Editor
R.H. Sills

Practical Algorithms in Pediatric Hematology and Oncology

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Practical Algorithms in Pediatric Hematology and Oncology

Editor
Richard H. Sills, Albany, N.Y.

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Preface

The term 'algorithm' is derived from the name of the ninth century Arabic mathematician *Algawrismi*, who also gave his name to 'algebra'. His 'algorismus' indicated a step-by-step logical approach to mathematical problem solving. In reading the final product, written by some of the finest pediatric hematologist-oncologists in the world and edited by my friend Dr Richard Sills, it is obvious that the spirit of the algorismus has been utilized to its best.

Practical Algorithms in Pediatric Hematology and Oncology is intended as a pragmatic text for use at the patient's bedside. The experienced practitioner applies step-by-step logical problem solving for each patient individually. Decision trees prepared in advance have the disadvantage of unacquaintedness with the individual patient. Yet, for the physician who is less experienced with a given problem, a prepared algorithm would provide a logical, concise, and cost-effective approach prepared by a specialist who is experienced with the given problem. In the process of writing this book, I served as the lay non-specialist reader. Twenty-five years after completing my pediatric residency, I discover that Pediatric Hematology-Oncology has become a sophisticated specialty with solid scientific background of which I know so little. I would still refer my patients to a specialist with many of the diagnoses, symptoms and signs discussed here. But, with the help of this outstanding book, I would refer them after an educated initial workup, and would be better equipped to follow the specialist's management.

Ze'ev Hochberg, MD, DSc

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Introduction

Algorithms are practical tools to help us address diagnostic and therapeutic problems in a logical, efficient and cost-effective fashion. *Practical Algorithms in Pediatric Hematology and Oncology* uses this approach to assist the clinician caring for children with blood disorders and possible malignancies. The book is designed for the general practitioner and pediatrician who are not exposed to these problems on a daily basis as well as residents and trainees in Pediatrics and Pediatric Hematology and Oncology.

In addressing oncologic problems, our goal is to efficiently determine whether children have malignant or benign disorders, and to establish the specific diagnosis. Details of specific therapeutic regimens for malignant disorders are not addressed because they should be determined individually in consultation with a pediatric oncologist. Algorithms also address the management of complications which may occur at the time of clinical presentation, such as superior vena cava syndrome, febrile neutropenia, and tumor lysis syndrome as well as an approach to recognizing the late effects of treatment.

The algorithms addressing hematologic disorders also concentrate on diagnosis, but include issues of management of conditions such as sickle cell anemia, hemophilia and red blood cell transfusions.

The format is designed to provide as much information as possible. The diagnostic algorithms sequentially move to specific diagnoses, and when space allows, to therapy. To provide a better sense of which diagnoses are more likely, very common diagnoses causing each problem are noted in **bold** text, the usually larger number of common diagnoses in standard font and rare diagnoses in *italics*. No algorithm can contain every possible diagnosis; many rare diagnoses are not included while others may be listed in the algorithm but not the text. Cross-references to other algorithms make the book easier to use. An appendix of age-dependent normal values and a convenient list of all abbreviations used are also provided.

As with any approach that attempts to simplify complex problems, there will always be exceptions. Each algorithm must be used in the context of the individual findings of each patient under examination and in conjunction with the current published literature. The clinician must always be aware that any individual patient's presentation may be atypical enough, or confounded by concomitant disorders or complications, to render our aproaches invalid. In addition, advances in diagnosis and management can render current approaches obsolete.

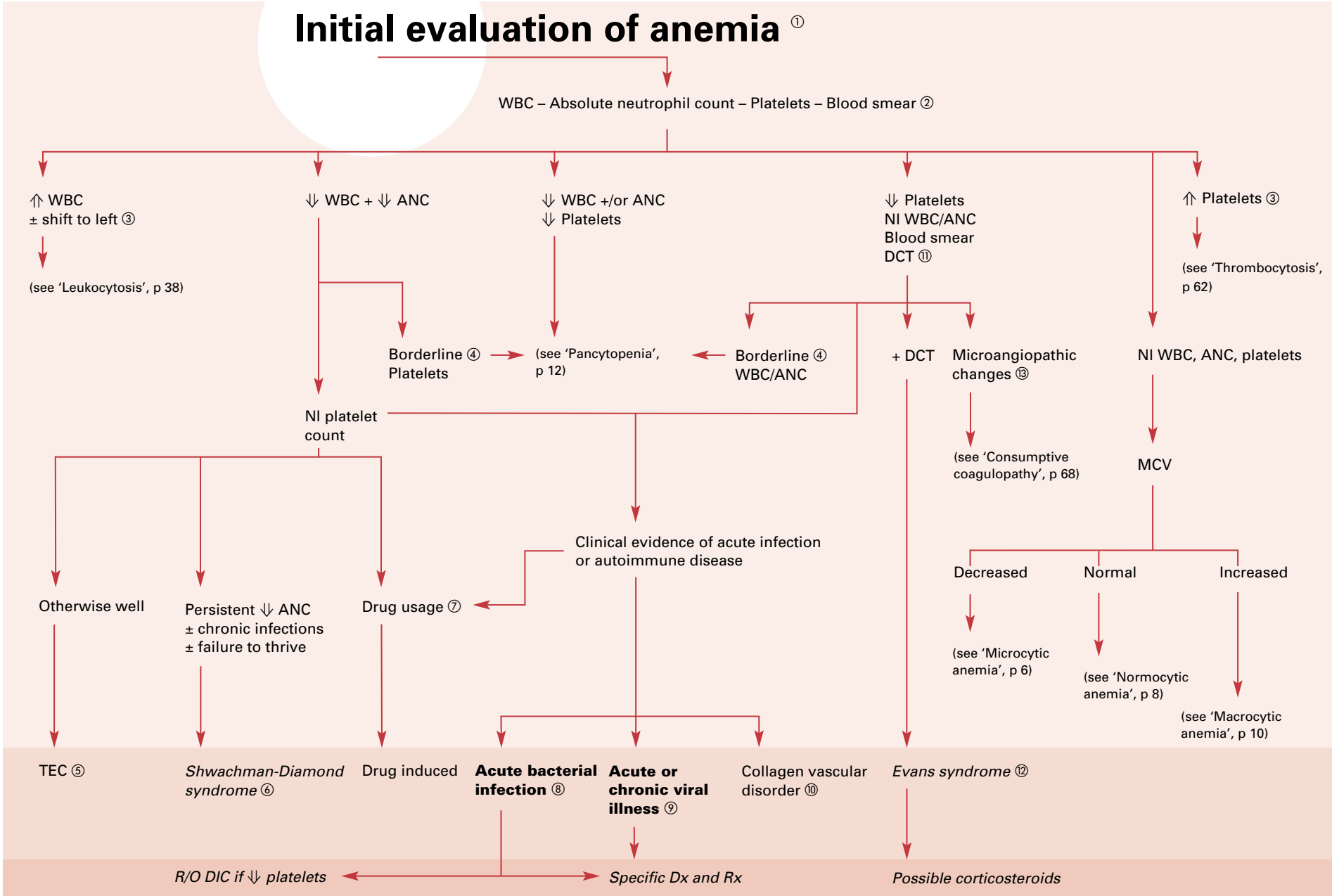
We hope you will find the book helpful in managing the children under your care.

Richard H. Sills, MD

My thanks to all the students, residents, attending physicians and staff at Albany Medical College who graciously took the time to review and edit the algorithms, and to Irene and Sara for their support and love.

I dedicate this book to the memory of my father, Sidney Sills.

Initial evaluation of anemia ①



① — Outline of the initial steps when evaluating anemia in children. While some specific diagnoses are discussed here, most will be found in the seven other algorithms, which are referred to in this stepwise approach.

② — The wide availability of electronic cell counters provides the advantage of having the RBC indices, WBC, platelet count and usually ANC obtained automatically with the Hb. With these data, the first step in evaluating anemia is to determine whether other cell lines are also affected. Make sure that the WBC, absolute neutrophil count (ANC = % bands + % polymorphonuclear neutrophils × total WBC) and platelet count are normal. One-third of the children with newly diagnosed leukemia will have a normal total WBC, but their ANC is usually reduced. The peripheral smear should be reviewed to ensure that there are no errors with the automated counts, as they do occur. The RBC indices, particularly the MCV and RDW, can be extremely helpful in organizing the differential diagnosis.

③ — Leukocytosis and/or thrombocytosis frequently accompany anemia. Many infections and inflammatory disorders cause leukocytosis; a shift to more immature neutrophils and/or morphologic changes in neutrophils (toxic granulation, Döhle bodies and vacuolization) are often noted, particularly with infection. These same disorders frequently cause the anemia of acute infection or of chronic disease. If blasts are in the peripheral blood, leukemia is expected. Thrombocytosis is a very nonspecific finding, which in children is almost always reactive and related to infection, any inflammatory or neoplastic process, stress, hemolysis, blood loss and iron deficiency. Primary thrombocytosis due to the myeloproliferative disorder, called essential thrombocytosis or thrombocythemia, is extremely rare in children.

④ — Early in the development of pancytopenia some cell lines may fall below the normal range before others; however, if one cell line is severely affected, the others are usually approaching the lower limits of normal.

⑤ — Leukopenia and neutropenia occur in at least 20% of patients with transient erythroblastopenia of childhood. The reticulocyte count is usually very low.

⑥ — Shwachman-Diamond syndrome is a rare autosomal disorder characterized by metaphyseal dysplasia, exocrine pancreatic insufficiency, failure to thrive, and neutropenia. Anemia and/or thrombocytopenia may also be noted. Neutropenia and anemia are also associated with copper deficiency; this is very rare and associated with either severe malnutrition or the inadvertent deletion of copper from intravenous nutrition.

⑦ — A wide variety of drugs cause anemia as well as neutropenia or thrombocytopenia. Cytotoxic drugs do this most commonly but others also do so on an idiosyncratic basis. Many of these drugs are used in acute infections already associated with anemia (such as trimethoprim/sulfamethoxazole or oxacillin), making it difficult to identify the actual cause of the anemia.

⑧ — Acute bacterial infection can result in anemia with neutropenia and/or thrombocytopenia. If the patient appears septic and is thrombocytopenic, complicating DIC should be considered.

⑨ — Acute viral illness is the most common cause of anemia with thrombocytopenia or leukopenia. The abnormalities are more likely to be mild and are almost always transient. In more chronic infection such as HIV or EBV, the hematologic findings may persist. Consider HIV with positive risk factors, other symptoms and failure to resolve.

⑩ — SLE and other collagen vascular disorders can present with these hematologic findings. Specific serologic studies may be indicated.

⑪ — The direct Coombs test identifies immunoglobulin and/or complement on the RBC surface and usually indicates AIHA.

⑫ — Evan's syndrome is the combination of ITP and AIHA, although commonly only one of these disorders is apparent at any one time. It is associated with substantial morbidity and mortality.

⑬ — Microangiopathic changes are due to mechanical destruction and include fragmented RBCs, schistocytes, irregular spherocytes, and usually thrombocytopenia.

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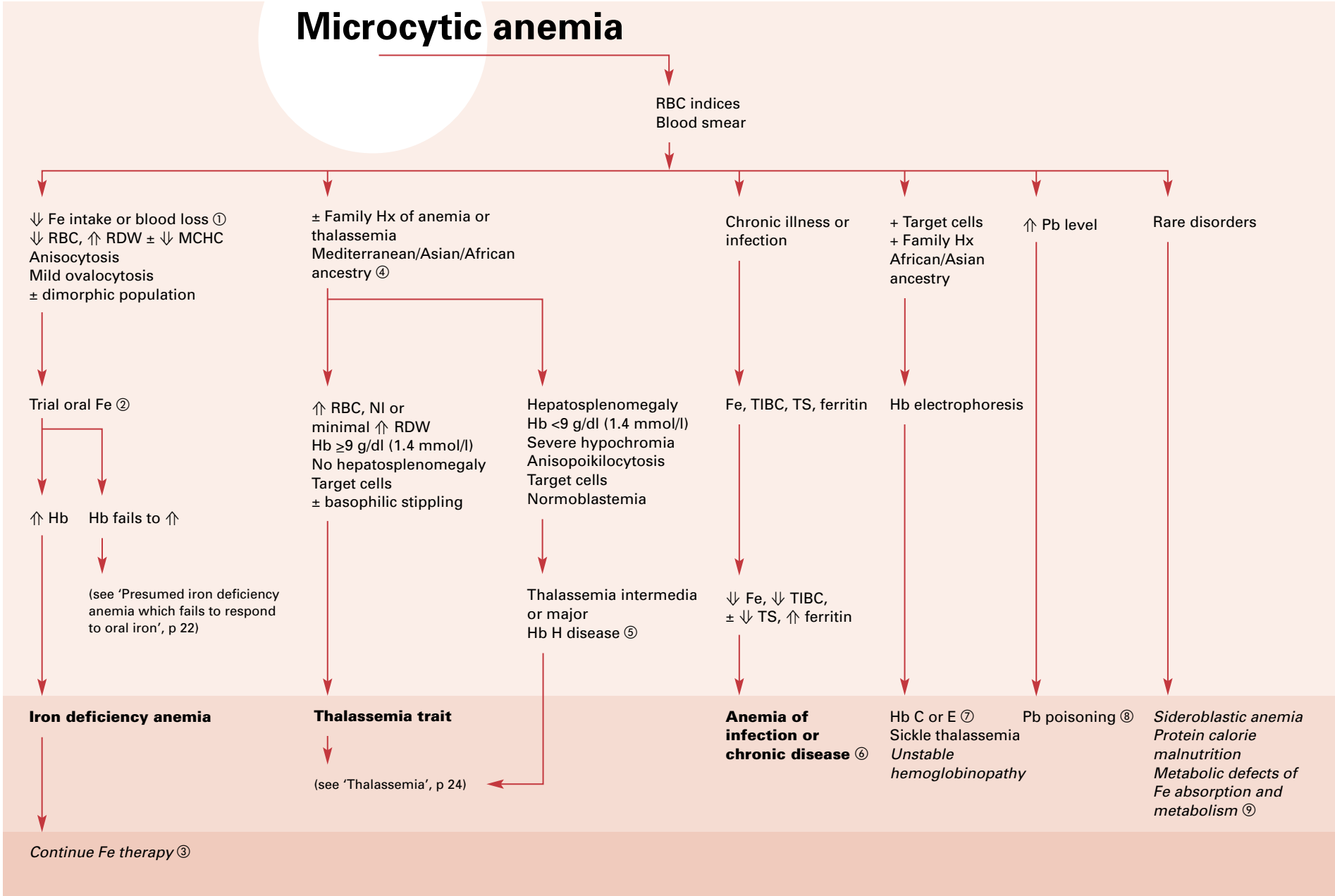
Microcytic anemia



① — Iron deficiency anemia (IDA) is most common in infants and young children with poor Fe intake (often cow's milk intake of a liter or more daily), but with malnutrition it is seen at any age. Blood loss should always be considered, but is more likely in older children and particularly in adolescent girls. An underlying bleeding disorder, such as von Willebrand disease, can cause excessive blood loss. Typical findings of IDA are ⇓ RBC and ⇑ RDW. Smear reveals hypochromia, microcytosis, and often ovalocytes. A dimorphic population (microcytic hypochromic cells mixed with normocytic, normochromic cells) is commonly present early in the disease or following the onset of Fe therapy.

② — The diagnosis of IDA is usually established by a successful trial of oral Fe therapy. Use ferrous sulfate in a dose of 2–3 mg/kg/day of elemental Fe (10–15 mg/kg/day of ferrous sulfate) divided t.i.d.; doses of up to 6 mg/kg/day of elemental Fe are used for severe Fe deficiency to increase the Hb to safer levels more quickly. If there is no response in 2–3 weeks, see the algorithm for failure of IDA to respond to Fe. The etiology of the Fe deficiency is usually apparent and measurements of serum Fe (⇓), TIBC (⇑), TS (⇓), and ferritin (⇓) are not usually necessary.

③ — Fe treatment is usually continued for at least 3–4 months to correct the anemia and rebuild Fe stores. Changes in diet (particularly a decrease in cow's milk intake) and management of blood loss, when appropriate, are necessary to prevent recurrence.

④ — Mediterranean, Asian or African ancestry is not universal, but is usually present. The Mentzer index (MCV/RBC) may be helpful to differentiate thalassemia minor. In IDA the index is generally >13, whereas in thalassemia trait it is usually <13.

⑤ — Hepatosplenomegaly, more severe anemia (typically Hb <9.0 g/dl, 1.4 mmol/l) and more severe hypochromia are consistent with β-thalassemia major or β-thalassemia intermedia, but are not expected in either α- or β-thalassemia trait. Hb levels can be as high as 10.0 g/dl (1.51 mmol/l) in Hb H disease. Normoblastemia, the presence of nucleated erythrocytes in peripheral blood, is prominent in severe forms of β-thalassemia. However, small numbers of normoblasts may be seen in severe anemia of any etiology.

⑥ — The anemia of chronic disease can be associated with any severe infection or inflammatory disorder. It is usually normocytic, but microcytosis occurs in 20–30% of patients. Anemia is usually fairly mild with Hb levels 2–3 g/dl (0.31–0.47 mmol/l) below expected normals for age. The combinations of a low serum iron and TIBC, with an elevated ferritin, are typical and help to differentiate it from IDA.

⑦ — Homozygous hemoglobin C or E disease, E-thalassemia and sickle thalassemia are associated with ⇓ MCV and prominent numbers of target erythrocytes. These are also seen in E trait, but without anemia. Rare unstable hemoglobins may be associated with microcytic anemia and the Hb electrophoresis may be normal; they are suspected with hemolysis of unidentified etiology. Hb stability studies can establish this diagnosis.

⑧ — Microcytic anemia in Pb poisoning is more often due to concomitant IDA and not the Pb poisoning itself; anemia is a late sign of Pb poisoning. Basophilic stippling is often but not consistently present.

⑨ — There are several rare etiologies of microcytosis. The hereditary sideroblastic anemias are a rare heterogenous group of disorders characterized by anemia, reticulocytopenia and abnormal patterns of iron deposition in marrow erythroblasts. Protein calorie malnutrition usually causes normocytic/normochromic anemia but it can cause microcytosis without IDA. There are a number of metabolic defects of Fe absorption and metabolism, but they are very rare.

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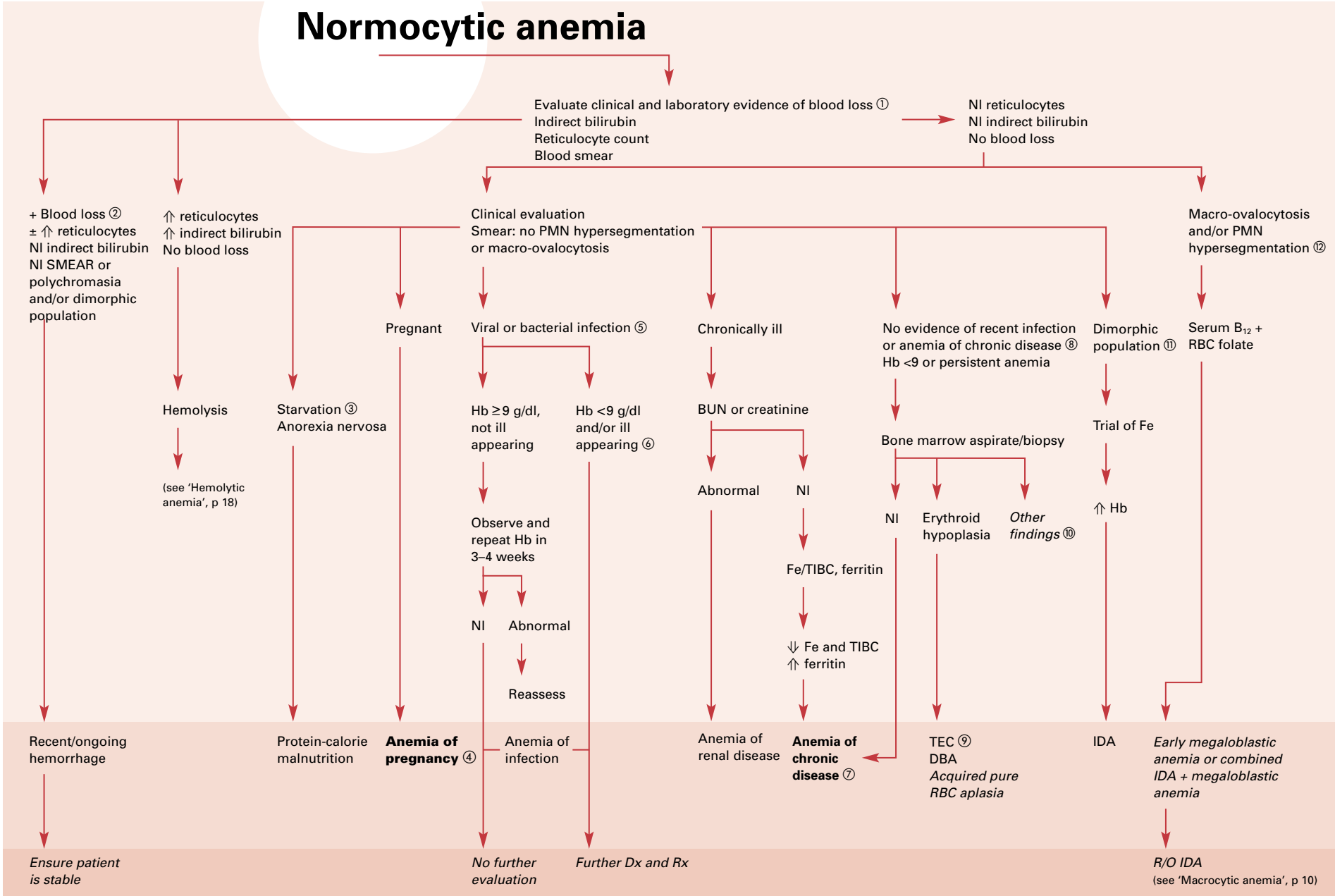
Normocytic anemia



① — Acute blood loss is usually obvious and most often due to epistaxis, hematemesis, hematochezia, hematuria, menorrhagia and trauma. Chronic GI blood loss may be occult and melena may not be recognized as significant; stools should be examined for occult blood. Consider blood sampling and postoperative losses. Typically, pallor is noted without icterus.

② — The reticulocytosis in response to hemorrhage is usually delayed 3–7 days after the onset of bleeding. Intercurrent infection or illness may also inhibit the reticulocyte response. Bilirubin should be normal (except in neonates with enclosed hemorrhage in whom it may be ⇑). Smear usually reveals polychromasia from the reticulocytosis, and a dimorphic population in early or partially treated iron deficiency anemia.

③ — Severe protein-calorie malnutrition is associated with normocytic anemia; 1/3 of patients with anorexia nervosa have normocytic anemia.

④ — Hb levels fall to as low as 10 g/dl (1.55 mmol/l) normally in pregnancy because of hemodilution. Lower values require investigation. Fluid overload in the absence of pregnancy can cause dilutional anemia, but this is usually clinically evident.

⑤ — The most common cause of anemia in children is viral and, less often, bacterial infection. If the anemia is mild (e.g. Hb ≥9.0 g/dl, 1.4 mmol/l) and the child is not very ill, observe the child and repeat the Hb in 2–4 weeks. It will then usually be normal and no further investigation will be necessary; if the anemia persists then reassessment should be undertaken to ensure a more serious diagnosis if not being missed. During active inflammation, the fall in Hb has been estimated at 13% per week.

⑥ — Infections such as bacterial septicemia (staphylococcal, streptococcal, pneumococcal), *Bartonella, Clostridia,* malaria, and HIV are often associated with severe normocytic anemia

⑦ — The anemia of chronic disease is common. Hemoglobin is usually 7–11 g/dl (1.09–1.7 mmol/l) and the MCV is normal in most patients. Endocrinologic disorders such as hypothyroidism can also cause anemia.

⑧ — If the anemia is mild (Hb 9–11, 1.4–1.7 mmol/l) it may be reasonable to observe the child since it might be due to an unrecognized viral illness. If the anemia is more severe or there are concerning clinical signs, a bone marrow aspirate and biopsy should be done. A concerning laboratory finding is myelophthisic anemia (leukoerythroblastosis) which usually results from bone marrow invasion; it presents with erythroblasts and immature WBCs, teardrop-shaped RBCs and giant platelets in peripheral blood.

⑨ — TEC is the most common cause of pure RBC aplasia in children. Other acquired etiologies are rare and usually occur in young adults and most have no recognized underlying disorder. Drug-induced RBC aplasia occurs with carbamazepine, phenytoin and valproate and usually resolves following discontinuation of the drug. Diamond-Blackfan anemia (DBA) is congenital pure RBC aplasia; although often macrocytic, it may be normocytic.

⑩ — Other rare diagnoses based on marrow findings include myelodysplastic syndromes, congenital dyserthyropoietic anemias and myelofibrosis.

⑪ — Particularly if the MCV is near the lower limit of normal, developing iron deficiency anemia should be considered. A dimorphic population of normal and hypochromic RBCs and an elevated RDW are usually evident and a trial of oral Fe is often diagnostic.

⑫ — Macro-ovalocytosis and PMN hypersegmentation (see *'Macrocytic anemia'*, p 10) may be evident before the development of macrocytosis in megaloblastic anemia. In addition, the combination of IDA with B_{12} and/or folate deficiency may remain normocytic; macro-ovalocytosis and hypersegmentation are still expected as is a high RDW reflecting marked anisocytosis (variation in cell size). The potential irreversible neurologic damage associated with B_{12} deficiency makes it critical to consider this diagnosis.

