine is; **myoglobinuria**
      - Presence of free hemoglobin in the urine; **hemoglobinuria**
  - Jaundice: Hemolysis
- Bleeding:
  - GIS related bleeding;
    - Rectal
      - Hematochesia
      - Melana
    - Hematemesis
  - Menorhagia
  - Hematuria
    - RBCs are present in the urine

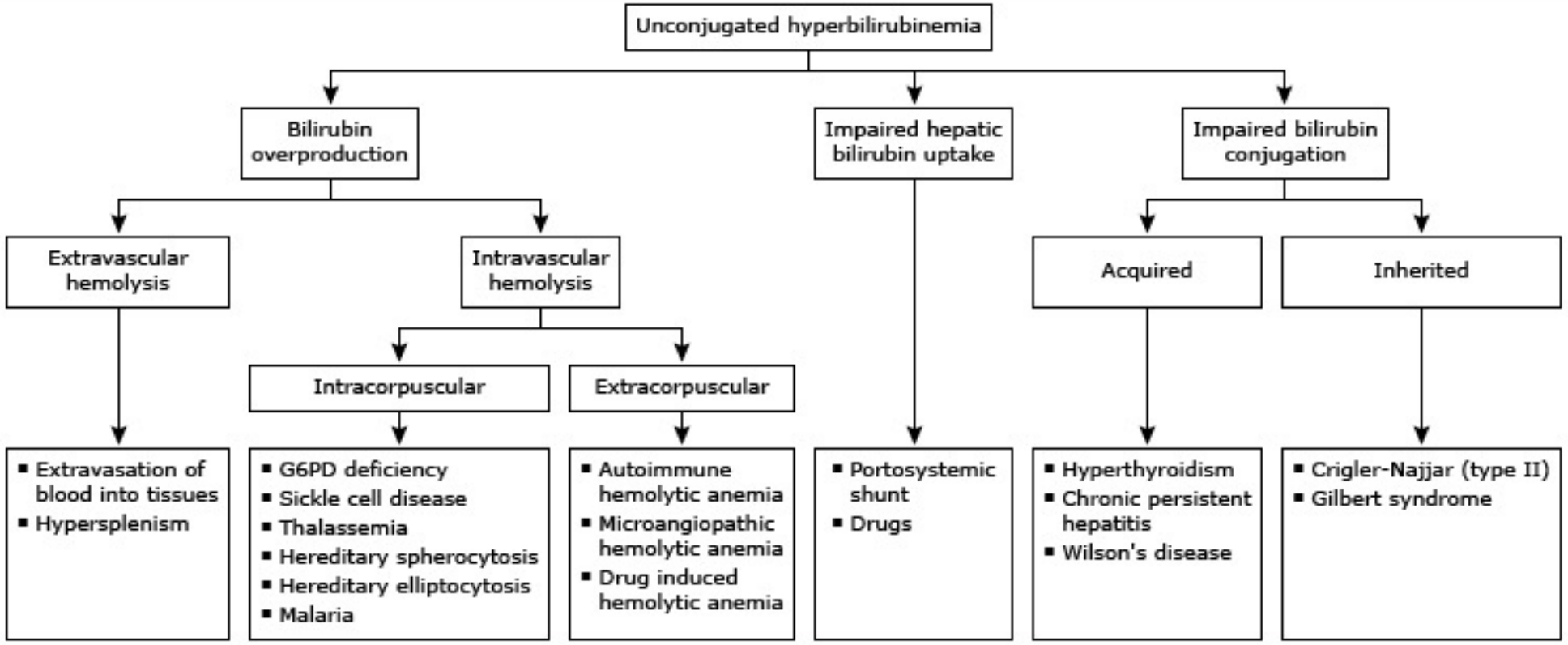
Jaundice

Jaundice

- Yellowish discoloration of the skin and sclerae
- Elevated bilirubin
  - >2 mg/dl



Classification of unconjugated hyperbilirubinemia in children and infants beyond the neonatal period



G6PD: glucose-6-phosphate dehydrogenase deficiency.

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  - Jaundice: Hemolysis
- **Bleeding:**
  - GIS related bleeding;
    - Rectal
      - Hematochesia
      - Melana
    - Hematemesis
    - Occult bleeding
  - Menorhagia
  - Hematuria
    - RBCs are present in the urine

Gastrointestinal bleeding

- **Melena**

  Digested blood in stool
  - black, tarry, oil like, fouly stools,
  - originates proximal to the ligament of Treitz
  - 50 ml blood is enough

- **Hematemesis**
  - digested or fresh blood in emesis
  - originates proximal to the ligament of Treitz

- **Hematochesia**
  - fresh blood from rectum
  - Originates form Lower GIS
  - Rarely huge bleeding from Upper GI can couse hematochesia

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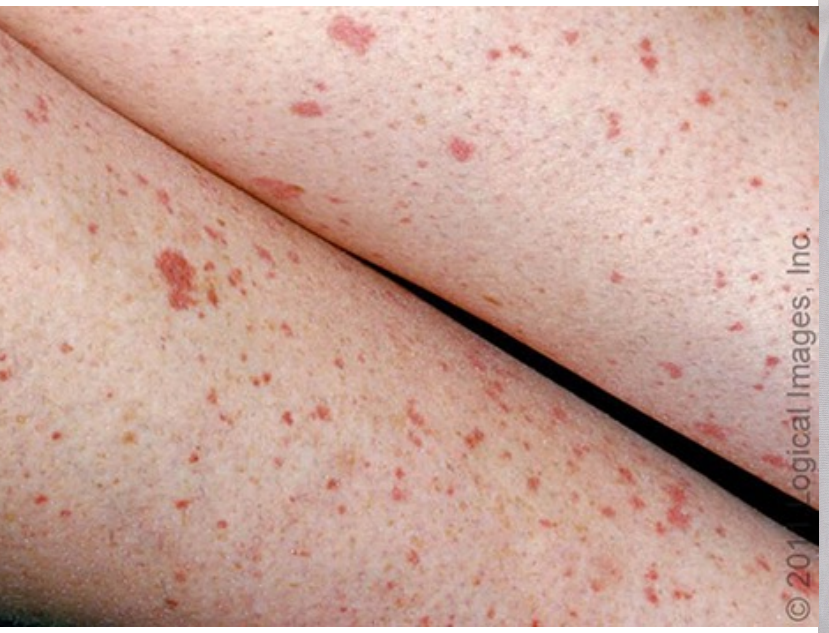
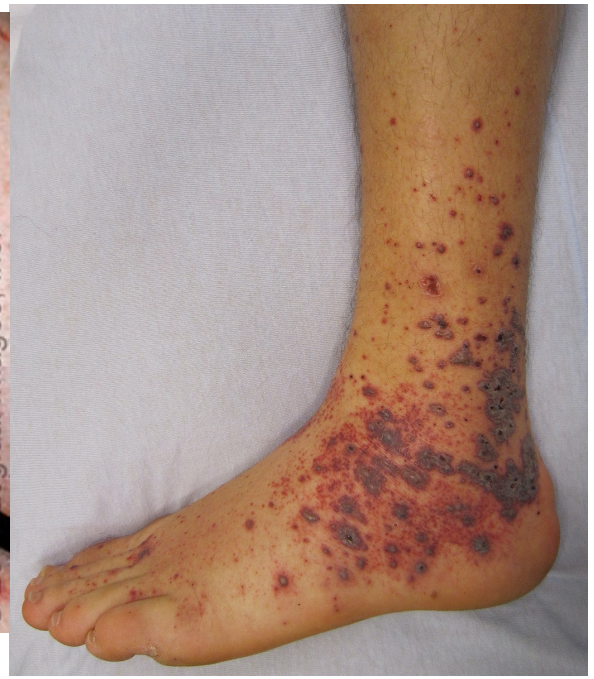
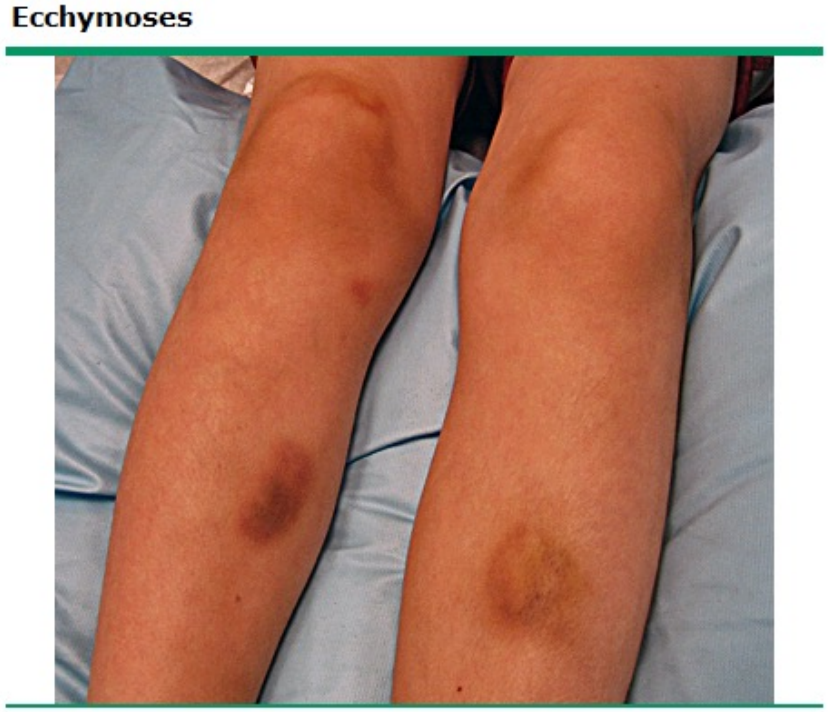
Thrombocytopenia