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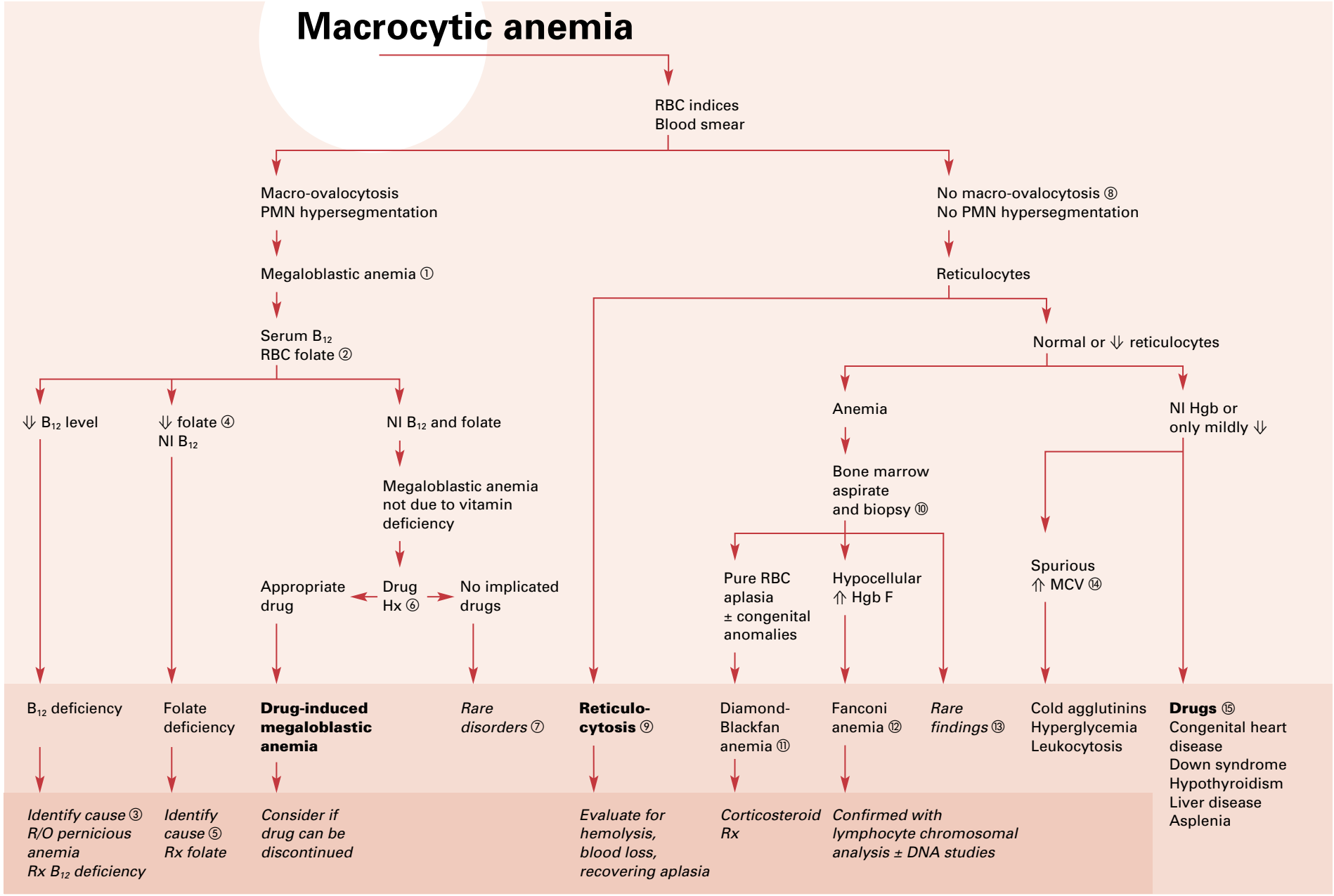
Macrocytic anemia



① — Megaloblastic anemia, most commonly due to B_{12} or folate deficiency, is the result of impaired DNA synthesis. It is critical to differentiate the megaloblastic anemias from the other etiologies of macrocytosis. Hypersegmented neutrophils (≥5% of PMNs with 5 nuclear lobes and ≥1% with 6 lobes) are found in 98% of patients with megaloblastic hematopoiesis. The combination of macro-ovalocytosis and neutrophil hypersegmentation has a specificity of 96–98% and a positive predictive value of 94% for either folate or B_{12} deficiency in studies in adults. In the absence of malnutrition, megaloblastic anemia is uncommon in children; no cases of folate or B_{12} deficiency were observed in 146 American children evaluated because of macrocytosis.

② — Serum folate reflects recent intake while RBC folate reflects longer term intake and is a more reliable indicator of folate deficiency. Serum B_{12} levels are usually diagnostic.

③ — B_{12} deficiency is most commonly caused by pernicious anemia, but may also be due to ileal disease, malabsorption, vegan diet, and fish tapeworm. The most common etiology in infancy may be selective malabsorption of cobalamin (Imerslund-Gräsbeck disease).

④ — It is critical to exclude B_{12} deficiency in megaloblastic patients because of its potential irreversible neurologic damage. Combined deficiency occurs, so even if folate levels are low B_{12} levels must be determined as well. Treatment of B_{12} deficiency with folate may correct the hematologic findings and the patient's improvement can mask the progression of neurologic disease. If the diagnosis is not certain, normal serum methylmalonic acid and total homocysteine levels effectively exclude B_{12} deficiency; a normal homocysteine alone suggests that it is not folate deficiency.

⑤ — Folate deficiency can be due to drugs (e.g. phenytoin, barbiturates, valproate, methotrexate, trimethoprim), malnutrition, malabsorption, diet of goat's milk, alcoholism, and increased cell turnover (hemolysis, pregnancy).

⑥ — Drug-induced macrocytic anemias are the most common etiology of macrocytosis in children in industrialized nations. The pathogenesis is not always clear, but it is likely due to megaloblastic changes and/or marrow injury. The drugs most commonly involved are chemotherapeutic agents (e.g. 6-mercaptopurine and hydroxyurea), but also anticonvulsants (most often carbamazepine, valproic acid, phenytoin, phenobarbital), zidovudine, immunosuppressive agents and sulfa drugs.

⑦ — Megaloblastic anemias unrelated to vitamin deficiencies or drugs are rare and may be congenital (deficiency of transcobalamin II or intrinsic factor, other metabolic defects or congenital dyserythropoietic anemia), or acquired (myelodysplastic syndrome, alcoholism). BMA and BMB may be necessary to exclude myelodysplastic syndrome.

⑧ — Even without macro-ovalocytosis and hypersegmentation, B_{12} (particularly important given its neurologic complications) and folate levels should be obtained if an obvious etiology for the macrocytosis is not identified.

⑨ — Reticulocytes are approximately 20% larger than mature RBCs so a substantially elevated reticulocyte count increases the overall MCV of an otherwise normocytic RBC population.

⑩ — Anemic children who have true macrocytic, non-megaloblastic anemia usually have diminished or abnormal erythropoiesis so both BMA and BMB are generally indicated.

⑪ — Diamond-Blackfan anemia is congenital RBC aplasia, which usually presents in the first 3 months of life. Most are macrocytic especially if diagnosed after the first months of life. Associated congenital malformations are common. Most patients require long-term corticosteroid therapy. TEC is not a macrocytic process unless recovery is occurring with a reticulocytosis.

⑫ — Fanconi anemia does not usually present with isolated anemia, but the macrocytosis often precedes other hematologic changes. Congenital anomalies are typical but are absent in approximately 25% of patients. Marrow hypoplasia is usually noted, but hyperplasia with dyserythropoiesis (disordered cell development) can be seen. Hb F is ⇑. The most utilized diagnostic finding is enhanced chromosomal breakages in peripheral blood lymphocytes stimulated in culture. Other rare bone marrow failure syndromes, such as dyskeratosis congenita, should be considered if Fanconi anemia is excluded.

⑬ — Other rare marrow disorders associated with macrocytosis include myelodysplasia, dyserythropoiesis and sideroblastic anemia. MDS is diagnosed on the basis of myelodysplastic changes in the marrow; the finding of a clonal chromosomal abnormality in a majority of patients is useful confirmation. Dyserythropoietic changes suggest the rare diagnosis of congenital dyserythropoietic anemia. Sideroblastic anemias demonstrate a ring of iron staining which surrounds the nucleus; some hereditary forms are associated with macrocytosis.

⑭ — Spurious macrocytosis is most often due to cold agglutinins which cause RBCs clumped together to be counted as a single cell; the same artifact decreases the RBC. Warming the sample normalizes the MCV. This cold agglutinin effect often occurs in the absence of hemolysis or anemia. Extreme hyperglycemia and leukocytosis occasionally cause spurious macrocytosis.

⑮ — A number of disorders, most associated with no or minimal anemia, can alter RBC size. Normal neonates are often mistakenly identified as macrocytic because the normal MCV of a full-term neonate is 98–118 fl. Drugs can cause isolated macrocytosis, including those that usually cause obvious megaloblastic changes. Congenital heart disease (usually cyanotic) and, independently, Down syndrome are also associated with macrocytosis; the mechanism by which this occurs is not well understood. Excessive membrane lipids can cause macrocytosis, usually without anemia, in hypothyroidism, liver disease and after splenectomy. In these instances, the RBCs have a larger surface area causing them to spread more widely on blood smears, but this may not be associated with an actual increase in measured volume (MCV).

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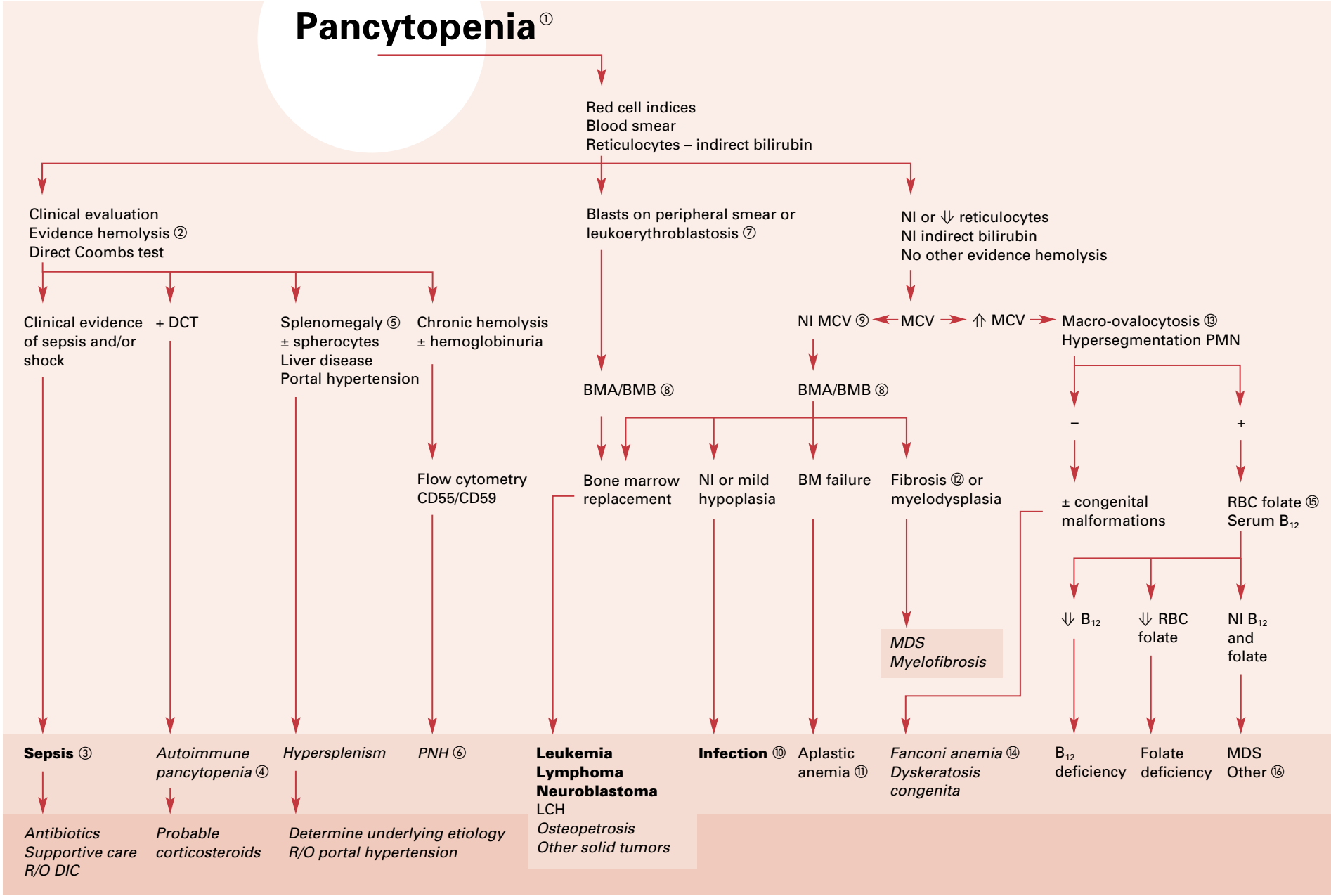
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NI indirect bilirubin
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Flow cytometry CD55/CD59
Bone marrow replacement
NI or mild hypoplasia
BM failure
Fibrosis ⑫ or myelodysplasia
± congenital malformations
RBC folate ⑮
Serum B_{12}
MDS
Myelofibrosis
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⇓ RBC folate
NI B_{12} and folate
Sepsis ③
Autoimmune pancytopenia ④
Hypersplenism
PNH ⑥
Leukemia
Lymphoma
Neuroblastoma
LCH
Osteopetrosis
Other solid tumors
Infection ⑩
Aplastic anemia ⑪
Fanconi anemia ⑭
Dyskeratosis congenita
B_{12} deficiency
Folate deficiency
MDS
Other ⑯
Antibiotics
Supportive care
R/O DIC
Probable corticosteroids
Determine underlying etiology
R/O portal hypertension

① — Pancytopenia consists of leukopenia, anemia and thrombocytopenia; if the WBC is normal, but the absolute neutrophil count is decreased (neutropenia), the patient should still be considered pancytopenic. More than 1/3 of the children with acute lymphoblastic anemia have a normal WBC, but most are neutropenic.

② — Evidence for hemolysis: indirect hyperbilirubinemia, reticulocytosis, abnormal smear (e.g., anisocytosis, RBC fragmentation, spherocytosis, elliptocytosis), ⇑ RDW (reflecting the variation in cell size with ⇑ numbers of larger reticulocytes and overall variation in cell size), ⇓ haptoglobulin, hemoglobinuria (if the hemolysis is intravascular), and ⇑ LDH (also ⇑ in many malignancies).

③ — Sepsis can cause pancytopenia due to both diminished production and/or increased destruction. DIC should be considered in critically ill children.

④ — Concomitant AIHA, ITP and autoimmune neutropenia occurs occasionally and the direct Coombs test is almost always positive. It may occur in isolation or in association with collagen vascular disorders, particularly SLE.

⑤ — Hypersplenism can result in mild-to-moderate (but rarely severe) pancytopenia from a combination of splenic sequestration and hemolytic anemia. Splenomegaly is usually prominent and its etiology is evident. Chronic liver disease and/or portal hypertension should be considered. Disorders such as cavernous transformation of the portal vein may present with only pancytopenia and/or splenomegaly.

⑥ — Paroxysmal nocturnal hemoglobinuria is a rare acquired clonal disorder which typically presents with chronic hemolytic anemia. It can also cause varying degrees of marrow aplasia so it should be considered in the child with pancytopenia and a reticulocytosis. The traditional screening tests (sucrose hemolysis test and Ham test) should be replaced by specific flow cytometric analysis for deficient CD55 or CD59.

⑦ — Blasts in peripheral blood are consistent with leukemia. Leukoerythroblastosis (myelophthisic anemia) is less common in children and usually results from bone marrow invasion. Anemia may be accompanied by several findings in peripheral blood, including erythroblasts (nucleated erythrocytes), more immature neutrophils, teardrop-shaped RBCs, and giant platelets. This is usually due to malignant replacement but is also caused by benign conditions such as osteopetrosis, storage disease, infection, myeloproliferative disorders, severe hemolytic disease, thalassemia major and hypoxia. Bone marrow examination should be performed.

⑧ — When examining the bone marrow, an aspirate is always done; in addition to more routine morphologic studies, including special stains, samples for chromosomal and flow cytometric analysis should be obtained. Unless a diagnosis of leukemia is strongly suspected, a bone marrow biopsy should also be done to provide information concerning cellularity, myelofibrosis, infiltrative processes and storage diseases.

⑨ — Bone marrow examination should be strongly considered in these children. If the pancytopenia is mild and consistent with a transient infection, marrow examination can be deferred.

⑩ — Many viral and bacterial illnesses cause pancytopenia, but the marrow is rarely aplastic and recovery usually coincides with resolution of the infection. Examples include EBV, CMV, HIV, brucellosis, tuberculosis, Q fever, and Legionaires disease.

⑪ — Aplastic anemia is idiopathic in approximately 3/4 of patients. Most others are drug- (chloramphenicol, gold compounds and non-steroidal anti-inflammatory agents most clearly implicated) or toxin-induced (most often benzene), related to infection (most often hepatitis not usually associated with a specific type), constitutional (Fanconi anemia, Shwachman-Diamond syndrome), and, very rarely, PNH.

⑫ — Rare findings include myelodysplasia or myelofibrosis. Myelodysplasia is an acquired clonal disorder of the bone marrow characterized by abnormal maturation of one or more hematopoietic cell lines. Chromosomal analysis of BMA is abnormal in 50–80%. Myelofibrosis is diagnosed by special staining of bone marrow biopsy specimens. It is very rare in children but when it occurs it is usually in toddlers with trisomy 21 and represents a form of acute megakaryoblastic leukemia.

⑬ — Pancytopenia is common in children with megaloblastic anemia. The simplest initial screen for megaloblastic anemia in the macrocytic patient is to review the peripheral smear. Hypersegmented neutrophils (≥5% of PMNs with 5 lobes and ≥1% with 6 lobes) are found in 98% of patients with megaloblastic anemias. The combination of macro-ovalocytosis and hypersegmentation has a specificity of 96–98% and the positive predictive value for either folate or B_{12} deficiency is ~94% in adult studies.

⑭ — Fanconi anemia is an autosomal-recessive disorder in which aplastic anemia develops later in the first decade. The MCV is often >100 fl even before anemia develops. Most patients have dysmorphic features which are present at birth. The hypersensitivity of chromosomes to diepoxybutane (DEB) establishes the diagnosis. Other rarer congenital aplastic anemias may be macrocytic, including dyskeratosis congenita.

⑮ — Serum B_{12} levels are generally reliable but assays of RBC folate are more accurate than serum levels.

⑯ — Megaloblastic anemias can occur in the absence of deficiencies of folate or B_{12} and include myelodysplasia, drug-induced changes (e.g. zidovudine, hydroxyurea), congenital dyserythropoietic anemia, and metabolic defects of folate or B_{12} metabolism (e.g. methylmalonic acidurias).

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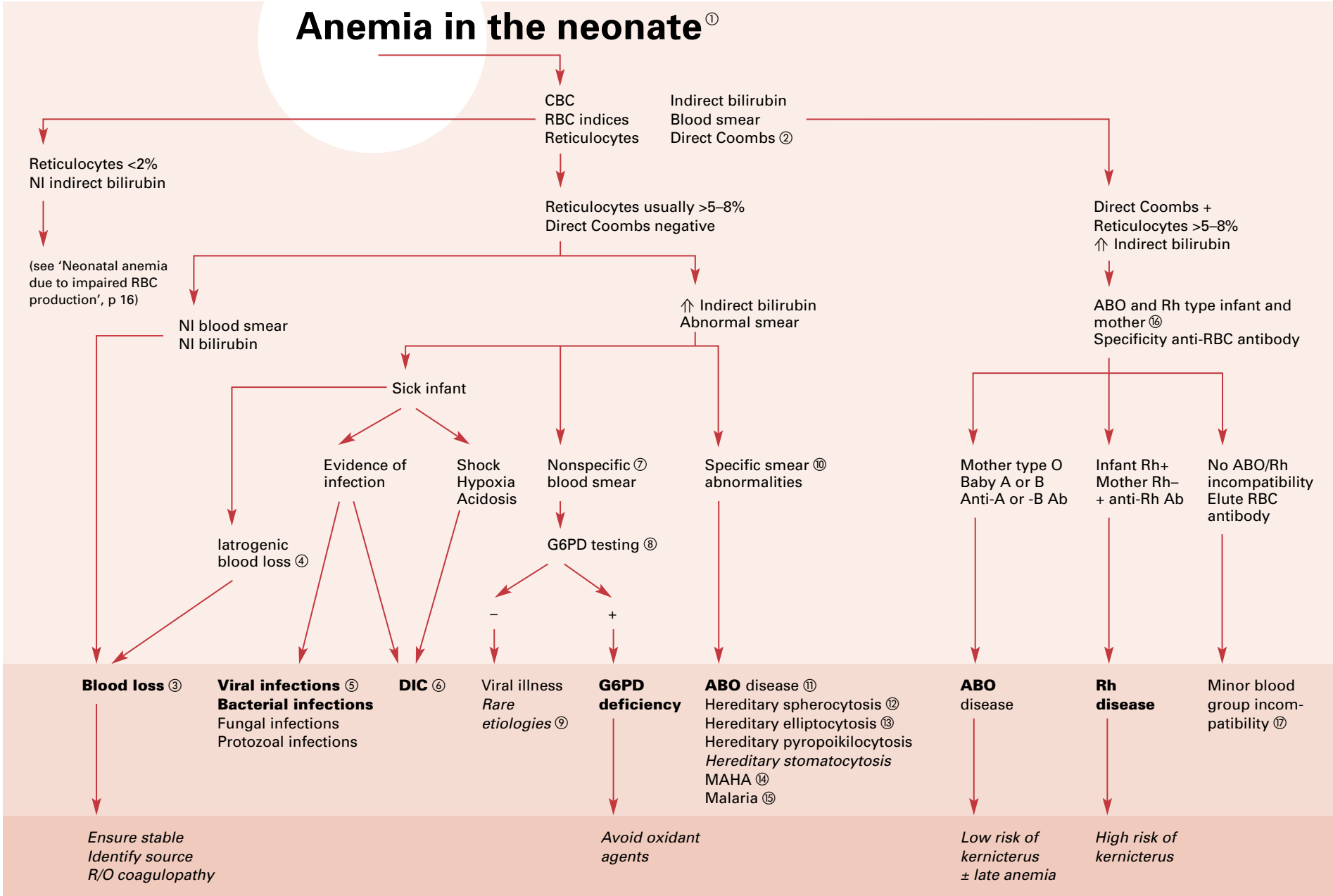
Anemia in the neonate ①



① — Neonatal pallor is a sign of asphyxia, shock, hypothermia and hypoglycemia as well as anemia. Pallor is usually apparent when the Hb is <7–8 g/dl (1.09–1.24 mmol/l). Neonatal anemia requires immediate investigation. Anemia at birth is usually due to hemorrhage or severe alloimmunization. Anemia manifesting in the first 2 days of life is often due to internal or external hemorrhage, while anemia after the first 48 h is usually hemolytic and associated with jaundice. When assessing whether a neonate is anemic, consider that capillary samples can average 3.5 g/dl (0.54 mmol/l) higher than venous samples. Hb also varies with age and with gestational age.

② — Reticulocyte counts vary from 3 to 7% of RBCs in the first 2 days of life, decreasing to 0–1% by 7 days. Most neonates with hemolysis have reticulocyte counts of 5–8% or higher. In the first few days of life, nucleated erythrocytes are normally seen in peripheral blood as are small numbers of spherocytes. As an indicator of hemolysis, indirect hyperbilirubinemia is limited by the frequency of hyperbilirubinemia in infants without hemolysis; however, hemolytic anemia in the neonate is almost always associated with a bilirubin level >10–12 mg/dl (171–180 µmol/l).

③ — Anemia unaccompanied by jaundice is usually due to hemorrhage in the first 24–72 hours of life. Ensure that the infant is not dangerously hypovolemic and that blood loss is not continuing. With acute blood loss, the Hb may not fall immediately, the MCV will be normal and a reticulocytosis is usually delayed for 3–7 days. Obstetrical complications cause anemia in approximately 1% of newborns; common etiologies include abruptio placentae, placenta previa, twin-twin transfusion, ruptured cord, emergency Caesarian section, cephalohematomas, and feto-maternal hemorrhage. The latter is very common and is most easily diagnosed using a Kleihauer-Betke test to identify fetal cells in maternal blood. Common etiologies of serious internal hemorrhage include intracranial or subgaleal, intra-abdominal (particularly hepatic or splenic rupture or hematomas), and pulmonary hemorrhage. Iatrogenic blood loss (phlebotomy, accidents with catheters) should be considered. The Apt test differentiates neonatal gastrointestinal hemorrhage from swallowed maternal blood. Bleeding disorders, such as vitamin K deficiency, DIC, neonatal alloimmune thrombocytopenia and hemophilia may be responsible for hemorrhage.

④ — Iatrogenic blood loss is a routine component of anemia in sick neonates.

⑤ — Viral and bacterial infections are often associated with hemolysis as well as impaired erythroid production. The hemolysis is usually a direct result of infection, but in very ill infants may also be a consequence of DIC. Infection is often associated with hepatosplenomegaly. One-half of the newborns with toxoplasmosis have anemia, which may be severe. CMV, rubella and herpes simplex are usually associated with mild anemia. Bacterial infection, whether complicated by DIC or not, is often associated with anemia. Malaria must be considered in endemic areas.

⑥ — Hemolytic anemia often accompanies neonatal asphyxia, regardless of etiology, and is often due to DIC. Shock, regardless of etiology, can trigger DIC.

⑦ — Anisocytosis, poikilocytosis, polychromasia, occasional spherocytes or fragmented erythrocytes, are findings which suggest hemolysis but are not specific.

⑧ — G6PD screening tests are useful, but false-negative results are common in mild variants during a reticulocytosis. Perform the more accurate G6PD assay or alternatively repeat the screen once the reticulocyte is normal. Note that 3% of the world population is G6PD deficient, with neonates most often affected in Mediterranean and Chinese populations.