Thrombocytopenia is defined as a platelet count of <150,000/microl

- Petechia: Pinpoint areas (less than 2 mm) of hemorrhage, which are reddish-purple lesions
- Purpura. 3-10 mm, ecchymoses: > 1 cm
- Petechia, and purpura do not bleach,







Courtesy of Leslie Raffini, MD.

Bleeding Diathesis

TABLE 38.1 Common Causes of Clinical Bleeding Symptoms

Mucocutaneous Bleeding

Immune thrombocytopenic purpura

Child abuse

Trauma

Poisoning with anticoagulants (rat poison)

Chronic/insidious

von Willebrand disease

Platelet function defect

Marrow infiltration/aplasia

Deep/Surgical Bleeding

Hemophilia

Vitamin K deficiency

von Willebrand disease

Generalized Bleeding

Disseminated intravascular coagulation

Vitamin K deficiency

Liver disease

Uremia

Flood V., Scott P. Bleeding and Thrombosis, Section 8: Hematologic Diseases in book, Nelson Pediatric Symptom Based Diagnosis, Elsevier, 2018.

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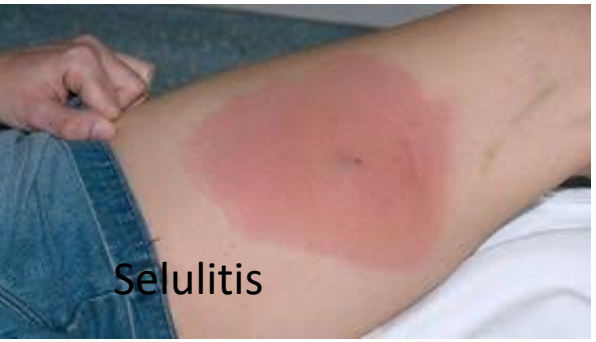
Neutropenia associated signs and symptoms