⑨ — Rare etiologies of hemolytic anemia include other enzyme deficiencies (pyruvate kinase and glucose phosphate isomerase deficiencies most frequently), vitamin E deficiency, oxidizing agents, and metabolic disorders (e.g. galactosemia, amino acid disorders and lysosomal storage diseases).

⑩ — Specific smear abnormalities can establish a diagnosis. Frequent spherocytes suggest hereditary spherocytosis or ABO incompatibility. Hereditary elliptocytosis and hereditary stomatocytosis are easily recognized by a large number of these cells in peripheral blood. Hereditary pyropoikilocytosis presents with microcytosis and bizarrely shaped, fragmented or budded red cells as well as elliptocytes and spherocytes. Microangiopathic hemolytic anemias are identified by the predominant pattern of red cell fragmentation usually accompanied by thrombocytopenia. Malarial parasites may be seen on routine smears, but thick smears may be necessary when the intensity of parasitemia is low.

⑪ — The direct Coombs test may be negative in ABO incompatibility, but this diagnosis may be confirmed by eluting and identifying anti-A or anti-B antibodies from neonatal erythrocytes.

⑫ — Half of the newborns with hereditary spherocytosis are icteric and some may require exchange transfusion. Anemia is frequent in the neonate but does not predict disease severity later in life. The family history will be negative in 1/4–1/3 of families.

⑬ — There is a strong relationship between hereditary elliptocytosis and hereditary pyropoikilocytosis; 1/3 of pyropoikilocytosis patients have family members with typical hereditary elliptocytosis and many patients with pyropoikilocytosis proceed to develop typical HE.

⑭ — See the *'Consumptive coagulopathy'* algorithm, p 68.

⑮ — Malaria must be considered in endemic areas since transplacental infection rates are as high as 9%. Most neonates are asymptomatic, developing manifestations at 3–12 weeks of age. Progressive hemolytic anemia is common and severe disease can resemble erythroblastosis fetalis.

⑯ — Hemolysis due to blood group incompatibility is very common in the first day of life. Maternal blood type should be determined if the baby is Rh+ or type A or B. The antigen specificity of anti-RBC antibodies in the neonate's sera or on RBCs should be determined when incompatibility is present or when the direct Coombs test is positive.

⑰ — Clinically apparent minor blood group incompatibility is usually due to Kell, E or c antigen incompatibility. Elution of the specific antibody from the neonate's red cells allows identification of the specific antigen involved. Maternal autoimmune hemolytic anemia can cause transient neonatal hemolysis but this is rarely seen.

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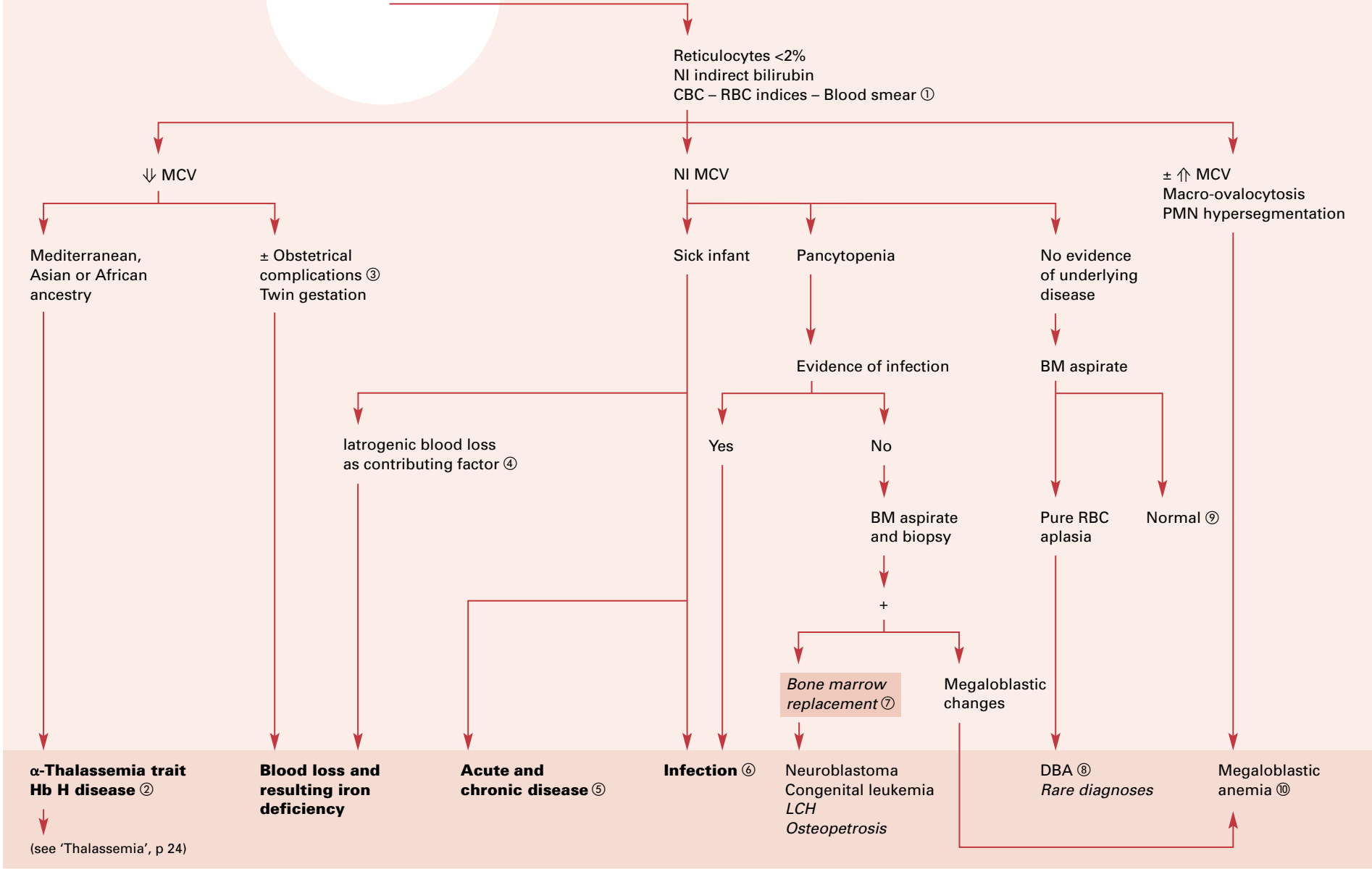
Neonatal anemia due to impaired RBC production



① — MCV normally varies with postnatal age as well as gestational age. The lower limit of normal in cord blood at term is 98, 95 in the first 3 days from capillary samples and 88 at 1 week of age.

② — α-Thalassemias manifest in the neonate because both Hb A and F contain α chains. Note that hydrops fetalis (which will be clinically obvious) and Hb H disease are almost never seen in people of African descent.

③ — Chronic blood loss, usually prenatal, causes iron deficiency and associated microcytosis. It is most often due to feto-maternal hemorrhage, twin-twin transfusions and placentae previa. The reticulocyte count is often decreased because iron deficiency inhibits reticulocyte production.

④ — Although iatrogenic and other types of blood loss are not disorders of impaired production, they often exacerbate anemia primarily due to impaired erythrocyte production. Blood loss can also cause Fe deficiency anemia.

⑤ — Critically ill neonates, usually with multiple medical problems, often develop anemia and reticulopenia. This is particularly common in infants with bronchopulmonary dysplasia.

⑥ — Viral, bacterial and other infections can impair erythroid production in the neonate; specific viral agents include rubella, cytomegalovirus, adenovirus and parvovirus.

⑦ — Bone marrow replacement is uncommon in the neonate. It is most often caused by neuroblastoma and congenital leukemia, but is also seen with Langerhans cell histiocytosis (which is particularly severe in neonates) and osteopetrosis. Aplastic anemia in the neonate is very rare; most forms of hereditary aplastic anemia, such as Fancon's anemia, present later in life.

⑧ — With no evident etiology for more severe or persistent anemia, Diamond-Blackfan anemia (congenital hypoplastic anemia) should be considered. Bone marrow aspirate reveals virtual absence of erythroid precursors. Other forms of hypoplastic anemia in neonates are rare and include drug-induced RBC aplasia, Aase syndrome (associated with skeletal anomalies), Pearson's syndrome (associated with hypoplastic sideroblastic anemia), and congenital dyserythropoietic anemia.

⑨ — Ill neonates may have persistent anemia without a recognized etiology and a normal bone marrow. Most often these are ill neonates with multiple and persistent medical problems.

⑩ — Megaloblastic anemia is rare in the newborn. Initially, macrocytosis, then anemia, and finally pancytopenia develops. B_{12} deficiency can be seen in breast-fed infants of vegan B_{12}-deficient mothers or infants with GI abnormalities such as necrotizing enterocolitis or short gut syndrome. Folate deficiency is seen in infants receiving goat's milk or milk that has been boiled, and in those with malabsorption. A number of rare metabolic defects, including transcobalamin II deficiency and orotic aciduria, can cause megaloblastic anemia at birth or soon after. Macrocytosis is often not evident because of the relatively high normal MCV in newborns.

Selected reading

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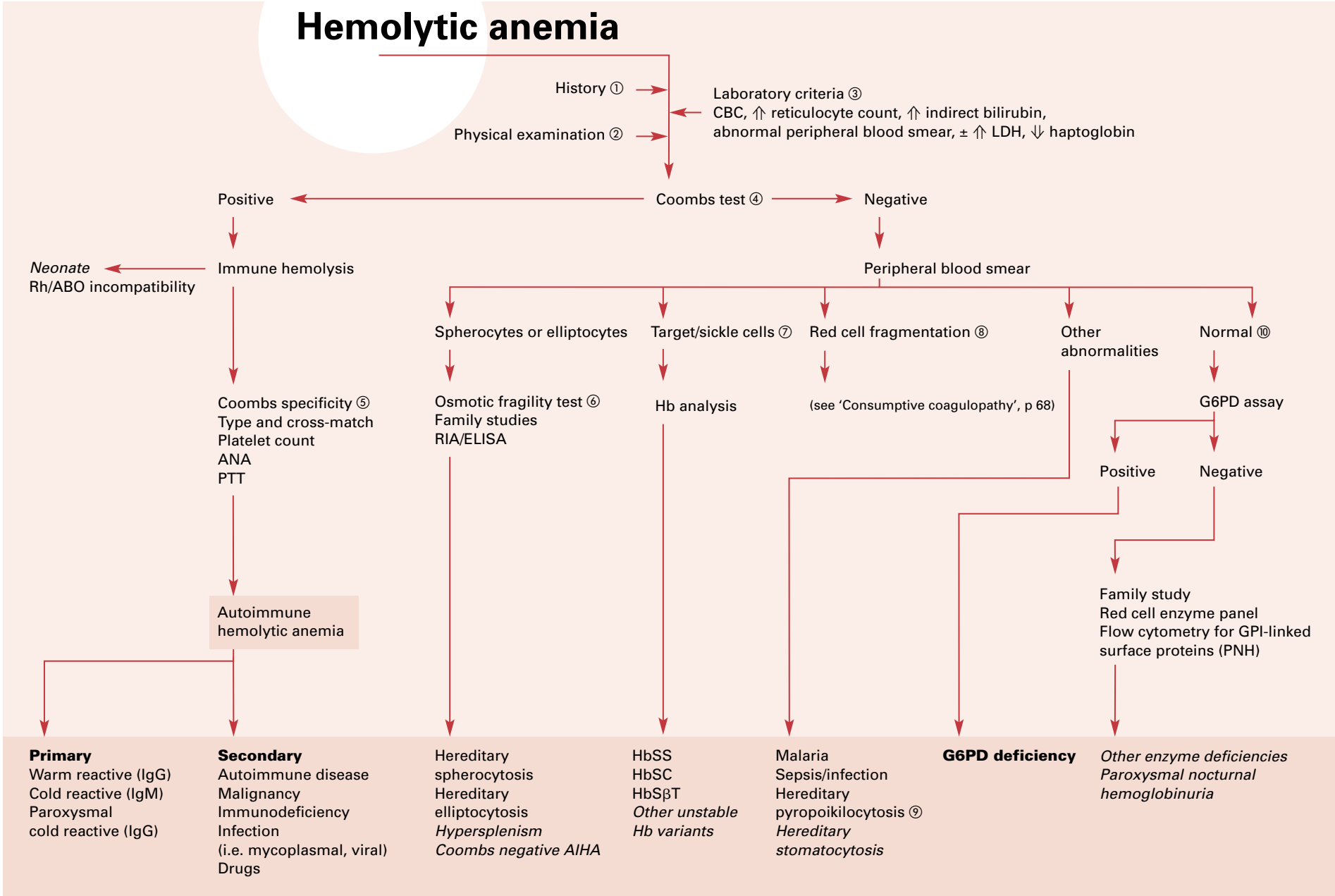
Hemolytic anemia



① — Symptoms that suggest severe hemolysis include headache, dizziness, syncope, fever, chills, dark urine (see on *'Hemoglobinuria'*, p 20) and abdominal/back pain. Possible precipitating factors include infection, medications, and foods (e.g. fava beans in G6PD deficiency). Past medical history should inquire about jaundice as a neonate or later. A history of recurrent infections, arthritis, rash, mouth ulcers or thyroid disease suggests autoimmune hemolysis. Family history should include ancestry (African, Mediterranean, or Arab ancestry suggests G6PD deficiency [mainly but not exclusively in males] or sickle cell disease) and address anemia, jaundice, splenectomy or unexplained gallstones (the latter especially in the young).

② — Clinical signs of anemia are dependent on Hb and cardiovascular dynamics: pallor, tachycardia, tachypnea, hypotension, or shock. Note fever as a sign for intravascular hemolysis, acute infection or autoimmune disease. Growth retardation suggests a longstanding anemia or autoimmune disease. Splenomegaly can be a cause or consequence of hemolytic anemia and petechiae or bruising are signs of coagulopathy or thrombocytopenia.

③ — CBC: A normal Hb does not exclude hemolysis. An increased reticulocyte count (ideally corrected for variation in RBC count) suggests hemolysis, but a low or normal reticulocyte count occurs when a hypoplastic crisis complicates hemolytic anemia. Microcytosis can be a sign of hemoglobinopathy or coexistent iron deficiency. Other criteria for hemolysis include elevated indirect bilirubin, decreased haptoglobin, free hemoglobin (acute/severe hemolytic anemia), and increased LDH (which is not very specific).

④ — Perform both direct and indirect Coombs tests. Direct Coombs test detects antibodies on the red cell surface, whereas indirect Coombs test identifies anti-erythrocyte antibodies in serum. Coombs negative autoimmune hemolytic anemia occurs, but is rare in children.

⑤ — Determine thermal amplitude (warm [23°C] vs. cold [4/10°C]), antigen specificity of the antibody and whether IgG, C3 or both are present on red cells. These tests differentiate warm-reactive (mostly IgG) from cold-reactive autoantibodies (mostly IgM, the exception being paroxysmal cold hemoglobinuria). Knowing the antigen specificity will help choosing a safe blood product. Attempt to find compatible units of packed RBCs, but avoid transfusion if possible. Most cases of autoimmune hemolytic anemia in childhood are idiopathic or related to infection, and are transient. Concomitant thrombocytopenia, neutropenia, prolonged PTT, or positive ANA suggest underlying autoimmune or other systemic disease, and in these patients the autoimmune hemolytic anemia is much more likely to be chronic.

⑥ — Spherocytes or elliptocytes occur in many clinical settings. Hereditary spherocytosis and elliptocytosis are usually autosomal-dominant and are common. Therefore, obtain blood smears from family members and look for splenomegaly. In hereditary spherocytosis, parents are normal in 5–10% of cases so that these patients are considered to have new mutations. In about 20% of cases both parents are clinically normal but have slight laboratory abnormalities that may suggest a carrier state as in autosomal-recessive diseases. Enhanced osmotic fragility usually confirms the diagnosis of hereditary spherocytosis. Membrane protein studies are helpful in selected cases. Coombs negative autoimmune hemolytic anemia can also cause spherocytosis and a pathological osmotic fragility; use RIA/ELISA to look for anti-erythrocyte antibodies if there is reason to suspect the diagnosis of AIHA. With hereditary elliptocytosis, the diagnosis is usually made simply by the presence of large numbers of elliptocytes on smear. The majority of patients are asymptomatic.

⑦ — Obtain a quantitative Hb analysis (electrophoresis) and, if necessary, DNA analysis. This should identify a hemoglobinopathy such as sickle cell anemia and its related diseases or other unstable Hb variants such as Hb Köln causing inclusion body anemia.

⑧ — Red cell fragmentation suggests a microangiopathic hemolytic process. Consider DIC or HUS in the acutely ill child, among other diagnoses. (see *'Consumptive coagulopathy'*). History/physical examination may identify a cardiac prosthesis as a cause of hemolysis.

⑨ — A variety of abnormalities on peripheral blood smear may lead to a diagnosis: malarial parasites, the classic fish mouth stomatocytes of hereditary stomatocytosis, the irregular fragments of pyropoikilocytosis, and findings of infection (toxic granulation, Döhle bodies, vacuolization, visible bacteria).

⑩ — Obtain G6PD testing, noting that screening tests can produce false-negative results in milder variants during a reticulocytosis. If the G6PD testing is negative, consider red cell enzyme panel to look for other enzyme deficiencies. A rare cause for hemolysis in childhood may be paroxysmal nocturnal hemoglobinuria (PNH), a clonal abnormality of a hematopoietic stem cell, characterized by a membrane protein defect that renders red blood cells susceptible to damage by serum complement. Diagnosis can be made by flow cytometry for GPI-linked surface proteins (such as CD 55/59) on erythrocytes and granulocytes.

Selected reading

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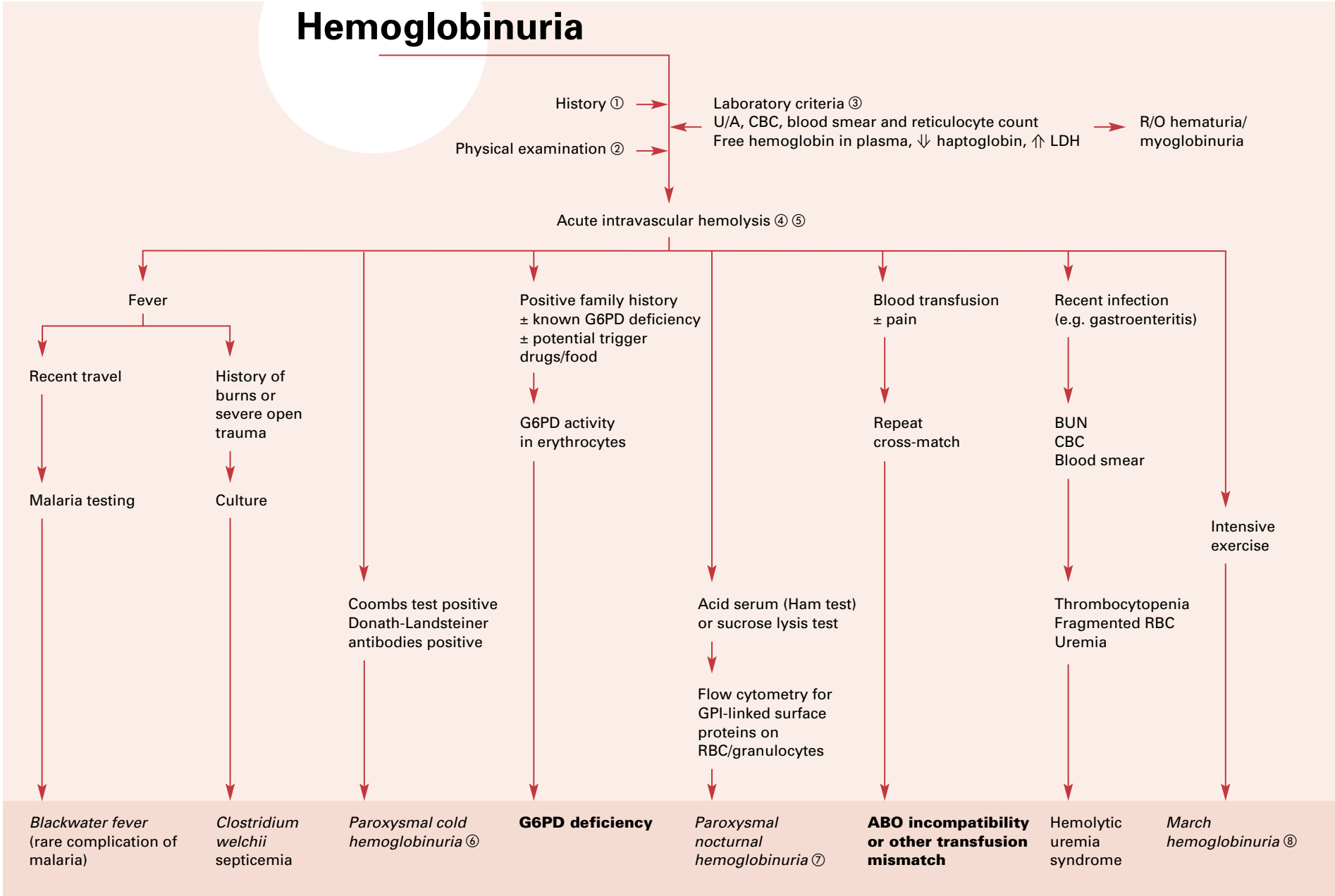
Hemoglobinuria



① — Note past medical and family history of hemolytic anemia, especially G6PD deficiency. Ask about potential trigger such as drugs, food, and recent travel (particularly to areas endemic for malaria). In cases with severe open trauma or burns, *Clostridium welchii* septicemia may cause acute hemolysis. Prior transfusion followed by abdominal pain and hemoglobinuria suggests a transfusion reaction. Consider hemolytic uremic syndrome in an acutely ill child with a history of recent gastroenteritis.

② — Look for clinical signs of anemia such as pallor, tachycardia/tachypnea, hypotension or shock. Note fever as a sign of intravascular hemolysis or acute infection.

③ — Hemoglobinuria occurs when the renal threshold for urinary excretion of Hb of approximately 150 mg/dl (0.023 mmol/l) is exceeded. Differentiate hematuria, and myoglobinuria from hemoglobinuria: urine test strips for Hb will be positive for all three. In hematuria, the color of centrifuged urine is normally clear and microscopic examination of unspun urine shows red blood cells. In myoglobinuria and hemoglobinuria, spun urine remains red. Myoglobinuria is excluded immunochemically. Additionally, in hemoglobinuria free Hb can be measured and even visually observed in plasma or serum.

④ — If acute intravascular hemolysis is identified, look for the underlying disease as discussed under note 1 above (and see *'Hemolytic anemia'*, p 18).

⑤ — Beware of renal failure as a complication of hemoglobinuria. The mechanism for acute renal failure in hemoglobinuria is not completely understood. The following could be involved: (1) Intranephronal obstruction resulting from precipitation or polymerization of the globin portion of Hb with acidic mucoproteins. (2) Renal ischemia due to concomitant release of vasoconstrictive substances. (3) Direct nephrotoxicity of breakdown products such as ferrihemate resulting in tubular necrosis. As prophylactic measures use forced diuresis and alkalinization of urine to pH >7.0 using i.v. sodium bicarbonate. In prolonged oliguria/anuria from acute renal failure, peritoneal or hemodialysis may be needed.

⑥ — Paroxysmal cold hemoglobinuria (PCH) is a form of primary autoimmune hemolytic anemia characterized by cold reactive anti-erythrocyte autoantibodies of the IgG subtype (Donath-Landsteiner antibodies). This class of antibodies binds the polysaccharide P autoantigen on RBC surfaces and fixes complement at 4°C. On warming to 37°C, the complement is activated and hemolysis induced. PCH should be considered if the patient has hemoglobinuria and C3 alone is present on the RBC. Children may develop PCH after a viral-like illness.

⑦ — A rare cause for hemolysis in childhood is paroxysmal nocturnal hemoglobinuria (PNH), a clonal abnormality of the hematopoietic stem cell. It is characterized by a membrane protein that renders red blood cells susceptible to damage by serum complement. Classically, patients have intermittent episodes of dark urine, most commonly in the morning.

⑧ — Hemoglobinuria can occur following strenuous physical exertion such as running on hard surfaces or after repeated blows to the hands from karate exercises. This phenomenon has been termed march hemoglobinuria and is caused by physical injury sustained by RBC in the affected blood vessels.

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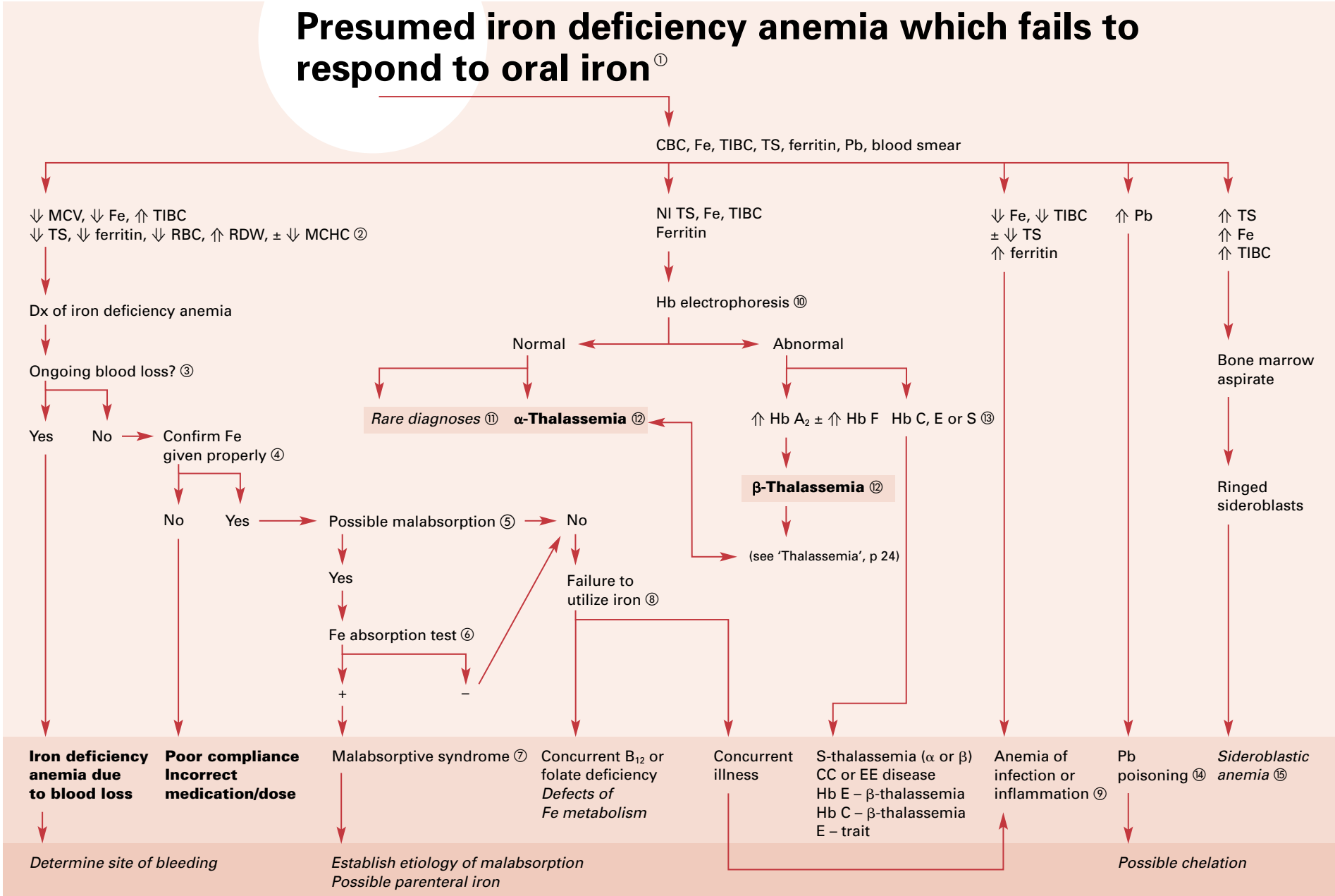
Presumed iron deficiency anemia which fails to respond to oral iron ①



① — Oral Fe therapy is 3 mg/kg/day of elemental Fe (maximum 200 mg) in the form of ferrous sulfate divided t.i.d. Doses up to 6 mg/kg/day of elemental iron (30 mg/kg/day of ferrous sulfate) may maximize the speed of response if the IDA is severe. A reticulocytosis is usually noted within 3–7 days and an increase in hemoglobin should be evident within 2–3 weeks.

② — These are the typical findings of IDA. However, false-negative and -positive results are frequent with these studies particularly in mild IDA. TS is the percentage of saturation of transferrin (TIBC) with Fe. The serum Fe and TIBC should be measured in the morning because of the diurnal variation in serum Fe. The blood smear demonstrates microcytosis, anisocytosis and mild ovalocytosis.

③ — Ongoing loss of blood (and therefore Fe) can result in failure to respond to oral Fe. Losses are most commonly due to gastrointestinal bleeding, menorrhagia, epistaxis, and in tropical areas, hookworm. Consider phlebotomy and blood donation losses when appropriate. Idiopathic pulmonary hemosiderosis is rare, but should be considered with chronic pulmonary symptoms.

④ — Review type of Fe given, dosage and interval, and if administered properly or at all. Stools often turn black during Fe replacement, but melena should be excluded by testing for occult blood. Fe therapy does not result in false-positive tests for occult blood. The Afifi test can be used to document the presence of Fe in the stools of patients who are actually taking Fe.

⑤ — Consider clues to an underlying malabsorptive state; diarrhea, bulky or fatty stools, failure to thrive, and increased gastric pH which inhibits Fe absorption (e.g. antacids, blocking agents).

⑥ — This study can document the failure of Fe absorption. Use ferrous sulfate in a dose of 10 mg/kg p.o., measuring serum Fe immediately before and 2 h later. The average increase in serum Fe is 274 µg/dl (49 µmol/l); an increase of <100 µg/dl (18 µmol/l) suggests malabsorption.

⑦ — Failure to absorb Fe is usually due to an underlying malabsorptive syndrome and further evaluation is indicated. IDA itself may impair intestinal absorption of Fe in some patients and may necessitate parenteral Fe for correction.

⑧ — Concurrent acute or chronic illness or vitamin deficiency (e.g. B_{12} or folate) may impair a response to Fe in IDA. Metabolic defects in Fe metabolism can impair Fe utilization, but are very rare.

⑨ — The clinical presentation is consistent with an underlying acute or chronic illness. The classic findings of the anemia of chronic disease are ⇓ Fe as found in IDA, but it is differentiated by ⇓ TIBC and ⇑ ferritin. Microcytosis occurs in 20–30% of patients. Hb rarely falls below 7 g/dl (1.09 mmol/l).

⑩ — Obtain routine Hb electrophoresis and quantitative assays of Hb A_2 and F. The quantitative assays are necessary for the diagnosis of β-thalassemia as their measurement by routine Hb electrophoresis is inaccurate.

⑪ — Other diagnoses are rare and include protein calorie malnutrition, congenital dyserythropoietic anemias and metabolic defects of Fe metabolism.

⑫ — Thalassemia minor is commonly confused with IDA. In thalassemia minor the RBC count is Nl or ⇑, RDW is Nl or only slightly ⇑ and Hb is ≥9.0 g/dl (1.4 mmol/l). In IDA there is ⇓ RBC, ⇑ RDW, and Hb often <9 g/dl (1.4 mmol/l). This may not be valid for more severe forms of thalassemia.

⑬ — MCV is decreased in hemoglobin CC disease, hemoglobin EE disease, E-β-thalassemia, C-β-thalassemia and may be decreased in either S-β-thalassemia or S-α-thalassemia. Individuals with E trait are microcytic but not anemic. Rare unstable hemoglobins may be associated with microcytic anemia and routine Hb electrophoresis may be normal; they are suspected with hemolysis of unidentified etiology. Hb stability studies are diagnostic.

⑭ — Pb poisoning itself does not usually cause a microcytic anemia unless it is severe. However, it is often associated with IDA (in part because of the pica, which is a complication of IDA).

⑮ — Sideroblastic anemias are a very rare heterogenous group of acquired and congenital disorders characterized by anemia, reticulocytopenia and abnormal patterns of iron deposition in marrow erythroblasts.

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Thalassemia

History ①
Physical examination ②
Laboratory criteria: ③
CBC: hypochromic microcytic anemia
Target cells on blood smear

Age of manifestation, clinical presentation, other cause of anemia excluded → (see 'Microcytic anemia', p 6)

Hb analysis ④

	α-Thalassemia			β-Thalassemia		
Clinical	Intrauterine death ⑤ Stillborn Hydrops fetalis	Neonatal anemia ⑥ Signs of hemolysis	Mild anemia or normal ⑦	Severe anemia in late infancy ⑧	Anemia beyond infancy ⑨	Mild, asymptomatic anemia
Hb analysis	No HbA/HbF Hb Barts (γ^4) 80–90% Hb Portland ($\zeta^2\gamma^2$)	Hb Barts 20–30% In later childhood, HbH (β^4) 4–20%	Neonate: Hb Barts 5–10% or normal Childhood: normal	No or ⇓⇓⇓ HbA HbF 90%	⇑⇑ HbF ⇑ HbA_2 ⇓ HbA	⇑ HbA_2 +/– ⇑ HbF
Genotype	α-globin gene: ––/––	α-globin gene: α–/––	α-globin gene: α–/α–, αα/––, or αα/α–	β-globin gene: β^0/β^0	β-globin gene: β^+/β^+ β^0/β (dominant) β^0/β + α-globin gene triplication β^0/β^0 + HPFH mutation or β-thalassemia $\delta\beta^0/\beta^0$ or β^0/β^{+-} + α-Thalassemia trait	β-globin gene: heterozgote β^+– or β^0-mutation
	α-Thalassemia major	HbH disease	**α-Thalassemia minor**	β-Thalassemia major	β-Thalassemia intermedia	**β-Thalassemia minor**
Therapy	*Prenatal transfusion ⑩* *Regular transfusion* *Iron elimination therapy* *BMT* *Family studies and counseling ⑪*	*Transfusion in hemolytic/aplastic crisis ± splenectomy* *Folic acid* *Family studies and counseling ⑪*	*Family studies and counseling ⑪*	*Regular transfusion ⑩* *Iron elimination therapy* *BMT* *Family studies and counseling ⑪*	*No or irregular transfusion ± Iron elimination therapy* *? Splenectomy* *Family studies and counseling ⑪*	*Family studies and counseling ⑪*

① — Consider age of presentation: patients with α-thalassemia major are symptomatic in the fetal or neonatal period, whereas patients with β-thalassemia usually develop symptoms in late infancy when fetal hemoglobin decreases and lack of HbA becomes apparent. Moderate to severe anemia in toddlers might be due to β-thalassemia intermedia. Ask for patients' ethnic origin, as the thalassemias are common in South East Asia, Mediterranean, Middle East and North/West Africa. Note positive family history especially for 'iron deficiency' that fails to respond to iron. The thalassemias are usually autosomal-recessive disorders.

② — Note signs of anemia (e.g. pallor, tachycardia, and tachypnea) and extramedullary erythropoiesis (e.g. hepatosplenomegaly). Patients with thalassemia major or thalassemia intermedia who are insufficiently transfused demonstrate typical bone deformities due to marrow hyperplasia.

③ — Perform a CBC and a blood smear. Most forms of thalassemia are associated with a hypochromic microcytic anemia of varying severity. Target cells, anisocytosis and poikilocytosis are seen in the peripheral blood smear. Exclude other causes of microcytic anemia such as iron deficiency. See the algorithms on (1) microcytic anemia, and (2) presumed iron deficiency anemia that fails to respond to iron.

④ — Diagnosis can usually be made clinically in combination with CBC and Hb analysis (Hb electrophoresis). In α- and β-thalassemia major, HbA is absent or severely decreased. In α-thalassemia major and HbH disease, α-globin deficiency leads to decreased (or absent) HbF ($\alpha_2\gamma_2$) and HbA formation ($\alpha_2\beta_2$). Excess γ- and β-globin chains form Hb Barts (γ^4) and HbH (β^4), respectively. These γ- and β-globin tetramers precipitate and thus cause hemolysis. In the neonate, α-thalassemia minor can be identified by the presence of Hb Barts, but in later childhood Hb analysis is usually normal. In β-thalassemia major, fetal hemoglobin is increased to >90%. In β-thalassemia intermedia, fetal hemoglobin and HbA_2 are also increased whereas HbA is moderately decreased. In β-thalassemia minor, HbA_2 is characteristically increased to 3.5–6%. HbF levels are variable and often slightly increased.

⑤ — The gene for α-globin on chromosome 16 is duplicated so there are normally 4 α-globin genes. α-Thalassemia major occurs when all 4 α-globin genes are deleted (––/––). In contrast to β-thalassemia, 95% of the known molecular defects of α-thalassemia are caused by deletions of DNA (deletional α-thalassemia). Deletion of 4 α-globin genes is usually fatal leading to intrauterine death or a stillborn (Hb Barts hydrops fetalis syndrome). There also are non-deletional forms of α-thalassemia due to point mutations. At birth, unexpected hemoglobins occur in the absence of α chains; Hb Barts is absent during normal fetal development, and Hb Portland (2 ζ chains and 2 γ chains) normally occurs only in early embryonic development.

⑥ — HbH disease is a chronic hemolytic disorder. HbH is found in small amounts as β chain synthesis increases following birth. Clinical severity is dependent on genotype. Classically, 3 of the 4 α-globin genes are deleted (α–/––). Clinically, this is usually mild (Hb range 7–12 g/dl [1.09–1.86 mmol/l]). In contrast, compound heterozygosity for deletional α-thalassemia and non-deletional α-thalassemia involving the α_2-globin gene (––/$\alpha^T\alpha$; α^T noting a non-deletional mutated gene) causes more severe disease that might include transfusion dependency. The frequency of α-thalassemias depends on ethnic origin. In people of African descent, homozygous α^+-thalassemia (–α/–α) is frequent (1.9%), but since the thalassemic genes are almost always paired with a normal gene on each chromosome, more severe disease (HbH disease and Hb Barts hydrops fetalis syndrome which require α ––/ conformation) is very rare. In Southeast Asia, all genetic variants are found. In Thailand, 10% of the population are heterozygous for α^+-thalassemia (–α/αα) and 10% for α^0-thalassemia (––/αα). Because of these gene frequencies, 1% of the population suffer from HbH disease (––/–α) and Hb Barts hydrops fetalis syndrome (––/––) occurs in 1:2,000 newborns. DNA analysis may be required for diagnosis.

⑦ — α-Thalassemia trait can result from the α-cis (––/αα), or trans (α–/α–) conformation. These children are asymptomatic but have a mild microcytic anemia. Mild elevations of Hb Barts are noted in the neonate but soon after the hemoglobin analysis is normal: HbH is not found. Individuals with a single gene deletion (–α/αα) are hematologically normal but may have up to 1–2% Hb Barts in the neonatal period.

⑧ — β-Thalassemia major is due to severe β-globin deficiency. The expression of the β-globin gene is inactivated in the β^0 form or expression is severely decreased in the β^+ form so that there is no or minimal HbA formation. Patients usually become symptomatic when HbF levels fall in late infancy and patients become dependent on transfusions. The frequency of heterozygous β-thalassemia also depends on ethnic origin. In Mediterranean countries the gene frequency ranges from 2 to 20%.

⑨ — β-Thalassemia intermedia is an ill-defined clinical form of β-thalassemia which varies in severity from an asymptomatic condition identified incidentally to relatively severe anemia requiring occasional transfusions. It results from a wide variety of distinct genotypes, including homozygosity for mild β^+-thalassemia, high persistent levels of fetal Hb, co-inheritance of α-thalassemia, and rare dominant forms of β-thalassemia. These patients may develop extramedullary erythropoiesis. Age of diagnosis, usually in the second year of life, is later than in β-thalassemia major.

⑩ — Patients with α- or β-thalassemia major are regularly transfusion dependent. For α-thalassemia major, early prenatal diagnosis is essential to institute prenatal transfusion therapy to allow survival. In both α- and β-thalassemia major, essential transfusions and increased iron resorption result in secondary hemosiderosis leading to dilatative cardiomyopathy, liver cirrhosis and extensive endocrine disorders. Therefore, iron chelation therapy with parenterally administered deferoxamine is important for increased life expectancy. Deferriprone, which can be given orally, is used in patients who fail to comply with deferoxamine. Matched related (unrelated) bone marrow transplantation is the only curative form of therapy.

⑪ — Family studies are important to identify couples at risk for offspring with thalassemia major and to allow for prenatal diagnosis when appropriate.

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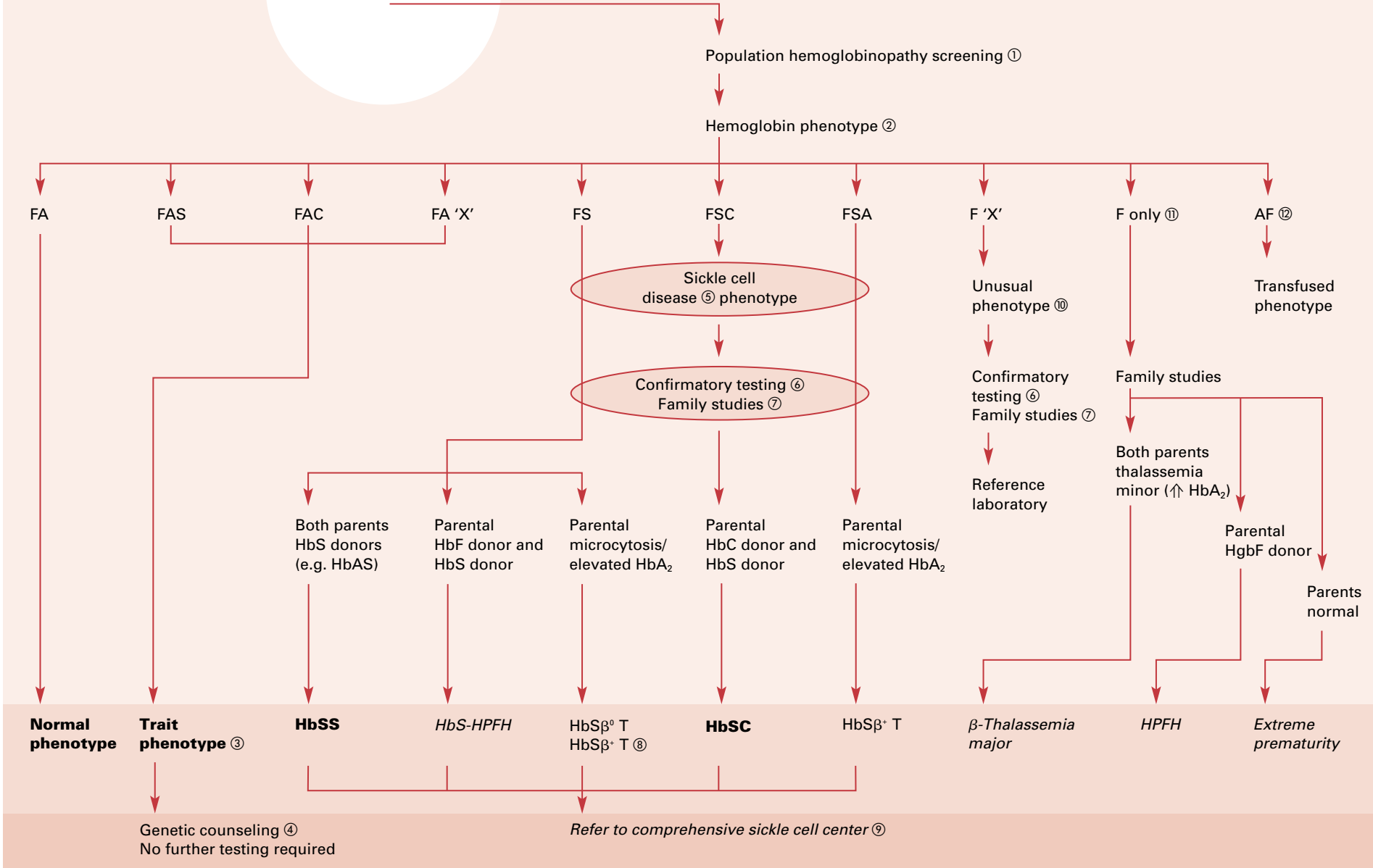
Newborn screening for hemoglobinopathies



① — This is usually combined with other newborn screening using capillary blood blotted onto filter paper, and identifies a group of autosomally co-dominant inherited disorders of β-globin. Identification of homozygous β^s (HbSS or sickle cell anemia) at birth allows comprehensive clinical care and decreases mortality. Compound heterozygotes where β^s from one parent is co-inherited with another interacting β-globin variant such as C, D_{Punjab}, E or O_{Arab} have similar but often less severe clinical problems. Compound heterozygotes of β^s and β-thalassemia (HbSβ^0T or HbSβ^+T) can be as clinically severe as HbSS depending on the severity of the β-thalassemia variant. Targeted screening of high-risk ethnic groups is more cost-effective than no screening, but universal population screening is recommended for most states in USA. Screening programs are also being used in Brazil, parts of France, the UK and a pilot program in Spain. Practitioners should be familiar with the screening programs in their area.

② — Hemoglobin phenotype nomenclature follows a standardized format in which the order of the letters indicates the relative quantity of hemoglobin present (i.e. HbFSA indicates HbF>HbS>HbA in the sample). Therefore, HbFSA (due to HbSβ^+T) and HbFAS (due to sickle cell trait) are not equivalent, and have significantly different implications for treatment and follow-up. HbF is the predominant hemoglobin of gestational life; shortly after birth the level decreases steadily to <2% by 12 months of age in normal infants.

③ — At birth, trait phenotypes are dominated by HbF, followed by HbA with either HbS, C or other β-globin variant (variously reported as 'X' for unknown, 'V' for variant, or 'U' for unknown). These require no specific hematological follow-up, but family studies with genetic counseling can clarify the risks of disease in future children, especially in populations with high carrier rates. Certain atypical results may require further elucidation with the aid of hemoglobin reference laboratories.

④ — Trait phenotypes have no significant medical concerns but have the potential to result in affected offspring. The 'X' refers to unknown or variant β-globins (e.g. D, E, G). These may need further elucidation by more specialized techniques (high-performance liquid chromatography, or β-globin sequencing) by hemoglobin reference laboratories.

⑤ — Identification of a disease phenotype is the primary goal of newborn hemoglobinopathy screening. These phenotypes can be divided into severe and less severe sickle hemoglobinopathies. The severe phenotypes, including HbSS, HbSβ^0 thalassemia, $HbSO_{Arab}$, require medical and preventive care. The less severe phenotypes may include compound heterozygotes for HbS and non-sickle hemoglobinopathies (β^+-thalassemia, HbC, HPFH) and require determination of the precise genotype and subsequent follow-up dictated by the exact hemoglobinopathy identified. Hemoglobin reference laboratories, in addition to family studies, may be required to elucidate the abnormality.

⑥ — High HbF levels of prematurity (<34 weeks) and exogenous HbA at the time of newborn screen (transfusion, materno-fetal transfusion) can mask disorders such as HbSS. Screening methods vary in sensitivity and accuracy. Sickle solubility tests are inadequately sensitive to the small quantities of HbS present at birth and cannot distinguish sickle cell disease from trait. Cellulose acetate electrophoresis is inexpensive, and widely used despite low sensitivity if HbS <10%; iso-electric focusing (IEF) gives improved resolution and is better suited to mass screening using filter paper blood samples; HPLC has advantages of high automation, speed, accuracy, reproducibility and the ability to accurately quantify many hemoglobin species, but is more expensive and may miss Hb Barts with standard set-up.

⑦ — Testing both biological mother and father is necessary for diagnostic precision and genetic counseling. At a minimum it should include hemoglobin electrophoresis to identify the parents' donation of β-globin variants to their infants (i.e. HbF, HbC, HbS, etc.). Complete blood count (with RBC indices and RDW) and quantitative HbA_2 are helpful in identifying the microcytosis and increased HbA_2 of β-thalassemia carrier parents. Beware of revealing non-paternity.

⑧ — Although typical of HbSβ^0-thalassemia, this may also represent HbSβ^+-thalassemia when small amounts of HbA are missed.

⑨ — The severe sickle cell phenotypes are best managed, when possible, with comprehensive sickle cell centers which emphasize parental education, symptom recognition, and preventive care measures including complete vaccination (including *Haemophilus influenzae* type b, *Streptococcus pneumoniae, Neisseria meningitides* and Hepatitis B), antibiotic prophylaxis and anticipatory guidance.

⑩ — Homozygous non-sickle β-globinopathies have variable clinical severity. β-Globin variant β^E has a high frequency in Southeast Asian populations. Newborns with FE or FAE are usually asymptomatic, but compound heterozygote HbEβ^0 thalassemia patients have the clinical features of β-thalassemia major and are usually transfusion dependent. Newborns with FC have either homozygous HbCC or HbC/β-thalassemia; these infants do not have a sickling hemoglobinopathy but should be followed intermittently with blood counts. The Hb Barts 'Fast Band' with an otherwise normal phenotype represents an α-thalassemia carrier. In high risk groups, this may represent Hb H disease (see 'Thalassemia', p 24). Hb Barts disappears quickly after the neonatal period. Other unusual phenotypes may require the aid of hemoglobin reference laboratories to help identify the β-globin mutation.

⑪ — The 'HbF only' phenotype indicates an absence of detectable β-globin production. It may represent β-thalassemia major (which will require intensive intervention), the more benign entities of hereditary persistence of fetal hemoglobin (HPFH) (either in its homozygous form or heterozygously with β^0-thalassemia trait), or extreme prematurity in which a HbA band may not yet be detectable. These usually can be differentiated using family studies and, with the exception of β-thalassemia major, there is no need for hematological follow-up. HPFH is a genetically heterogeneous failure to suppress γ-globin production post-natally, with elevated HbF throughout life without significant clinical consequence.

⑫ — 'HbAF' is normally found only outside the neonatal period. In newborns it indicates transfusion of HbA (materno-fetal or therapeutic). Repeat testing at 3–4 months of age will help establish the correct diagnosis.