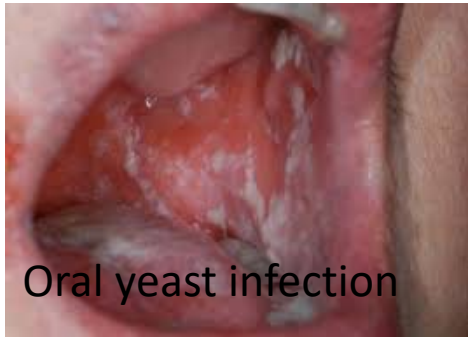
- Recurrent,
- Severe ,
- Oral cavity and mucous membranes,
- Systemic infections
  - Lung and blood born

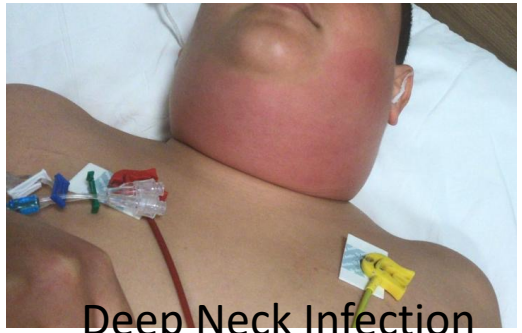
Relation of non-chemotherapy-related neutropenia and infection risk

	Absolute neutrophil count	Risk management
Normal neutrophile count	>1500/microL (>1.5 x 10^9/liter)	None
Mild neutropenia	1000 to 1500/microL	No significant risk of infection; fever can be managed on an outpatient basis
Moderate neutropenia	500 to 999/microL	Some risk of infection; fever can occasionally be managed on an outpatient basis
Severe neutropenia	200 to 499/microL	Significant risk of infection; fever should always be managed on an inpatient basis with parenteral antibiotics; few clinical signs of infection
<200/microL Severe neutropenia Agranulocytosis		Very significant risk of infection; fever should always be managed on an inpatient basis with parenteral antibiotics; few or no clinical signs of infection

The correlation between absolute neutrophil count and infectious risk only applies to conditions in which the bone marrow neutrophil reserve is diminished. Refer to UpToDate topics on neutropenia for further discussions of the causes of neutropenia and the estimation of infectious risk.


Selulitis


Oral yeast infection


Deep Neck Infection

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      - **Leucocytosis**
  - Bleeding diathesis
  - Thrombosis
  - **Disease related**

Bone pain

- A frequent symptom
- Mostly traumatic
- But there is a rare but important clinic that can be related to hematologic malinancies (leukemia)
  - Without a traumatic history
  - Persists, awakens the child
  - Does not respond to nonsteroidal anti-inflammatory drugs
  - Can be confused with growth pain
  - Associated symtoms that can be seen in hematologic malignacies

B symptoms

combination of three symptoms

Originally for classification of Lymphomas

A and B group

B group means; with worse prognosis

Can be seen most of childhood malignancies (leukemias, lymphomas, neuroblastomas…)

- Unexplained Fever – Temperature >38°C
- Unexplained Weight loss – Unexplained loss of >10 percent of body weight over the past six months
- Night Sweats – The presence of drenching night sweats

Lympadenopathy

- Common manifestation of many childhood diseases
- Most often related to infection (viral or bacterial)
  - Resolves spontaneusly or with ab treatment

Flood V., Scott P. Bleeding and Thrombosis, Section 8: Hematologic Diseases in book, Nelson Pediatric Symptom Based Diagnosis, Elsevier, 2018.
UpTodate