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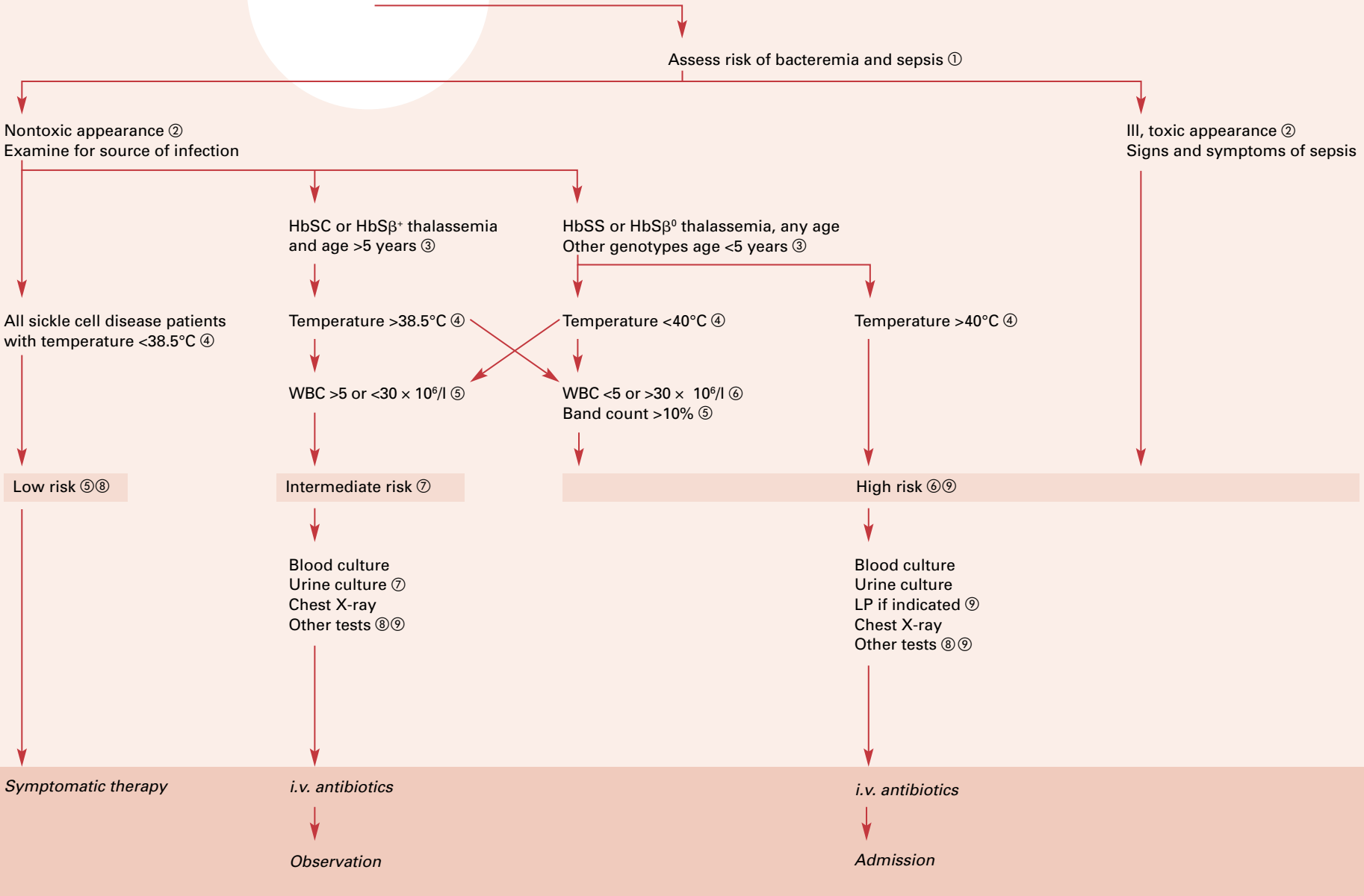
Sickle cell anemia with fever



① — Fever is the only reliable indicator of potential infection in patients with SCD. There are no rapidly available laboratory tests on hand that can rule out all bacterial infections such as pneumococcal bacteremia. All febrile children with SCD must be evaluated for serious bacterial infection. For children with HbSS younger than 5 years of age, the risk of acquiring sepsis and meningitis is more than 15% and mortality rate is 30–50%. Work-up and management depend on the clinical evaluation considering age, specific hemoglobinopathy, and physical examination. CBC with differential, reticulocyte count, and blood culture must always be obtained. Chest X-ray should be included in the evaluation of young patients, those with any pulmonary symptoms, and those with leukocytosis or with increased circulating immature neutrophils. Routine U/A and culture is mandatory for all infants, and older children with urinary symptoms, but therapy should not be delayed while awaiting urine collection.

② — SCD patients with fever should be triaged rapidly and evaluated immediately. After taking a brief history, focused physical examination should be done with emphasis on vital signs, O_2 saturation, degree of pallor, cardiopulmonary status, evidence of systemic and localized infection, spleen size (compared with baseline) and neurological examination.

③ — HbSC is generally milder disease than HbSS. However, children under 5 years of age with HbSC have an increased risk of bacteremia and fatal sepsis. In general, children with HbSC should be managed with the same degree of caution with regard to infection as those with HbSS. Children with HbSβ^0 thalassemia are considered to be of the same clinical severity as those with HbSS. However, those with HbSβ^+ thalassemia have a milder course, and their risk of infection is much less than high-risk patients.

④ — The height of initial fever is the most reliable indicator of septicemia. This is particularly true when the temperature is 40°C or greater, especially in children 24 months of age or younger, but sepsis can occur with any degree of fever. Recent antipyretics may reduce the fever but will not change the risk of bacteremia.

⑤ — Low-risk patients can be managed symptomatically like patients without sickle cell disease, but the higher risk of acute chest syndrome, osteomyelitis and other complications must be considered.

⑥ — The WBC count tends to be higher among bacteremic children in the first 2 years of life. Most studies show that the WBC count is not reliable for predicting sepsis in an individual child with SCD. However, among children 24 months of age or younger who have the highest incidence of sepsis, the presence of leukopenia or extreme leukocytosis with high fever are ominous signs.

⑦ — Intermediate risk patients should receive a long-acting antibiotic (e.g. ceftriaxone 50 mg/kg) immediately after obtaining the blood culture. The presence of a focus of infection (e.g. otitis) does not alter the urgency of giving parenteral antibiotics. Urine culture and chest X-ray should be done if clinically indicated. Patients should be observed for several hours to ensure they are clinically stable. Only if the family is reliable can the patient be discharged home with specific plan for out-patient follow-up. Minimum follow-up includes phone contact the next day. Repeated physical examination and a second dose of ceftriaxone may be advisable in some cases. Physicians should consider admission if patient is less than 1 year, or has a previous history of bacteremia or sepsis, or becomes toxic, or receives clindamycin as a substitute for ceftriaxone, or if there is any concern about the follow-up.

⑧ — Patients with chest X-ray infiltrate should have culture of blood, sputum and stool. Those with hypoxemia should receive supplemental oxygen to keep pulse-oximetry above 92%, and incentive spirometry to help prevent atelectasis. Blood transfusion should be given when oxygen carrying capacity is needed, but not as a routine. Because of the overwhelming incidence of pneumococcal pneumonia, patients should be treated with parenteral antibiotics (e.g. cefuroxime). Atypical pneumonia with *Mycoplasma pneumoniae* occurs commonly in SCD, and may lead to acute chest syndrome. Macrolide therapy (erythromycin or azithromycin) should be added to antibiotic coverage in treating SCD patients with pneumonia. A positive stool culture may be the only evidence for *Salmonella* pneumonia. Patients with clinical findings that are highly suggestive of septic arthritis or osteomyelitis should have needle aspiration and culture of the joint or bone. Antibiotic choice should include agents effective against *Salmonella* species and *Staphylococcus aureus*. Abdominal ultrasonography, liver function tests, amylase, and lipase should be considered for patients with RUQ, epigastric or severe abdominal pain to rule out cholelithiasis, cholecystitis, and pancreatitis.

⑨ — High-risk patients: Parenteral antibiotics should be administered immediately after obtaining the blood count and the blood culture, but before taking the radiograph and waiting for the laboratory results. Lumbar puncture should be performed on toxic children and those with signs of meningitis. Nontoxic children with temperature below 40°C, but with chest X-ray infiltrate, or with WBC >30 or <5 × 10^6/l should be admitted and treated with parenteral antibiotics. Antibiotic choice should be selected based on the ability to kill both *Pneumococcus* and *H. influenzae* and to penetrate into the CSF. Toxic patients or patients suspected of having meningitis should be treated with ceftriaxone (50–75 mg/kg) or cefotaxime (45 mg/kg/dose), and vancomycin (10–15 mg/kg/dose for resistant organisms). If the patient is known or suspected to have allergy to cephalosporin, clindamycin can be substituted. Documented sepsis should be treated parenterally for a minimum of 1 week. Bacterial meningitis should be treated for a minimum of 10 days or 1 week after the CSF has been sterilized. Patients can be discharged from the hospital if afebrile for 24 h with 48 h negative cultures, able to take oral fluids well, with resolution of any respiratory symptoms and adequate oxygenation on room air, and no evidence of worsening of anemia (e.g. aplastic or sequestration crisis).

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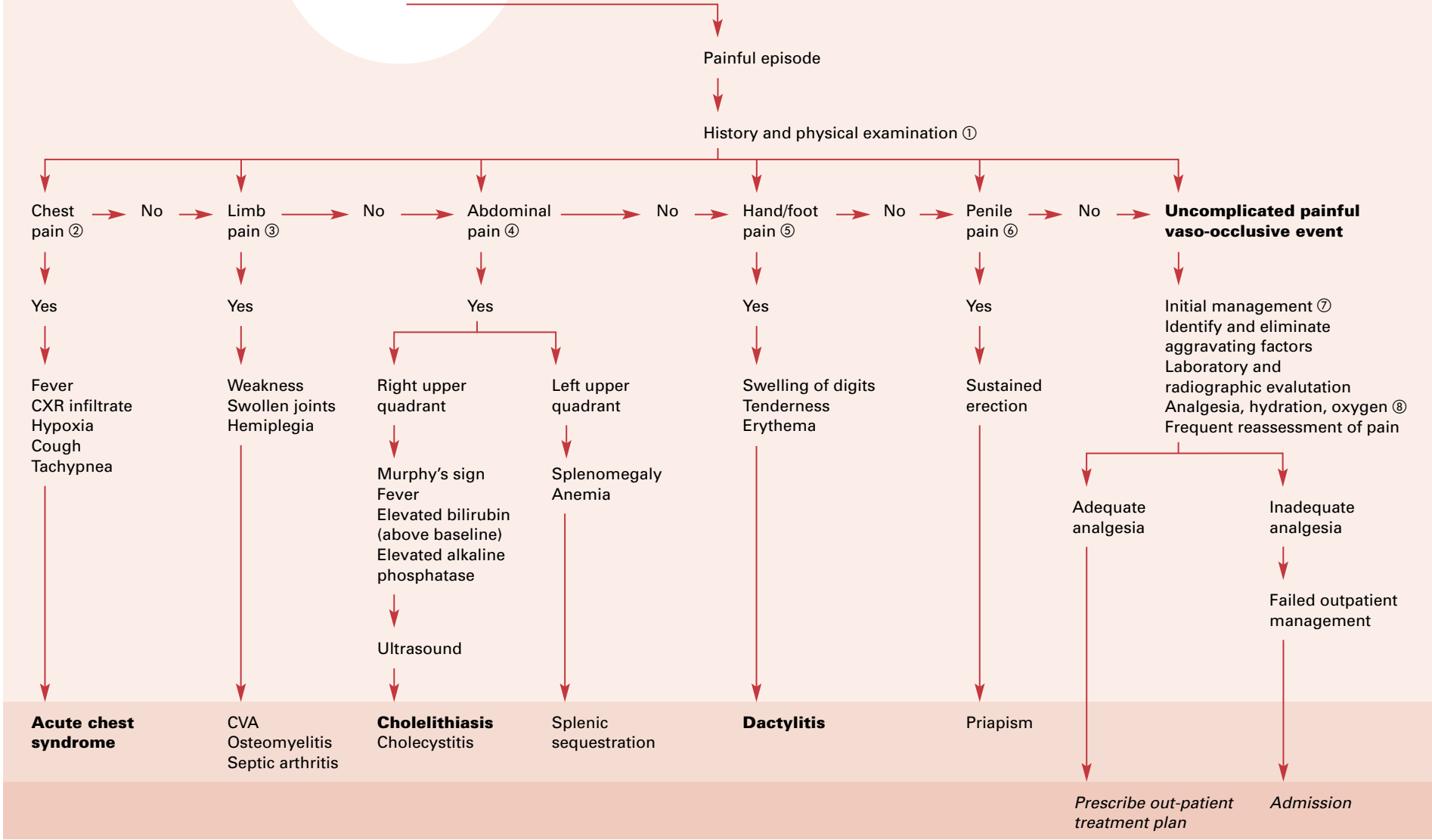
Management of painful vaso-occlusive episodes in sickle cell disease



① — Evaluate the onset, location, severity, quality, duration and response to therapy of pain using observation and patient reporting. Obtain history of self-directed treatment and prior experiences with pain and analgesics. Use accepted pain scales (numerical, color, facial expression) for serial evaluation of treatment efficacy. Recognize signs of other disease complications (e.g. fever, cough, dyspnea, vomiting, swelling, neurologic deficit) as well as disorders affecting normal children (e.g. viral gastroenteritis, appendicitis). Evaluate vital signs, O_2 saturation, spleen size, pallor, icterus, hydration status, joints, extremities, penis and neurologic function, and compare to the patient's baseline.

② — Focus on the location of the pain (chest wall, pleural or cardiac) and symptoms suggestive of a complicating diagnosis. With rib or sternal pain, secondary splinting and decreased diaphragmatic excursion may lead to atelectasis, V/Q mismatch and acute chest syndrome (ACS) if pain is not properly treated with analgesics and supplemented with incentive spirometry. Cough, tachypnea, fever or hypoxia requires CXR (PA and lateral). ACS, the most common cause of mortality in SCD, is defined as a new infiltrate, hypoxia, leukocytosis ± fever, and necessitates prompt intervention. Its etiology is often multifactorial. Therapy of ACS is determined by its severity and may include incentive spirometry, supplemental O_2 if hypoxic, broad-spectrum antibiotics, transfusion/erythrocytapheresis, serial bronchoscopy and mechanical ventilation.

③ — Limb and joint pain usually are due to a vaso-occlusive event, but one must differentiate limited mobility due to pain from neurologic deficit. Suspicion of neurologic deficit (e.g. hemiparesis, asymmetry in muscular tone, slurred speech/cranial nerve abnormality), should prompt immediate intervention and investigation of a possible cerebral vascular accident. Osteomyelitis (often with *Salmonella*), should be considered when focal tenderness, swelling or fluctuance and fever are present. Joint effusion and severely limited range of motion with fever can be caused by septic arthritis. Consider avascular necrosis of the femoral or humeral heads with chronic or recurrent pain localized to the hip or shoulder.

④ — Common diagnoses for normal children with abdominal pain should be considered, especially if surgical intervention is needed. Splenic sequestration is associated with increasing splenomegaly and a >2 g/dl decrease in Hb; thrombocytopenia, shock and an adequate reticulocyte count are frequent. Serial ultrasound studies estimating splenic volume may be helpful. Constipation secondary to opioid analgesics may cause left sided or generalized abdominal pain.

⑤ — Dactylitis ('hand-foot syndrome') is painful swelling of the hands and feet secondary to infarction of the small bones. It can be limited to a single digit or be generalized to all four extremities. This vaso-occlusive event can be recurrent but is seen almost solely in infancy.

⑥ — Priapism often starts at night and can be continuous or intermittent/stuttering. Timely detumescence is necessary to prevent future impotency secondary to fibrosis. Improvement should be observed within 24–36 h but complete resolution may require 5–10 days. Initially provide analgesia and hydration with progression to exchange transfusion/erythrocytapheresis if prolonged. Direct corporeal aspiration or irrigation with α-adrenergic agonists can be attempted by experienced personnel, while surgical corpus cavernosal shunting should be considered only if rigid tumescence persists despite exchange transfusion or erythrocytapheresis.

⑦ — Factors that aggravate or heighten sensitivity to pain include anxiety, cold exposure/hypothermia, and dehydration. Laboratory evaluation: CBC, differential, reticulocytes with comparison to baseline values. Presenting signs and symptoms dictate additional studies. Transfusion is not indicated in an uncomplicated vaso-occlusive painful episode but obtain a type and screen and determine if the patient's RBC phenotype is known; this ensures availability of blood product and a reduced risk of allo-immunization (which can be a serious problem for these children) should complications require transfusion. No empiric radiographic investigations are required. CXR to R/O ACS is indicated with hypoxia or pulmonary symptoms. If CVA is suspected, delay MRI/MRA until therapeutic exchange transfusion/erythrocytopheresis is performed. Dehydration should be corrected with bolus isotonic fluid administration. Maintenance fluids should be 150% of normal maintenance, using 0.25–0.5 normal saline to prevent intracellular dehydration associated with hypernatremia (goal serum Na 130–135). When concerned about excessive hydration (e.g. suspicion of ACS, CVA or aplastic crisis), use moderate fluid administration to 75–100% maintenance to prevent complications of overhydration (e.g. pleural effusions, pulmonary edema, cerebral edema). Intravenous is the preferred route of fluid administration, but total fluid intake should include i.v. plus p.o. Empiric supplemental O_2 is not indicated in an uncomplicated painful episode unless evidence of hypoxia, tachypnea or dyspnea.

⑧ — Vaso-occlusive pain is episodic, severe and should be considered a medical emergency. Analgesia is instituted quickly in a stepwise approach. Nonpharmacological treatment includes relaxation techniques, diversion and heating pads. Acetaminophen or NSAIDs may control mild pain and then weak opiods (e.g. codeine, oxycodone) are added. Stronger opioids (e.g. morphine, fentanyl, hydromorphone) are the mainstay of treatment of more severe pain, in combination with acetaminophen, NSAIDs and other adjuvant agents. Ambulatory treatment commenced early in an episode may abort debilitating pain and reduce hospitalization and school absence. Failure to achieve relief at home with oral hydration and analgesia necessitates parenteral opioid therapy. Patients may become tolerant to opioids so dosage should be titrated to effect. Physical dependence on opioid medication should never be mistaken for psychological dependence/addiction. As pain recedes, the opioid dosage can be tapered without withdrawal. Opioid toxicity includes hypoventilation and atelectasis (incentive spirometry required), constipation (stool softeners and cathartics required), nausea (antinauseants), urinary retention and pruritus (antihistamines and, if necessary, low-dose naloxone infusion).

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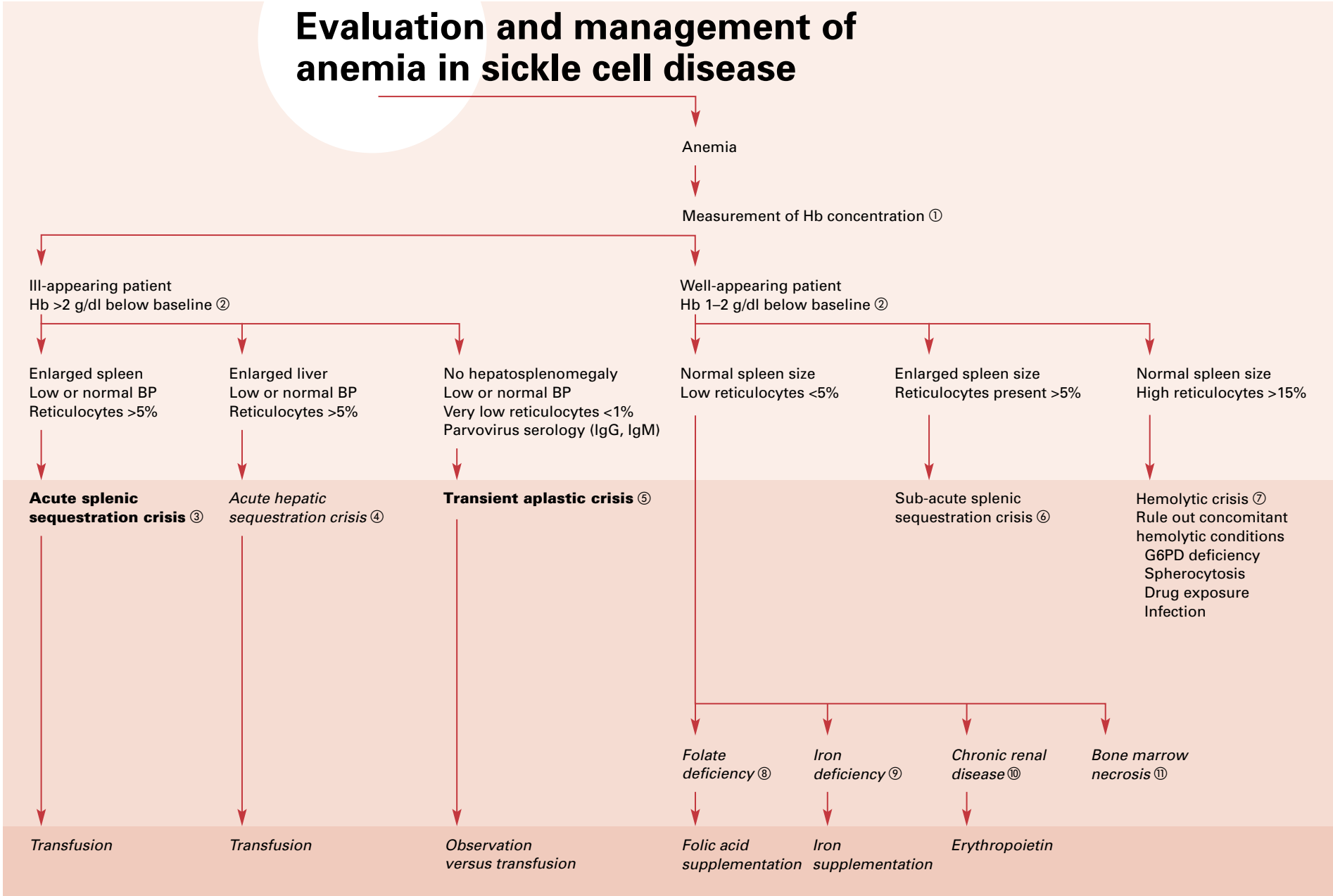
Evaluation and management of anemia in sickle cell disease



① — Although the degree of anemia in sickle cell disease is extremely variable among affected individuals, in any given patient the steady state Hb concentration after the age of 1 year, reticulocyte count, and degree of hemolysis are relatively constant. Measuring Hb concentration and comparing it with the baseline level is the first step to identifying an exacerbation of anemia.

② — Exacerbation of the usual degree of anemia is defined as a drop of more than 2 g/dl, or an absolute Hb concentration of less or equal to 5 g/dl. Patients with a slow and steady Hb drop are more stable than those with an acute drop who might present with shock.

③ — Acute splenic sequestration crisis (ASSC) is a sudden pooling of a large amount of blood into the spleen leading to acute splenomegaly, profound anemia, hypotension, and in severe cases, hypovolemic shock. Death may occur in a few hours. ASSC usually occurs prior to autoinfarction of the spleen, with the vast majority occurring before 2 years and almost all before 6 years of age. ASSC is less common in HbSC disease, but may occur in older patients, since splenomegaly persists into adulthood. ASSC often occurs in association with non-specific viral or bacterial infection. Parents should be taught to palpate the spleen regularly, and seek immediate medical care if the spleen enlarges. Laboratory findings may include severe anemia with increased reticulocytes and nucleated red cells, an increased WBC with shift to the left, and a decreased platelet count due to platelet trapping. The immediate treatment of ASSC is directed toward correction of hypovolemia and anemia. Isotonic volume support can be used acutely while awaiting blood for transfusion. The goal of transfusion is primarily to prevent shock, not to restore Hb to normal or to the steady state level. After transfusion the spleen shrinks and Hb often increases more than predicted due to the release of trapped RBC from the spleen. ASSC recurs in approximately 50% of cases. Long-term management for recurrent ASSC may include chronic transfusion therapy in the very young patient in order to avoid splenectomy.

④ — Although uncommon hepatic sequestration crisis does occur and is characterized by rapid enlargement of the liver accompanied by drop in the Hb. It should be approached in the same manner as ASSC.

⑤ — Transient aplastic crisis (TAC) is an exacerbation of anemia due to transient cessation of erythropoiesis, and can occur in all chronic hemolytic anemias including SCD. An acute aplastic crisis is often associated with infection, and parvovirus B19 is the causative agent in most severe cases. Patients present with signs of severe anemia, although the condition is often discovered incidently during an evaluation for febrile illness. If anemia is severe enough the patient should be admitted for observation. The decision to transfuse RBC should be based first on clinical presentation, the degree of anemia, and reticulocyte count. The goal of transfusion is to prevent congestive heart failure and shock, which occurs when the Hb is below 4–5 g/dl. An increased risk of stroke has been associated with severe anemia.

⑥ — Splenic sequestration is not always acute, but it can be subacute and even chronic. Splenomegaly associated with anemia and thrombocytopenia may be evidence of a subacute or chronic splenic sequestration. Close clinical observation and monitoring of the Hb concentration are mandatory. Many of these children eventually require splenectomy.

⑦ — Hyperhemolytic crisis is very unusual, but may ensue in association with certain drugs, acute infection or G6PD deficiency. Patients show increased scleral icterus and may have abdominal pain, fall in Hb, increased reticulocyte count and bilirubin. After several days hemolysis subsides.

⑧ — Folate deficiency as a cause of exaggerated anemia is a very rare event in the USA, but common worldwide. Nevertheless, it is a common practice to prescribe folic acid 1 mg to patients with SCD unless they have adequate dietary intake of folate. Macro-ovalocytosis from folate deficiency is difficult to recognize in a patient with reticulocytosis. Hypersegmentation of the neutrophil may provide a clue to the correct diagnosis.

⑨ — Iron deficiency is not a major problem in SCD. The diagnosis can be established by measuring serum ferritin, and an increase in Hb and MCV in response to iron therapy. Iron supplementation should never be prolonged since iron overload is a common long-term problem in many patients with SCD. The diagnosis should be considered when the MCV falls below the patient's baseline.

⑩ — SCD in older patients is associated with chronic renal disease. As a consequence of chronic renal failure, erythropoietin (Epo) production is impaired for the degree of the anemia. It is well established that administration of recombinant erythropoietin improves severe anemia in SCD patients with renal failure.

⑪ — Bone marrow necrosis is a rare event in pediatric patients with SCD, and is typically due to repeated vaso-occlusive infarction.

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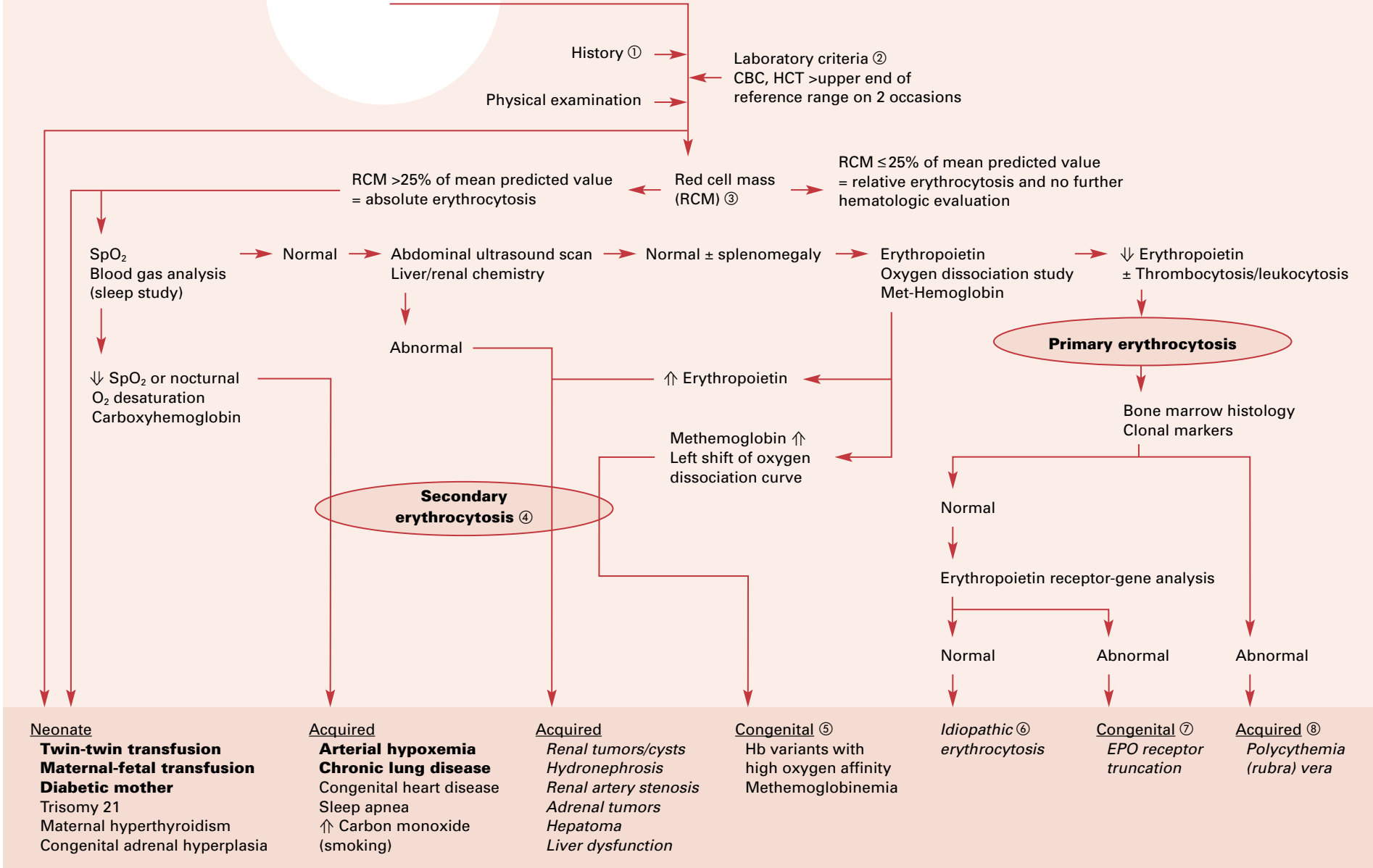
Polycythemia (erythrocytosis)



① — Consider patient's age; in neonates, ask about delayed cord clamping, maternal diabetes or other causes for chronic fetal hypoxia. Consider symptoms and signs of pulmonary or cardiac disease, such as dyspnea and cyanosis. Note positive family history of erythrocytosis. Dehydration can cause an increased HCT, but since the red cell mass is normal this represents relative and not absolute erythrocytosis.

② — Erythrocytosis should be considered if the HCT is above the upper age related reference range on two separate occasions. Note thrombocytosis and/or leukocytosis as signs of polycythemia vera.

③ — Red cell mass is determined to differentiate between absolute and relative (or apparent) erythrocytosis by ^{51}Cr- or ^{99m}Tc-red blood cell dilution method. In relative erythrocytosis, HCT is above normal range while red cell mass is not increased, e.g. due to reduced plasma volume. The erythrocytosis in these patients is not a clinical concern, although the cause of decreased plasma volume would be. In absolute erythrocytosis there is a true increase in red blood cell mass which needs investigation. When an underlying etiology of polycythemia is evident (e.g. chronic lung disease, congenital heart disease), evaluation of red cell mass may not be necessary.

④ — Secondary erythrocytosis is due to an excess of erythropoietin as a manifestation of decreased tissue oxygenation or inappropriate erythropoietin secretion from a tumor. The former occurs as a consequence of decreased renal oxygen supply either due to arterial hypoxemia in chronic lung disease or congenital heart disease or due to impaired renal perfusion, e.g. in renal tumors/cysts, hydronephrosis, and renal artery stenosis. Often serum erythropoietin is increased. Impaired liver function or hepatic tumors can also cause increased erythropoietin levels. Erythropoietin producing adrenal tumors (e.g. adrenocortical carcinoma, pheochromocytoma, hemangioblastoma, e.g. in Hippel-Lindau disease) can cause secondary erythrocytosis.

⑤ — Methemoglobinemia or hemoglobin variants with high oxygen affinity lead to decreased tissue oxygenation and therefore to secondary erythrocytosis. Ideally, perform an oxygen-dissociation curve of the patient's hemoglobin. Hemoglobin electrophoresis alone is insufficient, since many hemoglobins with abnormal oxygen affinity co-migrate with HbA and will be overlooked. Consider family studies and molecular genetic studies.

⑥ — This heterogeneous group of patients with idiopathic erythrocytosis emerges from those patients with an absolute erythrocytosis without a cause of primary or secondary erythrocytosis. In some patients a cause for secondary erythrocytosis becomes apparent during follow-up.

⑦ — In primary erythrocytosis, erythropoiesis is defective, in contrast to the secondary type, where erythrocytosis is increased in response to increased erythropoietin secretion. Primary erythrocytosis can be caused by truncation of the cytoplasmic portion of the erythropoietin receptor that is responsible for switching off the signal following erythropoietin binding. Erythroid precursor cells are then hypersensitive to erythropoietin leading to erythroid hyperplasia. This condition was shown to be dominantly inherited, but spontaneous somatic mutations have also been recognized. Consider family studies and molecular genetic studies.

⑧ — Polycythemia (rubra) vera is a myeloproliferative, monoclonal disease that is very rare in childhood. Red cell mass must be increased and other common findings include normal arterial oxygen saturation, splenomegaly, thrombocytosis, leukocytosis and bone marrow hypercellularity. A useful marker is the ability of peripheral blood cell fractions to form endogenous erythroid colonies in the absence of erythropoietin.

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Red cell transfusion①

Red cell destruction

Direct Coombs test

– → (see 'Hemolytic anemia', p18, and 'Evaluation and management of anemia in sickle cell disease' p 32)

Consider complication of chronic hemolysis (e.g. aplastic crisis, sequestration, Fe deficiency)

RBC studies (if needed) prior to transfusion ④
PRBC (5 ml/kg/4 h) × 2 if Hb <5 g/dl or child unstable
Leukodepleted PRBC if repeated transfusions likely ⑤
Match minor group antigens for SCD ⑥

+

Neonate

Rh, ABO or minor blood incompatibility

Maternal ABO/Rh type PRBC if Hb <8 g/dl or unstable (10 ml/kg)
Use leukodepleted PRBC compatible with baby and mother
Irradiate PRBC to prevent GvHD

Older

AIHA
Warm or cold antibody?

Warm AIHA ②

Corticosteroids
Consider PRBCs if Hb <5 g/dl to
⇑ Hb to 6–8 g/dl
PRBC 5 ml/kg/4 h slowly and repeat p.r.n.

Cold AIHA ③

Avoid cold
Steroids not usually helpful
PRBC if Hb <5 g/dl (5 ml/kg/4 h to ⇑ 6–8 g/dl)
Use blood warmer

Acute blood loss

Determine if unstable (shock/postural hypotension)
Identify cause

Hemodynamic instability ⑦

Stabilize bleeding
Infuse crystalloid/colloid 20 ml/kg rapidly
Infuse O– uncrossmatched PRBC until crossmatch-compatible blood available (≥10 ml/kg/h) and repeat p.r.n.
Monitor Hb q 2–4 h and transfuse p.r.n. until stable

Hemodynamic stablity

Stabilize bleeding and infuse crystalloid if indicated
PRBC 10–15 ml/kg/4 h p.r.n.
Monitor Hb q 6 h

Red cell production failure

Neonatal issues

Repeated crossmatch not necessary ⑧
Multiple-pack units ⇓ donor exposure
Irradiate PRBC
Leukodeplete when possible ⑤
Iron replacement
EPO alternative ⑨

Child/adolescent

If symptomatic (CHF, ⇑ lethargy, ⇓ feeding) or if Hb <5 g/dl + other concerns (e.g. bleeding, compliance, other medical complications), transfuse *slowly* ⑩

Transient disorder

Transfuse only if symptomatic

Malignancy/chemotherapy

Transfuse Hb <8 g/dl in most cases (10–15 ml/kg) ⑪
Leukodeplete and irradiate ⑫

Other chronic anemia

Hb <8 acceptable if child is well
Leukodeplete ⑤

BMT candidates ⑬

Irradiated/leukodepleted
Restrict family donors

Thalassemia major

Match minor group antigens ⑥

PRBC transfusion required

No

Observe for hypotension and CHF
Monitor Hb closely
Reconsider transfusion if Hb ⇓

Religious objection to transfusion ⑨

? Autologous donation ⑭
? EPO

Transfusion reaction ⑮

Yes

Immunocompetent

Leukodepletion if repeated transfusions likely

Immunocompromised (including neonate <4 months)

Irradiated PRBC ⑧
Leukodepleted PRBC
CMV-safe PRBC

① — PRBC transfusions increase the oxygen-carrying capacity in anemic patients. One unit of PRBC derived from a routine blood donation preserved in CPDA-1 anticoagulant = 250–300 ml RBCs, Hct = 75–80% and shelf life = 35 days. Stored in additive preservatives, Hct = 52–60% and shelf life = 42 days. 10 ml/kg of PRBC should raise the Hb by 2–3 g/dl (0.31–0.47 mmol/l). Leukoreduction of PRBC usually uses special filters, preferably immediately after blood donation rather than before the actual transfusion. Washed PRBC are mainly used to prevent recurrent allergic reactions. Frozen PRBC are used for storage of rare phenotypes or autologous units. Units of blood must be infused within 4 h of leaving the blood bank. With appropriate testing of units, the current estimated risk of infection = 1:1,930,000 for HIV, <1:543,000 for hepatitis C and 1:138,700 for hepatitis B.

② — In warm AIHA, IgG antibodies react at 37°C. RES blockade with prednisone or equivalent, 2–10 mg/kg/day, is the first-line therapy. Transfuse if needed because of the risk of fatal anemia. The antibody usually reacts with Rh-like antigens present on RBCs so an incompatible crossmatch is common. Slowly infuse small volumes of the most compatible units after pretreatment with steroids.

③ — Cold AIHA is usually due to IgM antibodies reactive at 0–30°C, fixing complement and causing hemolysis even after the blood warms centrally to 37°C. When transfusing, use a servotemperature blood warmer to reduce hemolysis of transfused cells.

④ — If the cause of hemolysis is unknown, obtain RBC enzyme, membrane and Hb analyses prior to transfusion so as not to mask the diagnosis once normal cells are transfused.

⑤ — WBC depletion using third-generation prestorage leukodepletion filters for blood and blood products is recommended for immunocompromised children, infants who have an immature immune system, and those expected to receive multiple transfusions. The reduction in WBC contamination may decrease febrile reactions, exposure to HLA antigens, and risk of CMV transmission. Frozen, washed red cells eliminate some WBC, but additional time for preparation and loss of RBC volume limit use.

⑥ — Patients of African descent have different rates of expression of common RBC antigens. 30% may become alloimmunized from chronic RBC transfusions. Alloimmunization may make it difficult or impossible to find compatible PRBC. To decrease this risk by ~80%, children with SCD should have a full RBC phenotype and should receive PRBC matched for C, D, E, and Kell antigens and any other specific antigen for which they have preexisting antibodies. This should also be done for patients with thalassemia major because they may require life-long transfusions. HbSS patients should be transfused, if necessary, to bring their Hb to 10 g/dl for general anesthesia, but preferably not higher.

⑦ — Massive blood loss requires urgent management of both hypovolemia and anemia. Rapidly infuse crystalloid/colloid until PRBC are available. If hypotensive, group O Rh-negative uncrossmatched PRBC may be necessary until group-specific or crossmatch-compatible PRBC are available; transfuse 10–20 ml/kg/h if necessary to maintain the Hb level and blood volume. Once stable, slow down to 10–20 ml/kg/4 h as determined by clinical status and Hb. Dilutional thrombocytopenia, coagulopathy and metabolic complications may occur with massive transfusion (>75 ml/kg/24 h); monitor and correct ionized hypocalcemia due to citrate toxicity. Hypothermia from refrigerated blood can be avoided by using a blood warmer.

⑧ — Sick or premature newborns frequently require transfusions. The neonatal immune system typically does not respond to RBC antigen stimulation. If the initial ABO, Rh is compatible and antibody testing is negative, repeat crossmatching and antibody screening is unnecessary prior to subsequent transfusions. The blood bank should divide a compatible unit into multiple small aliquots for infants requiring multiple small volume transfusions which should be irradiated to prevent GvHD and be CMV safe, either prestorage leukodepleted or CMV-negative.

⑨ — Recombinant erythropoietin (EPO) support is effective in treating anemia associated with HIV, renal failure, and prematurity. Routine use of EPO in pediatric oncology patients remains controversial.

⑩ — Severe but less acute anemia (e.g. TEC, Fe deficiency) raises vascular volume and can cause CHF. Even if relatively stable, too rapid transfusion can precipitate CHF. Transfuse as slowly as 1 ml/kg/h (usually 4–5 ml/kg/4 h). To limit the number of donor exposures, request sterile splitting of PRBC into small aliquots.

⑪ — Myelosuppressive chemotherapy often requires PRBC support that can prevent GvHD and CMV transmission. In other chronic anemias the Hb may fall lower before PRBC are indicated.

⑫ — Irradiation of blood prevents transfusion-associated GvHD caused by engraftment of donor lymphocytes. Irradiated blood is indicated for fetuses requiring intrauterine transfusions, some neonates and infants up to 4 months, acquired or congenital immunodeficiency states, chemoradiotherapy, hematopoietic stem cell and solid organ transplant recipients, and those receiving blood from HLA homozygous or haploidentical donors including blood relatives.

⑬ — Bone marrow transplant candidates with aplastic anemia should be transfused only when absolutely necessary to minimize transfusion-induced HLA alloimmunization which complicates engraftment. Hb as low as 5–6 g/dl may be tolerated well. If forced to transfuse, avoid family members who may serve as transplant donors.

⑭ — The medical, ethical and legal issues of religious objections to transfusions (e.g. Jehovah's Witnesses) are complex. The effectiveness of blood substitutes remains unproven. EPO increases hemoglobin but requires 2–3 weeks for a noticeable effect.

⑮ — The incidence of transfusion reactions is allergic > febrile nonhemolytic > hemolytic > anaphylactic > septic. Allergic reactions cause pruritus, rash/urticaria and flushing at the infusion site and respond to briefly pausing the transfusion and giving antihistamines. Febrile/nonhemolytic reactions demonstrate fever elevated to >1°C ± rigors, headache, malaise, and emesis; stop the transfusion, give antipyretics and initiate a blood bank transfusion reaction workup. Hemolytic reactions are characterized by fever, chills, back pain, Hburia, lowered BP, and DIC; stop the transfusion immediately and support BP and renal function with fluids/diuretics/pressors as needed. Blood bank transfusion reaction workup is critical. Septic contamination of blood and especially platelets causes febrile reactions, which can be fatal.

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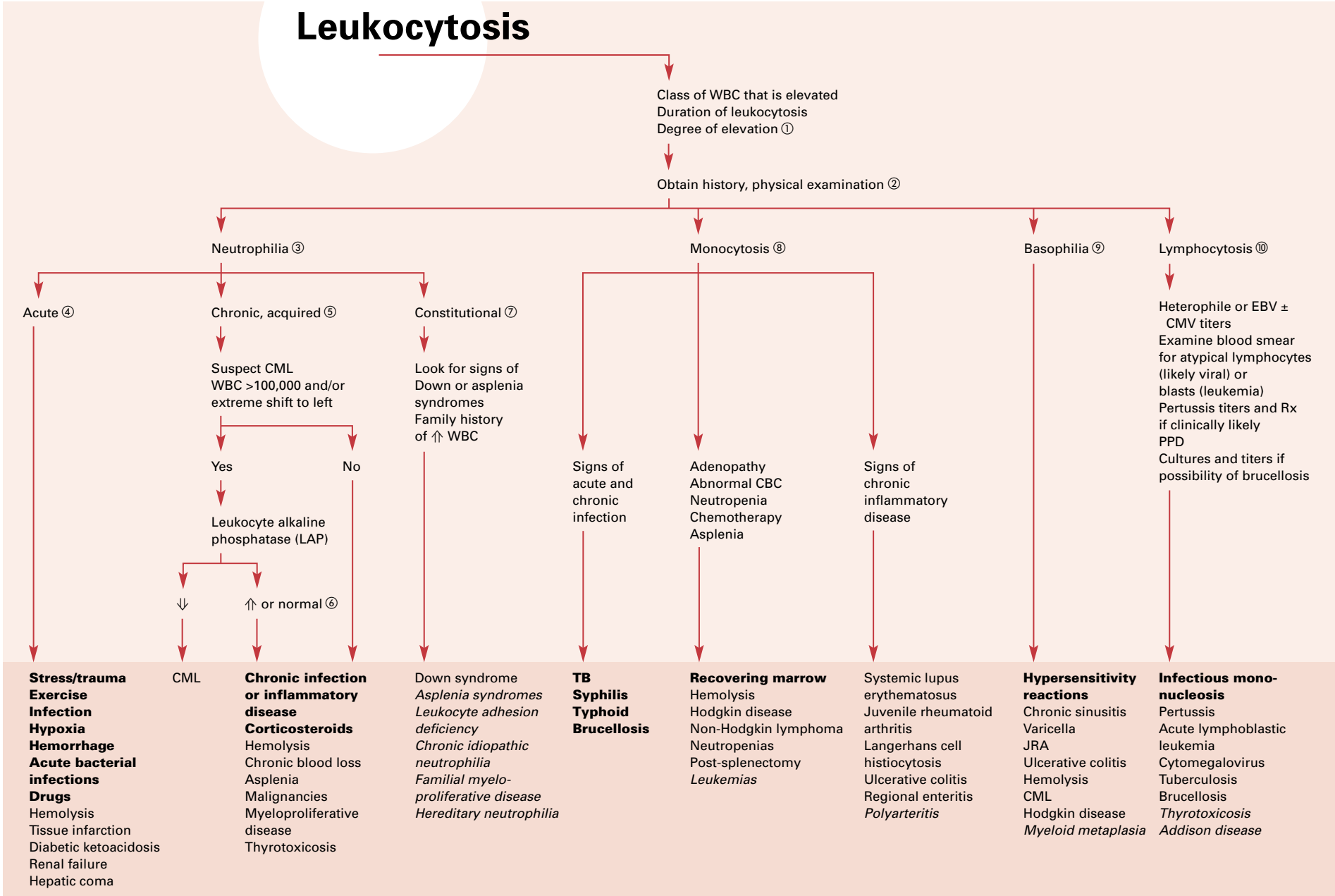
Leukocytosis



① — To evaluate the patient with leukocytosis, it is important to determine which class or classes of white blood cells are elevated. Next it is important to determine the duration and extent of the leukocytosis. Each blood count should be evaluated on the basis of the absolute number of cells/µl (e.g. the absolute eosinophil count) and *not* on the basis of the differential count percentage. A relatively high percentage of neutrophils may not be abnormal if the total WBC is not high. All normal ranges remain at ± 2 SD of large population samplings. Consideration must be made of the age of the patient because the leukocyte values change during childhood (see tables of normal values). Often the etiology of the leukocytosis will be evident (e.g. acute infection, drugs, trauma) and no specific evaluation is necessary.

② — Once the specific cell type that is elevated is determined, the clinician must review the history and physical examination of the patient and focus on those features that can differentiate the specific diagnosis under consideration.

③ — Neutrophilia refers to an alteration in the total number of neutrophils in the blood that is in excess of about 7,500 cells/µl in adults. During the first few days of life, the upper limit of the normal neutrophil count ranges from 7,000 to 13,000 cells/µl for neonates born prematurely and at term, respectively. It then drops to as low as 4,300 at 2 months of age, reaches 8,000 through most of childhood and then reaches the adult upper limit of 7,500. Africans have somewhat lower neutrophil counts than Caucasians. Neutrophilia arises from a disturbance in the normal equilibrium involving neutrophil bone marrow production, movement in and out of the marrow compartments into the marginating (found along endothelial cells in small blood vessels) and circulating pools, and neutrophil destruction.

④ — Acute neutrophilia occurs rapidly within minutes in response to exercise or epinephrine-induced reactions. It is caused by a shift of cells from the marginal to the circulating pool. Acute neutrophilia also occurs as a consequence of release of marrow cells from the storage pool. This mechanism produces acute neutrophilia in response to inflammation and infection. The neutrophilia arises following an increase in TNF, IL-1 and a cascade of other cytokine growth factors. Glucocorticoids may also cause the release of the neutrophils from the marrow reserve pool as well as slow the egress of neutrophils from the circulation into tissue. Acute neutrophilia is also seen in trauma, tissue infarction associated with sickle cell crisis and burns, hypoxia, diabetic ketoacidosis, renal failure, hepatic coma, hemolytic anemia, and hemorrhage. The specific etiology of the leukocytosis is often evident and usually transient, so further evaluation is often unnecessary. If the leukocytosis persists or increases in severity, evaluation may be indicated.

⑤ — In patients with a longer history in whom neutrophilia is acquired, a different list of possibilities than for acute causes of neutrophilia needs to be considered and diagnostic evaluation is indicated more often. Neutrophil production rate can increase severalfold with chronic infections and in response to exogenously administered hematopoietic growth factors (G-CSF and GM-CSF). Chronic inflammation associated with vasculitis, pleuritis, or pericarditis, Hodgkin disease, and a variety of tumors including non-Hodgkin lymphomas initiate chronic neutrophilia. Elevated neutrophil counts can be the presenting sign of chronic myelogenous leukemia, but this is usually suspected on the basis of a profound shift to the left (with metamyelocytes, myelocytes and promyelocytes constituting an average of 25% of the neutrophilic series) and a total WBC usually >100,000/µl. In pursuing the differential diagnosis of chronic neutrophilia, the chemical stain of circulating white blood cell leukocyte alkaline phosphatase is useful. The result is near zero in chronic myelogenous leukemia (CML) and is normal to elevated in reactive secondary neutrophilias. If the result is low, bone marrow aspiration for cytogenetics to detect the chromosomal translocation t(9:22) should be performed to confirm the diagnosis of CML.

⑥ — If the leukocyte alkaline phosphatase result is normal or elevated, specific measures to identify or rule out the causes of persistent reactive neutrophilia should be pursued. Chronic infection or inflammatory states (such as autoimmune disorders or inflammatory bowel disease) do this most commonly. Hemolysis and chronic blood loss can result in a mild-to-moderate leukocytosis (usually < 25,000 cells/µl).

⑦ — Sustained moderate neutrophilia occurs with anatomic or functional asplenia and arises from failure to remove circulating neutrophils by the spleen. Down syndrome and familial myeloproliferative disorders are also associated with neutrophilia. Neutrophilia is associated with functional disorders of the neutrophil associated with impaired adhesion or motility such as that found in patients with leukocyte adhesion deficiency types I and II. There is an autosomal-dominant form of hereditary neutrophilia as well as a form of chronic idiopathic neutrophilia.

⑧ — The upper range of normal of monocyte counts is 1,900 cells/µl in the neonate, as low as 900 at 1 year, and then 1,300 through adolescence.

⑨ — Basophilia occurs when the basophil count exceeds 100–120 cells/µl. Basophilia is a nonspecific sign of a wide variety of disorders and is usually of limited diagnostic importance.

⑩ — Normal lymphocyte count varies considerably with age, from upper limits of normal of 7,300 cells/µl in neonates, to 11,500 at 6 months of age, to 6,500 at 10 years, and 4,500 in adolescents and adults. Lymphocytosis is associated with many infections, particularly infectious mononucleosis, acute infection lymphocytosis and pertussis, as well as a variety of other disorders including the lymphocytic leukemias.