TABLE 4.2 Differential Diagnosis of Lymphadenopathy

1. **Nonspecific reactive hyperplasia (polyclonal)**
2. **Infection**
   a. Bacterial: *Staphylococcus*, *Streptococcus*, anaerobes, tuberculosis, atypical mycobacteria, *Bartonella henselae* (cat scratch disease, brucellosis, *Salmonella typhi*, diphtheria, *Chlamydia trachomatis* lymphogranuloma venereum), *Calymmatobacterium granulomatis*, *Francisella tularensis*
   b. Viral: Epstein–Barr virus, cytomegalovirus, adenovirus, rhinovirus, coronavirus, respiratory syncytial virus, influenza, coxsackie virus, rubella, rubeola, varicella, HIV, herpes simplex virus, human herpes virus 6 (HHV-6)
   c. Protozoal: Toxoplasmosis, malaria, trypanosomiasis
   d. Spirochetal: Syphilis, *Rickettsia typhi* (murine typhus)
   e. Fungal: Coccidioidomycosis (valley fever), histoplasmosis, *Cryptococcus*, aspergillosis
   f. Postvaccination: Smallpox, live attenuated measles, DPT, Salk vaccine, typhoid fever
3. **Connective tissue disorders**
   a. Rheumatoid arthritis
   b. Systemic lupus erythematosus
4. **Hypersensitivity states**
   a. Serum sickness
   b. Drug reaction (e.g., Dilantin, mephenytoin, pyrimethamine, phenylbutazone, allopurinol, isoniazid, antileprosy, and antithyroid medications)
5. **Lymphoproliferative disorders** (Chapter 16)
   a. Angioimmunoblastic lymphadenopathy with dysproteinemia
   b. X-linked lymphoproliferative syndrome
   c. Lymphomatoid granulomatosis
   d. Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease)
   e. Castleman disease benign (giant lymph node hyperplasia, angiofollicular lymph node hyperplasia)
   f. Autoimmune lymphoproliferative syndrome (ALPS) (Canale–Smith syndrome)
   g. Posttransplantation lymphoproliferative disorder (PTLD)
6. **Neoplastic diseases**
   a. Hodgkin and non-Hodgkin lymphomas
   b. Leukemia
   c. Metastatic disease from solid tumors: neuroblastoma, nasopharyngeal carcinoma, rhabdomyosarcoma, thyroid cancer
   d. Histiocytosis
      i. Langerhans cell histiocytosis
      ii. Familial hemophagocytic lymphohistiocytosis
      iii. Macrophage activation syndrome
      iv. Malignant histiocytosis
7. **Storage diseases**
   a. Niemann–Pick disease
   b. Gaucher disease
   c. Cystinosis
8. **Immunodeficiency states**
   a. Chronic granulomatous disease
   b. Leukocyte adhesion deficiency
   c. Primary dysgammaglobulinemia with lymphadenopathy
9. **Miscellaneous causes**
   a. Kawasaki disease (mucocutaneous lymph node syndrome)
   b. Kikuchi–Fujimoto disease (self-limiting histiocytic necrotizing lymphadenitis)
   c. Sarcoidosis
   d. Beryllium exposure
   e. Hyperthyroidism
   f. Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA syndrome)

LanzkowskyP. Chapter 4: Lymphadenopathy and Diseases of the Spleen. In Book Lanzkowsky's Manual Of Pediatric Hematology and Oncology, 6th Edition, 2016.

Causes of peripheral lymphadenopathy*

Cause	Examples
Infections	
Bacterial	
▪ Localized	Streptococcal pharyngitis; skin infections; tularemia; plague; cat scratch disease; diphtheria; chancroid; rat bite fever; early Lyme disease; early (primary) syphilis
▪ Generalized	Brucellosis; leptospirosis; lymphogranuloma venereum; typhoid fever; secondary syphilis
Viral	Human immunodeficiency virus; Epstein-Barr virus; herpes simplex virus; cytomegalovirus; mumps; measles; rubella; hepatitis B; dengue fever
Mycobacterial	*Mycobacterium tuberculosis*; atypical mycobacteria
Fungal	Histoplasmosis; coccidioidomycosis; cryptococcosis
Protozoal	Toxoplasmosis; leishmaniasis
Cancer	Squamous cell cancer head and neck; metastatic; lymphoma; leukemia
Lymphoproliferative	Angioimmunoblastic lymphadenopathy with dysproteinemia
	Autoimmune lymphoproliferative disease
	Rosai-Dorfman disease
	Hemophagocytic lymphohistiocytosis
Immunologic	Serum sickness; drug reactions (phenytoin); IgG4-related disease
Endocrine	Primary adrenal insufficiency (Addison's disease)
Miscellaneous	Sarcoidosis; lipid storage diseases; amyloidosis; histiocytosis; chronic granulomatous diseases; Castleman disease; Kikuchi disease; Kawasaki disease; inflammatory pseudotumor; systemic lupus erythematosus; rheumatoid arthritis; Still's disease; dermatomyositis; eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

IgG4: immunoglobulin G4.
* NOTE: This is a partial list and is not meant to be all-inclusive.