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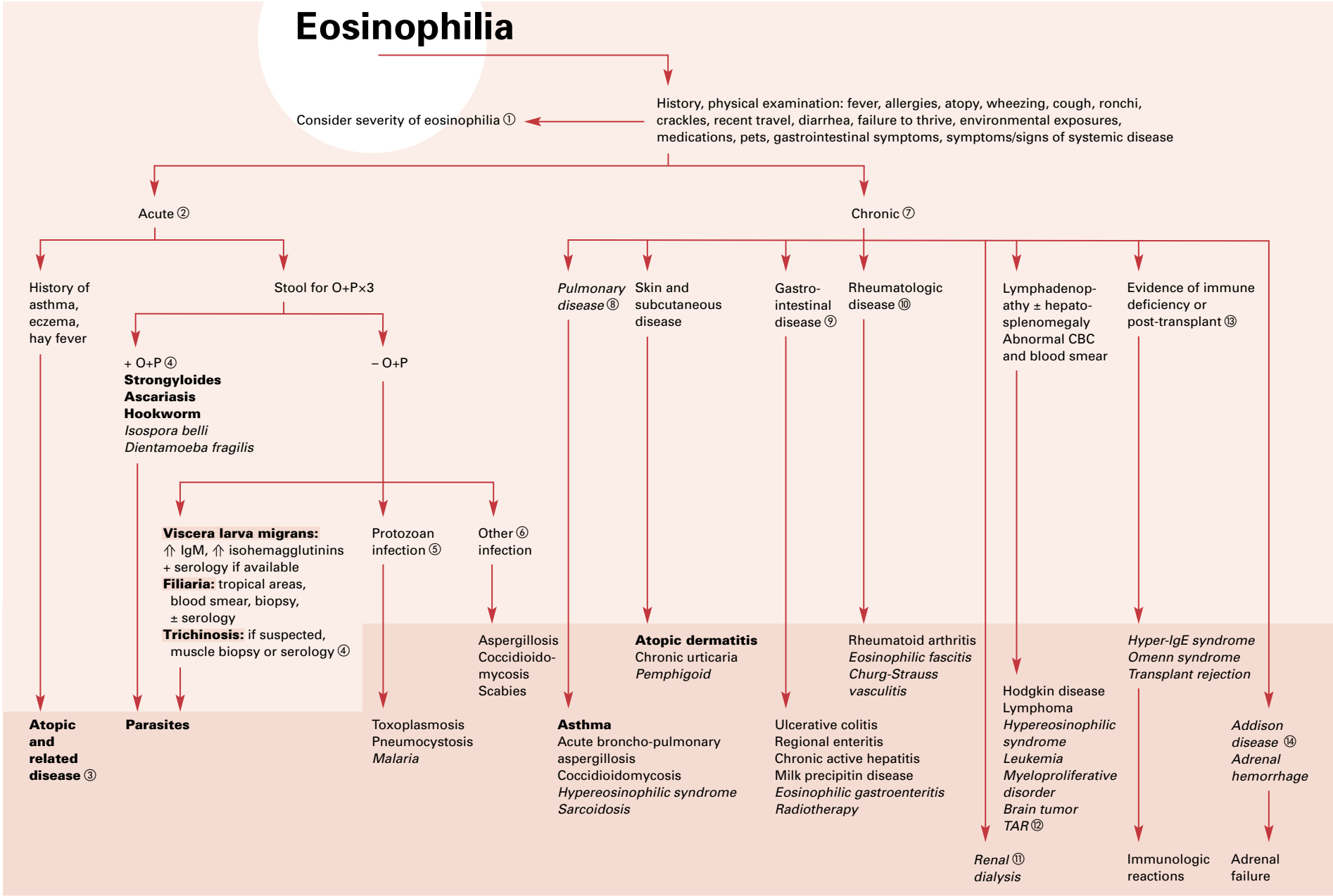
Eosinophilia



① — Mild eosinophilia (450–1,500 cells/μl) is very common and often transient. When chronic but clearly associated with atopic diseases further investigation may not be necessary. Moderately severe eosinophilia (1,500–5,000/μl) often has no obvious etiology and merits more intensive investigation. Severe eosinophilia (> 5,000/μl) is by far most commonly due to visceral larva migrans, but is rarely due to hypereosinophilic syndrome, and extremely rarely due to leukemia. Occasionally, disorders usually associated with moderate eosinophilia result in severe eosinophilia (e.g. trichinosis, hookworm, drugs, and Hodgkin disease).

② — Patients who present with acute eosinophilia need to be evaluated for the two most common causes, i.e. atopic and related diseases and parasitic infections. Atopic disease is the most common cause of eosinophilia in industrialized countries while parasitic disorders are more common elsewhere.

③ — Allergic rhinitis and asthma are commonly associated with eosinophilia. If the eosinophilia is mild, no further evaluation is usually indicated. Hypersensitivity reaction to drugs and foods is another cause.

④ — Parasitic diseases are extremely common worldwide. Certain parasites including helminths induce greater degrees of eosinophilia than protozoan infestations. The level of eosinophilia tends to parallel the magnitude and extent of tissue invasion especially by larvae. In evaluating the patient with unexplained eosinophilia, geographic and dietary histories are the keys to identifying potential exposure to helminthic parasites. Stool examinations for diagnostic ova and larvae should be performed, and for evaluation of *Strongyloides* infection, an enzyme-linked immunosorbent assay for antigens should be carried out. For a number of helminthic parasites that cause eosinophilia, diagnostic parasite stages are not present in feces; therefore, an examination of blood and appropriate tissue biopsy material as guided by the clinical findings and history of exposure may be needed to diagnose specific tissue infection including trichinosis, filaria/infections and visceral larva migrans. *Toxocara* species causes visceral larva migrans, usually in young children with pica. Most children are asymptomatic but some develop the full-blown syndrome with fever, pulmonary symptoms, hepatomegaly, hypergammaglobulinemia and severe eosinophilia. Isohemagglutinins (anti-A, anti-B) are often elevated. Serologic tests are becoming more widely available, and demonstrate that approximately 5% of US schoolchildren are seroconverted.

⑤ — *Pneumocystis carinii* infection and toxoplasmosis are protozoan infections associated with eosinophilia.

⑥ — Allergic bronchopulmonary aspergillosis, coccidioidomycosis, malaria and scabies can cause eosinophilia.

⑦ — Eosinophils can be inappropriately stimulated by activated T cells releasing both IL-3 and IL-5. The eosinophil granule contents irritate and deform the normal structures they come in contact with including vascular walls, endocardial surfaces and mesenchymal tissues. Because of these effects, persistent eosinophilia signifies a serious parasitic infection or other serious disorders that stimulates eosinophilia through generalized T cell activation.

⑧ — Blood eosinophilia can infrequently accompany pleural fluid eosinophilia, secondary to chest eosinophilia including trauma and repeated thoracenteses. Both acute and chronic eosinophilic pneumonia can be seen with allergic bronchopulmonary aspergillosis.

⑨ — Eosinophilic gastroenteritis, ulcerative colitis and regional enteritis are often associated with blood eosinophilia. Chronic active hepatitis, milk precipitin disease, and radiation therapy for intra-abdominal neoplasia can engender blood eosinophilia.

⑩ — Approximately 10% of patients with rheumatoid arthritis will develop a mild eosinophilia. Similarly, eosinophilic fascitis and Churg-Strauss vasculitis (asthma, eosinophilia as well as pulmonary and neurologic involvement) are associated with blood eosinophilia.

⑪ — About one third of patients undergoing chronic hemodialysis develop blood eosinophilia, and, similarly, chronic peritoneal dialysis may cause an eosinophilic peritonitis accompanied with elevated blood eosinophils.

⑫ — Eosinophilia is frequently present in the thrombocytopenia with absent radii (TAR) and familial reticuloendotheliosis with eosinophilia syndromes. Hodgkin disease and non-Hodgkin lymphoma are frequently associated with eosinophilia. Brain tumors and myeloproliferative disorders are also associated with blood eosinophilia. Hypereosinophilic syndrome is very rare in children. It is associated with various systemic symptoms and a diversity of potential organ involvement. Eosinophil counts are usually > 5,000/μl. One of the most serious and more frequent complications in this disorder is cardiac disease secondary to endomyocardial thrombosis and fibrosis. Mortality is very high with a mean survival of 9 months.

⑬ — Several immune deficiencies including the hyper-IgE syndrome, Omenn syndrome as well as transplant rejection of lung, kidney and liver are associated with blood eosinophilia.

⑭ — Hypoadrenalism associated with Addison disease and adrenal hemorrhage are associated with blood eosinophilia.

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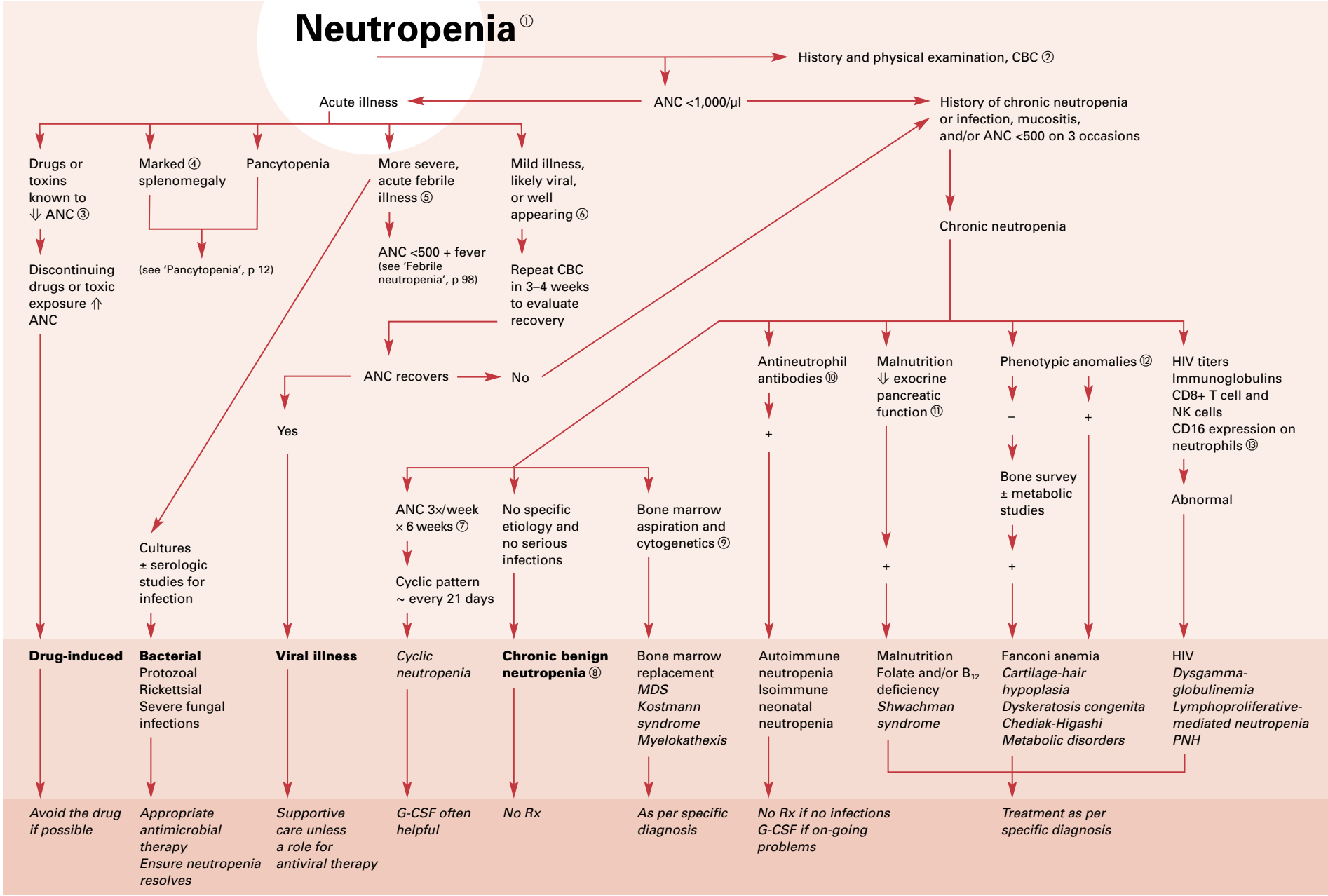
Neutropenia ①



① — Leukopenia results from either neutropenia and/or leukopenia, but neutropenia is much more commonly an important clinical problem. The risks of neutropenia are discussed in *'Febrile neutropenia'* (p 98). Neutropenia is quantified using the absolute neutrophil count (ANC) = WBC × % (band + PMN). Although the lower limit of absolute neutrophil count is 1,500–1,800 at most ages, the risk of serious infection increases when the ANC is <500. Acute neutropenia is generally evaluated when the ANC is <1,000. The more extensive evaluation of chronic neutropenia is usually undertaken when the ANC is <500, in the absence of other clinical clues to a specific etiology. The average ANC is 200–600 cells/µl lower in people of African descent.

② — History and physical examination must consider whether the neutropenia is acute or chronic, occurrence of unexpected infections (cellulitis, abscess, stomatitis, pneumonia, perirectal infections, and the frequency, symptom-free interval, response to treatment), failure to thrive, drugs/toxins, family history of leukopenia or unusual infections. Physical examination focuses on failure to thrive or recent weight loss. Scarred tympanic membranes, postnasal drip or cervical adenopathy suggest chronic respiratory infection. Recurrent cough, wheezing or chest deformity may indicate pulmonary disease. Lymphadenopathy, hepatosplenomegaly, pallor, wasting or weight loss suggests a systemic disease. Gingivitis and aphthous ulcers often accompany chronic neutropenia. Documentation of fevers is important, but rectal temperatures should be avoided because of the risk of initiating perirectal cellulitis. Examine the entire CBC and blood smear.

③ — Drugs frequently cause neutropenia by immune, toxic, or hypersensitivity reactions. While neutropenia is expected with chemotherapy, drug-induced neutropenia usually involves an idiosyncratic reaction. This most commonly involves antimicrobials (penicillins and sulfonamides), antirheumatics (gold, phenylbutazone, penicillamine, ibuprofen), sedatives (barbiturates and benzodiazepines), phenothiazines, and antithyroid drugs. Toxic exposures are uncommon. Very rarely the neutrophil fails to recover after discontinuation of the drug.

④ — Marked splenomegaly (usually at or below the umbilicus) can cause hypersplenism with resulting neutropenia, usually accompanied by moderate thrombocytopenia and anemia. Milder degrees of splenomegaly often accompany many of the illnesses which cause neutropenia.

⑤ — Bacterial sepsis frequently causes neutropenia, but also consider that pre-existing severe neutropenia can result in a high risk of bacterial or fungal sepsis. Empiric, broad-spectrum antibiotic therapy may be indicated, particularly if the ANC is below 500 cells/µl. The CBC should be repeated 3–4 weeks later to ensure that the neutropenia was a result of the infection and that it has resolved. If the neutropenia persists, further evaluation may be indicated.

⑥ — The overwhelmingly most common cause of transient neutropenia is viral infection. The neutropenia may persist for 3–8 days during acute viremia. These patients do not generally require the intensive use of broad-spectrum antibiotics during febrile episodes unless there is evidence suggesting a more chronic and severe form of neutropenia that is not likely to resolve quickly. The most reasonable approach in uncomplicated illnesses is simply to repeat the CBC 3–4 weeks later when the neutropenia has usually recovered. Persistent neutropenia raises the question of hepatitis (A, B or C), HIV, or an alternative, nonviral diagnosis such as autoimmune neutropenia.

⑦ — Cyclic neutropenia is sporadic or inherited often in an autosomal-dominant fashion, and is characterized by regular, periodic (21 ± 4 days) oscillations in the number of peripheral neutrophils from a peak usually <1,900 cells/µl to profound neutropenia. The nadir is often accompanied by fever, stomatitis and cervical adenitis. Most of these children have symptoms, usually cyclical, which prompt further evaluation (including sequential neutrophil counts). These patients have mutations in the neutrophil elastase gene. G-CSF can be helpful in preventing infections.

⑧ — No specific diagnosis is established in many children with chronic granulocytopenia. There is often no history of complicating infections in spite of fairly severe neutropenia. This was labeled as chronic benign granulocytopenia of childhood in young children, but most are now believed to have autoimmune neutropenia. There remain many children and young adults who have chronic benign neutropenia who are asymptomatic and no underlying diagnosis is ever established. Occasionally, these are familial.

⑨ — Bone marrow replacement with leukemia, lymphoma or metastatic solid tumors that infiltrate the bone marrow more often cause pancytopenia rather than isolated neutropenia. Bone marrow biopsy is invaluable in assessing marrow cellularity, which is markedly diminished in aplastic anemia and myelofibrosis. Severe congenital neutropenia (Kostmann syndrome) is characterized by an arrest in myeloid maturation at the promyelocyte stage of the bone marrow resulting in an ANC less than 200/µl; it is also often caused by mutations in the neutrophil elastase gene. These patients suffer from recurrent severe pyogenic infections, especially of the skin, mouth, and rectum. Marrow cytogenetics is important for diagnosing myelodysplasia. Myelokathexis can also be diagnosed by marrow findings. In general, neutropenia is caused rarely by intrinsic defects in myeloid cells or their progenitors.

⑩ — This most common cause of chronic neutropenia in infants is identified by the presence of antineutrophil antibody. Most patients have a fairly benign clinical course with few if any infections. Isoimmune neutropenia, analogous to Rh isoimmunization, occurs transiently in neonates and may last for several weeks.

⑪ — Patients with a history of malabsorption from infancy should be evaluated for Shwachman syndrome; this includes skeletal films (25% have metaphyseal dysplasia), a bone marrow (aspirate, biopsy and cytogenetics), and an evaluation of exocrine pancreatic function. Severe malnutrition can cause neutropenia directly or via folate and/or vitamin B_{12} deficiency (the latter two usually associated with anemia or pancytopenia, macrocytosis, macro-ovalocytosis and hypersegmentation of neutrophils).

⑫ — Congenital neutropenias can be associated with specific physical findings, bone abnormalities or metabolic diseases (e.g. hyperglycinuria, methylmalonic aciduria, tyrosinemia).

⑬ — Neutropenia may accompany dysgammaglobulinemia as well as hyper-IgM syndrome. A lymphoproliferative-mediated neutropenia may also be associated with circulating large granular lymphocytes (i.e. suppressor T cells or NK cells). Paroxysmal nocturnal hemoglobinuria (PNH) is often accompanied by anemia and occasionally neutropenia and thrombocytopenia. Diagnosis is established by the failure of expression of CD16 on circulating neutrophils.

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The child with recurrent infection: leukocyte dysfunction

Undertake evaluation if evidence of frequent or unusual infections ①

History, family history, physical examination ①
Leukocyte, platelet, reticulocyte, and differential counts + leukocyte morphology ②

→ **Anatomic or obstructive defect** ⑨

Abnormal examination, CBC, or leukocyte morphology

← Abnormal

→ Normal

Evaluate IgG/complement/cellular immunity
IgG, IgM, IgA, IgE levels and IgG subclasses 1–4
Titers to vaccine antigens (tetanus, diphtheria, measles, *H. influenzae* polysaccharide)
Delayed hypersensitivity skin tests *(Candida,* tetanus toxoid, mumps, *Trichophyton,* streptokinase-strepodornase)
Total T, T-helper, T-suppressor cells and helper/suppressor ratio
C3, C4, CH50
Chest and sinus X-rays

↓

Abnormal

↓

IgG/complement/cellular immunity disorder

↓

⇓ immunoglobulins ⑭
⇒ hypogammaglobulinemia syndromes
⇓ cellular immunodeficiency ⇒ severe combined immunodeficiency, AIDS, DiGeorge syndrome ⑮
⇓ complement ⇒ hypocomplementemia syndromes ⑯
IgE >2,000 ⇒ hyper IgE syndrome ⑰

← Normal

Phagocyte evaluation
Nitroblue tetrazolium (NBT test)
Superoxide (O_2^-) assay
Chemotaxis assays
Rebuck skin window
In vitro assay with patient and control sera

↓

Abnormal

↓

Phagocytic defect

↓

Absent O_2^- or abnormal NBT test
⇒ chronic granulomatous disease ⑬
Abbreviated O_2^- production ⇒ *glutathione synthetase or reductase deficiency*
Abnormal chemotaxis only ⇒ complement deficiency, acquired humoral defects
Absent O_2^- production ⇒ *PMN G6PD deficiency*
Chemotaxis abnormal with serum control
⇒ *LAD, Chediak-Higashi, specific granule deficiency,* Rac-2 deficiency

← Normal

Further phagocyte evaluation
Myeloperoxidase stain
CD11/CD18 PMN surface glycoprotein
Quantitative ingestion assays (patient and control sera as opsonins)
PMN L-selection by flow cytometry
Rolling on L-selection ligand
Assess interferon-γ-interleukin-12 axis

↓

Other phagocytic defects

↓

Myeloperoxidase absent
⇒ myeloperoxidase deficiency ⑩
⇓ ingestion with patient's sera
⇒ opsonin defect
Absent CD11/CD18 + ⇓ ingestion ⑪
⇒ *LAD type 1*
⇓ ingestion with control serum
⇒ *PMN actin deficiency*
Absent L-selection ⇒ *LAD type 2*
Rolling on L-selection ligand
⇒ *Rac-2 deficiency*
Abnormal interferon-γ-interleukin-12 axis ⑫

↓

Easily identified disorders of neutrophil function

↓

Hemolytic anemia ⇒ *G6PD deficiency* ③
Howell-Jolly bodies ⇒ hyposplenia ④
Thrombocytopenia + eczema
⇒ *Wiskott-Aldrich syndrome* ⑤
Abnormal granules + Pelger-Huët anomaly ⑥ ⇒ *Specific granule deficiency*
Partial albinism, abnormal granules
⇒ *Chediak-Higashi* ⑦
Neutrophil count <1,500 ⑧ and, if normal, consider serial ANCs to R/O cyclic neutropenia

↓

(see 'Neutropenia', p 42)

① — An evaluation should be initiated on patients who have one of the following clinical features: more than two systemic bacterial infections; three serious respiratory infections or bacterial infections per year; presence of an infection at an unusual site; infection with unusual pathogens *(Aspergillus* pneumonia, disseminated candidiasis, or infection with *Serratia marcescens, Nocardia* spp., *Burkholderia cepacia);* infections of unusual severity; dissemination of recurrent mycobacterial infections. In general, the more unusual the individual infection the less frequently it needs to occur before meriting further study. The evaluation is complicated by the knowledge that children with recurrent bacterial and fungal infection seldom have an identifiable defect of leukocyte function.

② — Attention to the values obtained in the complete blood count, differential count and morphology of the neutrophils may indicate some either quantitative or qualitative disorder of the neutrophil. When these studies are normal, the continuing evaluation becomes increasingly complex and dependent upon experienced laboratory support. Many of these tests are bioassays with substantial test-to-test variability. This further emphasizes the importance of carefully selecting which children merit further investigation.

③ — Findings consistent with both hemolytic anemia and recurrent infections with catalase-positive organisms should initiate quantitation of neutrophil G6PD levels. If the activity of G6PD is below 5%, this would be consistent with a variant form of CGD. Although hemolytic anemia due to G6PD is very common, neutrophil dysfunction causing infections is very rare because the level of G6PD must be less than 5% of total.

④ — Howell-Jolly bodies observed on peripheral smear in a patient with a history of recurrent bacterial infections with encapsulated organism suggests functional or anatomical asplenia.

⑤ — Patients who have a triad of symptoms including recurrent infections involving encapsulated bacteria, hemorrhage secondary to thrombocytopenia and platelet dysfunction, and atopic dermatitis should be evaluated for Wiskott-Aldrich syndrome.

⑥ — Patients with a history of recurrent bacterial infections (especially soft tissue abscesses), Pelger-Huët anomaly (2-lobed neutrophil nuclei with a dumbbell shape) and absence of neutrophil specific granules should be evaluated for specific granule deficiency by quantitating absolute levels of neutrophil lactoferrin.

⑦ — Patients who present with a history of recurrent skin infections or more serious infections associated with an albinism-like phenotype should be evaluated for the presence of giant granules in their myeloid cells. If giant granules are present, these patients have features of Chediak-Higashi syndrome.

⑧ — Patients who have a history of recurrent mouth ulcers, gingivitis, and cellulitis and neutropenia should be further evaluated for a severe chronic neutropenia disorder.

⑨ — Approximately 10% of children who present with a history of recurrent infections have underlying chronic disease or a structural defect that predisposes them to recurrent infections. Most children with a possible nonimmunologic cause for recurrent infections should undergo laboratory tests such as a complete blood count, chest X-ray, sweat test and cultures of involved sites.

⑩ — Individuals with a history of recurrent *Candida* infection and diabetes should have their neutrophils evaluated for myeloperoxidase deficiency by performing a myeloperoxidase stain.

⑪ — Individuals who have a history of delayed separation of the umbilical cord, persistent neutrophilia and a history of recurrent pyogenetic infections should have flow cytometry measurements of CD11/CD18 integrin expression on neutrophils. Individuals lacking expression of CD11/CD18 have leukocyte adhesion deficiency (LAD) type I. In contrast, patients with a history of pyogenic infection, neutrophilia, mental retardation, Bombay red cell phenotype likely have LAD type II. Their neutrophils normally express CD11/CD18 but are unable to express L-selectin on their surface.

⑫ — Infants presenting with a history of disseminated atypical microbacteria infection, recurrent *Salmonella* infection or fatal BCG infection following vaccination should have evaluation of the interferon-γ-interleukin-12 axis.

⑬ — Patients who have recurrent lymphadenitis, hepatic abscesses, osteomyelitis at multiple sites or in the small bones of the hands or feet, or documentation of a family history of recurrent infections or unusual catalase-positive microbial infections suggest the disorder of chronic granulomatous disease. The diagnosis is usually made by using the dye NBT, in which the yellow, water-soluble tetrazolium dye is reduced to the blue insoluble form of formazan pigment by O_2^- generated from normal Ig-activated phagocytes. Phagocytes from patients who have chronic granulomatous disease fail to reduce NBT because they cannot produce O_2^-.

⑭ — Individuals with recurrent pyogenetic infections involving multiple sites or organ systems should be evaluated for possible neutrophil dysfunction and opsonic defects involving antibody or complement levels because 80% of patients with primary immune deficiencies also have an antibody deficiency. Tests for antibody function as well as immunoglobulin level determinations are appropriate.

⑮ — In contrast to the antibody deficiency disorders, defects in T cell function predispose individuals to opportunistic infections. Severe combined immunodeficiency syndrome with diversity of genetic causes and profound deficiencies of T and B cells usually presents in the first few months of life with diarrhea and failure to thrive. Diagnostically, the infant with severe combined immunodeficiency has lymphopenia. The lymphocytes of these children fail to proliferate in vitro when challenged with mitogens. The levels of serum immunoglobulin are low.