Red flags for lymphadenopathy

- Weight loss, recurrent fevers, night sweets, systemic signs
- Bone pain
- Complete blood count abnormality (cytopenias for more than 1 cell linages)
- Supraclavicular location
- Associated with Hepato/spleneomegaly, or abdomina mass
- Irresponsive to antibiotic treatment
- Generalized lymphadenopathy
- Fixed nontender nodes in the absence of other symptoms; matted nodes
- Nontender lymph nodes ≥2 cm in diameter that increase in size from baseline or do not respond to 2 weeks of antibiotic therapy
- Persistently elevated ESR/CRP or rising ESR/CRP despite antibiotic therapy
- In immunosupressive children
  - Increased risk of infection
  - Increased risk of malignancy

Flood V., Scott P. Bleeding and Thrombosis, Section 8: Hematologic Diseases in book, Nelson Pediatric Symptom Based Diagnosis, Elsevier, 2018.
UpTodate

Splenomegaly

- Can be related to childhood hemtologic diseases
  - Leukemias
  - Myeloprolipherative diseases
  - Hemolytic anemias
  - Extramedullary hematopoiesis …

Causes of splenomegaly

Diagnostic category	Suggestive findings	Additional evaluation*
Infectious mononucleosis	▪ Fever, pharyngitis, fatigue, and lymphadenopathy ▪ Lymphocytosis and atypical lymphocytes on peripheral blood smear	▪ Diagnosis is made with EBV and CMV serologies and/or heterophile antibody testing
Systemic infection ▪ Tuberculosis ▪ Infective endocarditis ▪ Malaria ▪ HIV ▪ Cat scratch disease ▪ Babesiosis	▪ Persistent fevers, weight loss, malaise, lymphadenopathy ▪ Travel to an endemic region (malaria, tuberculosis, babesiosis) ▪ HIV risk factors (unprotected sex, IV drug use) ▪ Cat scratch (*Bartonella*) ▪ Tick bite (babesiosis)	▪ Testing is guided by clinical findings and may include: • TST to evaluate for TB • Serial blood cultures to evaluate for IE • Malaria blood smear (if relevant exposure) • HIV testing (if there are relevant risk factors) • *Bartonella* titers (if relevant exposure) • Blood smear and/or PCR for babesiosis (if relevant exposure)
Hematologic malignancy ▪ Acute lymphoblastic leukemia ▪ Acute myelogenous leukemia	▪ Persistent fevers, anorexia, weight loss, decreased activity level, bone pain, and/or easy bruising ▪ Cytopenias (neutropenia, anemia, and/or thrombocytopenia) ▪ Abnormal immature cells (blasts) in the peripheral blood	▪ Bone marrow aspiration/biopsy
Lymphoproliferative diseases ▪ Lymphoma ▪ Langerhans cell histiocytosis ▪ Hematophagocytic lymphohistiocytosis ▪ Autoimmune lymphoproliferative syndrome ▪ Castleman disease and POEMS syndrome	▪ Lymphadenopathy (particularly if lymph nodes are massively enlarged and/or rapidly increasing in size) ▪ Chest radiograph findings of hilar adenopathy or mediastinal mass	▪ Contrast-enhanced CT of the chest and abdomen ▪ Lymph node biopsy ▪ Bone marrow biopsy
Hemolytic anemias ▪ RBC membrane defects ▪ RBC enzyme defects ▪ Hemoglobinopathies ▪ Autoimmune hemolytic anemia ▪ Other acquired hemolytic anemias	▪ Low hemoglobin, unconjugated hyperbilirubinemia, and reticulocytosis ▪ Clues on the peripheral blood smear include polychromasia and spherocytes ▪ Certain congenial RBC disorders may have specific findings on the blood smear (eg, elliptocytes, xerocytes, sickle cells)	▪ Serum markers of hemolysis (LDH, free hemoglobin, haptoglobin) ▪ Testing for specific causes of hemolytic anemia
Liver disease ▪ Biliary atresia ▪ Viral hepatitis ▪ Wilson disease ▪ Other metabolic liver disease (eg, galactosemia) ▪ Primary sclerosing cholangitis ▪ Alpha-1-antitrypsin deficiency ▪ Alagille syndrome ▪ Cystic fibrosis	▪ Jaundice, hepatomegaly, firm liver edge, ascites, and/or spider angiomata ▪ Abnormal liver function tests ▪ Abnormal findings on abdominal imaging (eg, focal or diffuse liver abnormalities; slow or reversed portal blood flow suggestive of portal hypertension)	▪ Testing for specific causes of pediatric liver disease ▪ Liver biopsy may be warranted in some cases
Portal vein thrombosis	▪ Patients may have abdominal pain or may be asymptomatic ▪ Underlying risk factor for thrombosis (eg, invasive catheter [UVC], liver disease, malignancy, inherited thrombophilia, antiphospholipid antibodies) ▪ Abnormal abdominal ultrasound (ie, filling defect or absence of flow Doppler images)	▪ Diagnosis is made with Doppler ultrasound ▪ Additional evaluation may be warranted to determine cause of thrombus
Autoimmune disease ▪ SLE ▪ JRA	▪ Rashes and/or joint swelling ▪ Laboratory findings include nonspecific markers of inflammation (eg, leukocytosis, elevated ESR or CRP)	▪ Antinuclear antibody titers are obtained as a screening test ▪ Further evaluation is based on the clinical findings
Primary immunodeficiency ▪ Common variable immunodeficiency	▪ History of recurrent infections and/or failure to thrive ▪ Lymphopenia may be noted on CBC	▪ Diagnosis is based on immunoglobulin levels and antibody function studies (ie, vaccine response)
Storage disorders ▪ Gaucher disease ▪ Niemann-Pick disease ▪ Mucopolysaccharidoses ▪ Other lysosomal storage disorders	▪ Other organ involvement (eg, hepatomegaly, skeletal abnormalities, neurologic involvement) ▪ Plain radiographs may show bone abnormalities ▪ Focal splenic masses may be noted on abdominal ultrasound	▪ Diagnosis is confirmed by testing for specific enzyme deficiencies and/or genetic mutations
Space-occupying lesions ▪ Hemangioma ▪ Hamartoma ▪ Cysts ▪ Intracapsular hematoma (trauma)	▪ Hemangiomas: • Skin hemangiomas may be noted ▪ Cysts and hamartomas: • Most are asymptomatic • May be noted as incidental findings on abdominal imaging studies obtained for other reasons ▪ Intracapsular hematoma: • In most cases, there is a clear preceding history of substantial blunt abdominal trauma • Relatively minor trauma can cause splenic rupture in children with underlying splenomegaly due to anot etiology (eg, mononucleosis)	▪ Additional imaging studies (eg, CT or MRI) may be warranted ▪ Diagnosis is based on imaging findings

Signs and symptoms related to Hematologic Diseases

Symptoms

- Fatique
- Prolonged fever
- Recurrent infection
- Bruising
- Mucosal bleeding
  - Nose, mouth, GIS
- Pallor
- Jaundice
- Weight loss
- Bone pain

Signs

- Hematochesia
- Melena
- Petechia
- Purpura
- Hemarthrosis
- Hepatomegaly
- Splenomegaly
- Lymphadenopathy

Sign and Symptoms in Pediatric Hematological Diseases

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