⑯ — Individuals with a history of frequent infection with high-grade pathogens such as pneumococci and findings consistent with glomerulonephritis, vasculitis or systemic lupus erythematosus should have quantitation of C2, C3, C4 and CH50. Patients deficient in C5, C6, C7, C8 or C9 have a higher-than-normal prevalence of gonococcal and meningococcal disease because of a propensity to neisserial infections.

⑰ — Patients who have a history of severe dermatitis, recurrent infections including pneumonia, staphylococci abscesses and eosinophilia should have IgE levels determined. If the levels exceed 2500 IU, the findings are consistent with hyper IgE syndrome. These patients as well as those with Chediak-Higashi syndrome and specific granule deficiency have impaired chemotaxis.

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Lymphadenopathy①. 1. Generalized lymphadenopathy

History: duration, fever, weight loss, night sweats – evidence of systemic infection, inflammatory disease or neoplasia, sexual history, travel ②

Respiratory difficulties, wheezing, facial swelling, plethora or orthopnea ⑪ → **Possible superior vena cava syndrome** (see 'Recognition and management of superior vena cava syndrome', p 96)

Examination: distribution (localized or generalized) ③, size, consistency, tenderness, warmth, surrounding erythema ④

→ **Localized adenopathy** (see 'Lymphadenopathy. 2. Localized adenopathy', p 48)

Generalized adenopathy

CBC, blood smear, ESR, LDH, uric acid, renal and hepatic function, ± CXR ⑤

Flu-like symptoms, rhinitis, pharyngitis, malaise, headache ⑥
Fever expected but not specific
Nodes relatively soft, often tender, non-erythematous, rash, mild-to-moderate hepatosplenomegaly
Normal CBC or mild leukopenia, ± atypical lymphocytes, normal uric acid
ESR often normal if viral illness

Infection likely
Consider **EBV, CMV, varicella,** rubella, mumps, toxoplasmosis, measles, chlamydia, HIV, TB, syphilis, fungal
Consider collagen vascular and inflammatory disorders

Appropriate serology if indicated: EBV, CMV most commonly
Appropriate studies for bacterial and fungal diseases if indicated

Suspicion of malignancy still persists ⑦

Yes → *Lymph node biopsy and/or bone marrow aspirate ± biopsy*

No → *Treat/observe as appropriate for the specific infection or inflammatory disorder*

Weight loss, night sweat, bone pain
Painless, progressive node enlargement and/or supraclavicular adenopathy, nodes firm/rubbery and fixed to skin/underlying tissues ⑧
Abnormal CBC, smear, ↑ uric acid, ↑ LDH, abnormal CXR

High risk for malignancy
Uric acid, Ca, P, K, BUN, CXR
Lymph node biopsy and/or bone marrow aspirate or biopsy ± cultures
(marrow studies first if CBC consistent with bone marrow involvement)

(see 'Management of biopsy tissue in children with possible malignancies', p 100)

– for malignancy → **Infection or other inflammatory state likely**

+ for malignancy → **Hodgkin disease** ⑧
Non-Hodgkin lymphoma
Leukemia
Neuroblastoma
Rhabdomyosarcoma
Histiocytic disorders (usually non-malignant)

Chemotherapy ± radiation protocol for each specific malignancy or as per protocol for the specific histiocytic disorder

↑ uric acid, P, K, BUN
(see 'Recognition and management of tumor lysis syndrome', p 94)

Still consider malignancy if no other etiology apparent

Suggestive of collagen vascular disease or chronic inflammation
Vasculitic rash, arthritis/arthralgia
Symptoms often chronic
Medication use
± ↑ ESR, abnormal renal function

No
Leukocyte assays for storage diseases if very prominent splenomegaly ⑨
Positive → *Storage disease*
Gaucher
Nieman-Pick
Therapy as per specific storage disease

Yes
Anti-ds-DNA antibodies and ACE
Drug use ⑩
Rheumatoid arthritis
SLE
Sarcoidosis
Serum sickness
Drug-induced lymphadenopathy ⑩
Therapy dependent on the specific diagnosis and the individual presentation

① — Lymph nodes are not generally palpable in the neonate. During childhood, nodes are not considered enlarged unless at least 1 cm in diameter for cervical and axillary nodes or 1.5 cm for inguinal nodes. Most children have shotty adenopathy in the cervical, posterior auricular and inguinal areas. Even using these standards, lymphadenopathy is still very common in children and is most often due to routine, uncomplicated intercurrent infections.

② — History should include travel (e.g. tuberculosis, histoplasmosis), possible food contamination (brucella, mycobacterium), pets (cats for cat scratch or toxoplasmosis), medications, allergies, and sexual history (HIV, lymphogranuloma venereum). Fever, drenching night sweats (classically necessitating changing of bedclothes) and weight loss of >10% in the previous 6 months represent the 'B' symptoms classically associated with Hodgkin disease; these are not specific for this disorder, but the latter two particularly necessitate further evaluation.

③ — Generalized (≥ 2 non-contiguous lymph node groups) lymphadenopathy is indicative of systemic disease. Localized enlargement suggests a local cause in the area of drainage. Concomitant splenomegaly suggests a systemic disorder, but this occurs with generalized adenopathy due to malignant or benign disorders. The evaluation of localized lymphadenopathy is continued in the next algorithm, *'Lymphadenopathy. 2. Localized adenopathy'*, p 48.

④ — Tenderness, warmth, and erythema are usually due to bacterial infection. Fluctuance suggests secondary abscess development. These findings are usually localized.

⑤ — One of the difficult decisions is which initial laboratory studies to perform. Although the vast majority of minor lymphadenopathy and flu-like symptoms in children are due to minor viral illness, these can be presenting features of leukemia and other malignancies. In a child whose clinical picture is very typical of a viral illness and whose adenopathy is mild, it may be reasonable to simply follow the child without laboratory studies. However, if the history and physical examinations provide any concerns that this may be more than a simple, transient viral illness, laboratory tests are essential. CBC, blood smear, ESR, LDH, uric acid, as well as renal and hepatic function studies, are reasonable initial screening studies. EBV titers are done if the clinical picture suggests infectious mononucleosis or if a substantial percentage of atypical lymphocytes are noted on blood smear. Clearly, normal blood cell counts and mildly raised transaminases suggest a viral illness whereas depressed hemoglobin and platelet count with ⇑⇓ WBC would suggest bone marrow infiltration. Examination of the blood film may yield further clues before proceeding to possible lymph node biopsy and/or bone marrow examination. LDH often increases in malignant disorders, but also does in hepatic disease and hemolysis. Elevated uric acid, P and BUN and lowered Ca are components of tumor lysis syndrome and suggest a malignancy. A CXR should be done if there are any chest symptoms, adenopathy surrounding the thorax or concerns about malignancy; it may identify, among others, mediastinal adenopathy due to malignancy, mycobacterium or sarcoidosis. Mediastinal widening on CXR is most likely due to malignancy (see *'Assessment of a mediastinal mass'*, p 76).

⑥ — 'Flu-like' symptoms without weight loss suggests a viral illness. Weight loss (especially >10%) infers a more serious diagnosis such as malignancy, tuberculosis, or HIV infection. The clinical picture, a high WBC or shift to the left and an elevated ESR suggest bacterial infection. Consider TB exposure, high-risk sexual activity, substance abuse, and history of transfusions.

⑦ — No specific diagnosis is established in many children who are presumed to have a viral illness. In such children, the possibility of an underlying malignancy should always be kept in mind. If the adenopathy continues to increase over a 2-week period or fails to resolve over a 6-week period, or there are other changes (e.g. development of a more firm or matted consistency of the nodes, supraclavicular adenopathy, weight loss, night sweats or respiratory distress), biopsy should then be done.

⑧ — Malignant nodes are often fixed to the skin and/or underlying tissues and the nodes are often large, firm or rubbery and may be matted together. Supraclavicular adenopathy is very concerning and usually indicative of malignancy or other serious pathology. It must be remembered that not all malignant infiltration presents with large lymph nodes. In particular, in acute lymphoblastic leukemia shotty lymphadenopathy can be a presenting feature – clues to this diagnosis will be obtained from the CBC. The lymphadenopathy of Hodgkin lymphoma may wax and wane leading to apparent 'responses' to antibiotic therapy and diagnostic delay. Note that tuberculous nodes can be firm, matted and fixed to surrounding tissues, leading to diagnostic confusion.

⑨ — Although storage diseases cause adenopathy, massive splenomegaly is usually much more obvious. Contemplation of such a diagnosis without splenomegaly should prompt repeat abdominal examination with splenic palpation beginning in the left iliac fossa.

⑩ — A number of drugs can result in lymphadenopathy alone or as part of a systemic lupus erythematosus-like disorder, including phenytoin, isoniazid, hydralazine, dapsone, procainamide and allopurinol.

⑪ — These symptoms suggest mediastinal adenopathy or a mass causing superior vena cava syndrome, or a malignant effusion (see *'Recognition and management of superior vena cava syndrome'*, p 96).

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Lymphadenopathy ①. 2. Localized adenopathy

History: recent fever, weight loss, night sweats, duration of symptoms, 'B symptoms', recent injuries/wounds/infections/surgery/dental complications, pets, sexual history, recent travel ①

Examination: involves a single set of nodes or contiguous sets of nodes – size, consistency, warmth, erythema, tenderness, fluctuance, dental disease, rashes, wounds ②

Localized

Occiptal	Periauricular	Cervical	Submaxillary	Supraclavicular	Axillary	Mediastinal	Abdominal	Ilioinguinal
Scalp infections ③ Rubella Roseola *Malignancy*	Cat-scratch disease ④ Eye infections Skin infections *Tularemia*	**Streptococcal tonsillitis** ⑤ **Upper respiratory infection** **Acute adenitis** **EBV** Malignancy ⑥ Kawasaki disease ⑦ Toxoplasmosis Nonlymphoid masses ⑧ *Sinus histiocytosis*	**Local infection of teeth and mouth** Acute lymphadenitis Hodgkin or non-Hodgkin lymphoma Tuberculosis *Malignancy*	**Malignancy** ⑨ TB Histoplasmosis Coccidioidomycosis	**Infections of arm and axilla** **Cat-scratch disease** ④ Reactions to immunizations Malignancy	**ALL** **Hodgkin disease** **Non-Hodgkin lymphoma** Neuroblastoma Tuberculosis Fungal infection Teratoma *Thyroid cancer* *Thymoma* *Sarcoidosis* ⑩ *Cystic fibrosis*	**Non-Hodgkin lymphoma** **Hodgkin disease** Mesenteric adenitis *Other malignancies*	**Infections of leg/groin** Syphilis Lymphogranuloma venereum *Plague*

Assess all clinical data ⑪ and determine if likely infectious, inflammatory or malignant

Likely acute adenitis or related to bacterial infection

Trial of antibiotics, surgical drainage if suppurative

Failure to improve, symptoms or laboratory findings suggestive of malignancy

Suspected viral illness – observe for 2–6 weeks

Laboratory studies if ? about diagnosis, progressing adenopathy, new symptoms or signs or failure to resolve in 6 weeks

Failure to improve, symptoms or laboratory findings suggestive of malignancy

Suspicion of malignancy – CBC, blood smear, renal/hepatic function, LDH, uric acid, Ca, P, CXR, possible CT scan of involved region

Early lymph nodes biopsy (and/or marrow aspirate/biopsy if CBC evidence of marrow involvement); biopsy the largest, most recently enlarging lymph node and not always the easiest one

(see 'Management of biopsy tissue in children with possible malignancies', p 100)

? if this is a non-lymphoid mass

Radiologic studies – US, plain films, ? CT or MRI

Possible biopsy or excision depending on individual case

① — History should also include recent wounds or surgery, dermatologic or dental problems, food contamination, recent immunizations or injections, medications, allergies, illicit drug use, pets (e.g. cats for cat scratch or toxoplasmosis or other animals), and sexual history.

② — Normal node size varies with the group of nodes and age. Nodes are not generally palpable in the neonate but often become palpable in the first year. During childhood, nodes are not considered enlarged unless they are at least 1 cm in diameter for the cervical and axillary nodes or 1.5 cm for the inguinal nodes and 5 mm for the epitrochlear nodes. However, cervical lymph nodes up to 2.5 cm in diameter are not uncommon with intercurrent infections. Most children have shotty adenopathy in the cervical, posterior auricular and inguinal areas. Erythema, tenderness, warmth and fluctuance are most often due to bacterial adenitis. Signs of malignant adenopathy are described in *'Lymphadenopathy. 1. Generalized lymphadenopathy'* (p 46).

③ — Occipital adenopathy is most often caused by scalp infections, often related to pediculosis capitus, tinea capitis, and secondary infection of seborrheic dermatitis.

④ — Cat-scratch disease is caused by infection with the organism *Bartonella henselae,* typically following a scratch from a kitten or young cat. A papule develops at the site of the trauma and usually 1–2 weeks later localized lymphadenopathy develops which may persist for several months. A small percentage may suppurate and unless secondarily infected, bacteriological culture is negative. Serological testing is specific and quite sensitive. Lymph node biopsy shows granulomata and organisms (with a Warthin-Starry silver stain). Treatment is not always indicated in the immunocompetent host and needs discussion with the Infectious Disease Department.

⑤ — Cervical lymphadenopathy is common and is usually due to viral illnesses and group A streptococcal pharyngitis. Acute adenitis, in which the nodes become tender, erythematous and may suppurate, is usually caused by group A streptococcus or *Staphylococcus aureus.*

⑥ — Acute leukemias, non-Hodgkin lymphoma, neuroblastoma and rhabdomyosarcoma predominate in this region in the first 6 years of life while Hodgkin disease and non-Hodgkin lymphoma are most common after 6 years of age. 80–90% of Hodgkin disease and 40% of non-Hodgkin lymphoma present with cervical adenopathy. Thyroid cancer, nasopharyngeal carcinoma and fibrosarcoma are much less common.

⑦ — An acute inflammatory condition characterized by combinations of prolonged (at least 5 days) high, often spiking fevers, bilateral conjunctivitis, strawberry tongue and injected nasopharyngeal mucosa, cervical lymphadenopathy, skin rashes, desquamation of the hands and feet, and most seriously coronary arteritis. High-dose aspirin is traditionally given for symptomatic relief. Intravenous immunoglobulin may reduce the frequency of coronary artery abnormalities.

⑧ — Nonlymphoid masses can be mistaken for nodes, especially in the cervical region. Examples include cystic hygroma, goiter, thyroid carcinoma, branchial cleft cysts or sinuses, sternocleidomastoid tumors, teratomas, dermoid cysts and hemangiomas.

⑨ — Supraclavicular lymphadenopathy is very concerning, often indicating a malignant process located in the mediastinum or abdomen. Should baseline investigations prove unremarkable, these children certainly warrant consideration of an early biopsy.

⑩ — Sarcoidosis classically presents with bilateral hilar lymphadenopathy. More severe cases also have pulmonary parenchymal infiltration and hypercalcemia. Elevated levels of serum angiotensin-converting enzyme (ACE) are a useful diagnostic pointer.

⑪ — Nodes larger than 1 cm, particularly in the cervical region, are usually due to common viral and bacterial illnesses. In these instances the nodes usually decrease in size within 2–6 weeks. Adenopathy persisting for more than 6 weeks or continuing to increase for more than 2 weeks is concerning, and biopsy should be considered in the absence of an established etiology (e.g. EBC, CMV). Firm nontender nodes are more likely malignant while nodes enlarged due to infection or inflammation are often tender, warm and may have overlying erythema and fluctuance. If there is concern in the clinical evaluation of malignancy, the studies noted should be obtained. Pancytopenia, neutropenia, thrombocytopenia, more-than-mild anemia, elevated LDH, P and uric acid are all red flags for malignancy and alone may justify lymph nodes biopsy. Mild anemia is common in infectious adenopathy. The location of the enlarged nodes is also important in considering biopsy; isolated low cervical and/or supraclavicular adenopathy is more likely to be malignant than high cervical adenopathy. However, biopsies of enlarged lymph nodes in the asymptomatic child have a low yield. The biopsy should usually examine a recently enlarging node and not the easily reached most superficial one.

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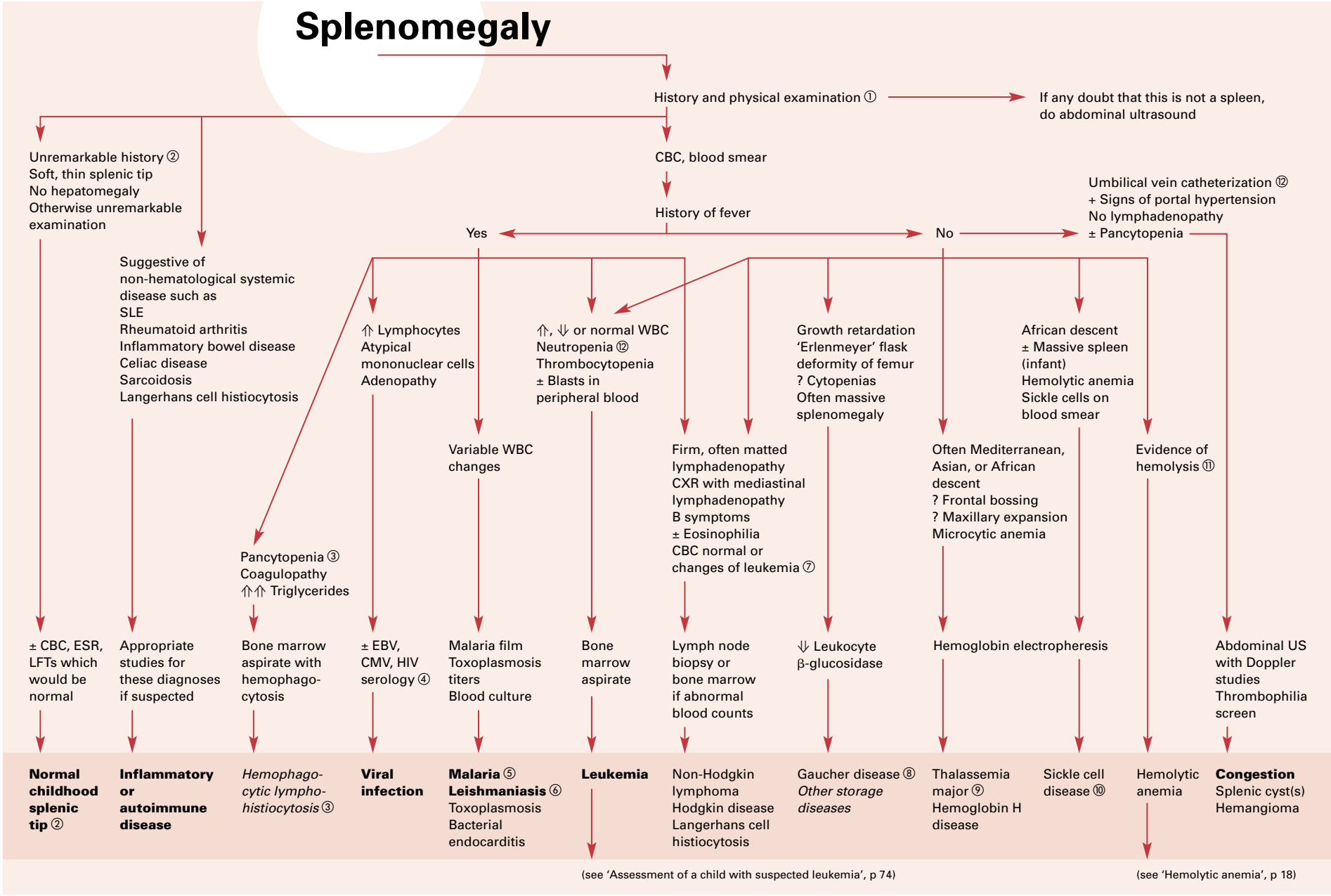
Splenomegaly



(see 'Assessment of a child with suspected leukemia', p 74)
(see 'Hemolytic anemia', p 18)

① — Massive splenomegaly, defined as a spleen below the level of the umbilicus, has few causes in children – splenic sequestration in sickle cell disease, thalassemia major, Gaucher disease and, occasionally, leukemia or portal hypertension. The causes of lesser degrees of splenomegaly are innumerable and require careful history and examination before extensive laboratory investigation. A very firm spleen is more consistent with non-infectious etiologies. Caution should be observed in assuming that a left upper quadrant abdominal mass is a spleen. Retroperitoneal tumors (neuroblastoma and Wilms tumor) can be mistaken for a spleen. Abdominal ultrasound can distinguish splenic from nonsplenic masses if in any doubt.

② — A soft, thin spleen tip can be palpated in 15% of neonates, 10% of healthy children and 5% of adolescents and is not indicative of any pathological process. Baseline investigations, particularly if there are other clinical concerning issues, should include a CBC, ESR, and kidney and liver profiles; however, a soft spleen tip in an otherwise well child does not always necessitate further investigation. Associated hepatomegaly can occur in most disorders causing splenomegaly, but would not be expected in the well child with a palpable spleen tip.

③ — A rare but important diagnosis as prompt treatment can be life-saving. Hemophagocytic lymphohistiocytosis is divided into primary – an autosomal-recessive disease that typically has a florid presentation in infancy, and secondary – (sporadic) that occurs at an older age. The diagnosis is made by the combination of peripheral cytopenias, bone marrow hemophagocytosis, coagulopathy (with hypofibrinogenemia predominating), ⇑ ferritin (may be ⇑⇑⇑) and ⇑ fasting triglycerides. The primary form requires bone marrow transplantation for cure.

④ — Serologies are often not necessary in mild cases, so clinical judgement should be used. HIV should be considered with appropriate risk factors or chronicity.

⑤ — Hyper-reactive malarial splenomegaly syndrome, formerly known as tropical splenomegaly, occurs widely throughout Africa, India and SE Asia and is probably caused by an immune 'over-reaction' to chronic malaria infection. It is characterised by massive splenomegaly, weight loss, ⇑ anti-malaria antibody titres, ⇑ serum IgM and a slow resolution with prolonged anti-malarial prophylaxis.

⑥ — Visceral leishmaniasis (Kala-Azar) is caused by protozoan organisms belonging to the *Leishmania donovani* complex transmitted by various species of sand fly. Visceral Leishmaniasis involves the liver, spleen, bone marrow and lymph nodes, and can be acquired on a short vacation to an affected area. Incubation is typically 1–3 months. Diagnosis is based upon identification of 'L-D bodies' in macrophages in the bone marrow or specific serology. Relatively easily treated in the immunocompetent host but can be much harder to eradicate in the immune suppressed.

⑦ — Sixty percent of children with ALL present with fever. Most have neutropenia, anemia and thrombocytopenia, and half of them have elevated WBCs. Those with low WBC counts may not have blasts in the peripheral blood. Children with lymphadenopathy due to non-Hodgkin lymphoma can also present with marrow involvement. The distinction between these disorders is ill defined, with many using the arbitrary criteria of more than 25% of blasts in the marrow as signifying leukemia and not lymphoma. With marrow involvement it may be possible to diagnosis the lymphoma using pathology and flow cytometry on bone marrow, avoiding lymph node biopsy.

⑧ — Gaucher disease is divided into 3 subtypes and is due to deficiency of the enzyme β-glucosidase (glucocerebrosidase). Large lipid-filled macrophages (Gaucher cells) accumulate in the bone marrow, spleen and liver. Type I (⇑ prevalence in Ashkenazi Jews) is the most common and leads to splenomegaly which may be massive by adolescence. Hypersplenism (pooling of cellular components of blood within the spleen) is common. Bony abnormalities are caused by lipid accumulation in the bone marrow. The diagnosis is now established based on leukocyte β-glucosidase activity and no longer requires bone marrow examination. Types II and III are much rarer and are characterized by progressive neurological disease (absent in type I) and an extremely fulminant course. Replacement recombinant enzyme therapy (Cerezyme®) is now available and has produced benefit in type I disease. Niemann-Pick type B, Hunters and Hurlers disease are other rare causes of splenomegaly secondary to infiltration because of metabolic enzyme deficiency.

⑨ — Untreated β-thalassemia major and intermedia can lead to massive splenomegaly, secondary to extra-medullary hematopoiesis. Hypertransfusion (typically aiming to keep the nadir Hb >10 g/dl) suppresses the extramedullary hematopoiesis and may reduce the splenomegaly. The carrier state of either α- or β-thalassemia minor is not associated with splenomegaly. The more severe forms of α-thalassemia (hemoglobin H disease and α-thalassemia major) are associated with splenomegaly.

⑩ — The spleen removes damaged red cells and thus is often palpable in the early years of life in a child with sickle cell disease. However, by adulthood the spleen has been replaced by a fibrous nubbin secondary to multiple vaso-occlusive events – auto-splenectomy. Splenomegaly can persist into adulthood in patients with hemoglobin S-C disease and sickle cell β-thalassemia. Splenic sequestration crisis involves the sudden pooling of a large proportion of the blood volume in the spleen of infants with sickle cell disease with consequent and often massive splenomegaly; it can be rapidly fatal if not recognized and treated promptly. Parents should be taught splenic palpation to allow for early recognition and treatment.

⑪ — Jaundice in the absence of any overt liver disease can be an early indicator of hemolysis. Pallor and anemia are usually noted. The hyperbilirubinemia is unconjugated (see *'Hemolytic anemia'*, p 18).

⑫ — Neonatal umbilical vein catheterization and consequent thrombosis causing portal hypertension is becoming a much more common cause of isolated splenomegaly in the developed world. A detailed ultrasound examination with Doppler estimation of portal pressures and flow is necessary to confirm the diagnosis. Pancytopenia can result from 'hypersplenism'. Splenomegaly secondary to cardiac or liver failure is uncommon in children and would not normally provoke a hematology referral. Thrombophilia is becoming increasingly recognized as a cause of portal hypertension in children and certainly all children without a history of umbilical vein catheterization require a thrombophilia screen (see *'Thrombophilia evaluation for a newborn infant with thrombosis'*, p 70).

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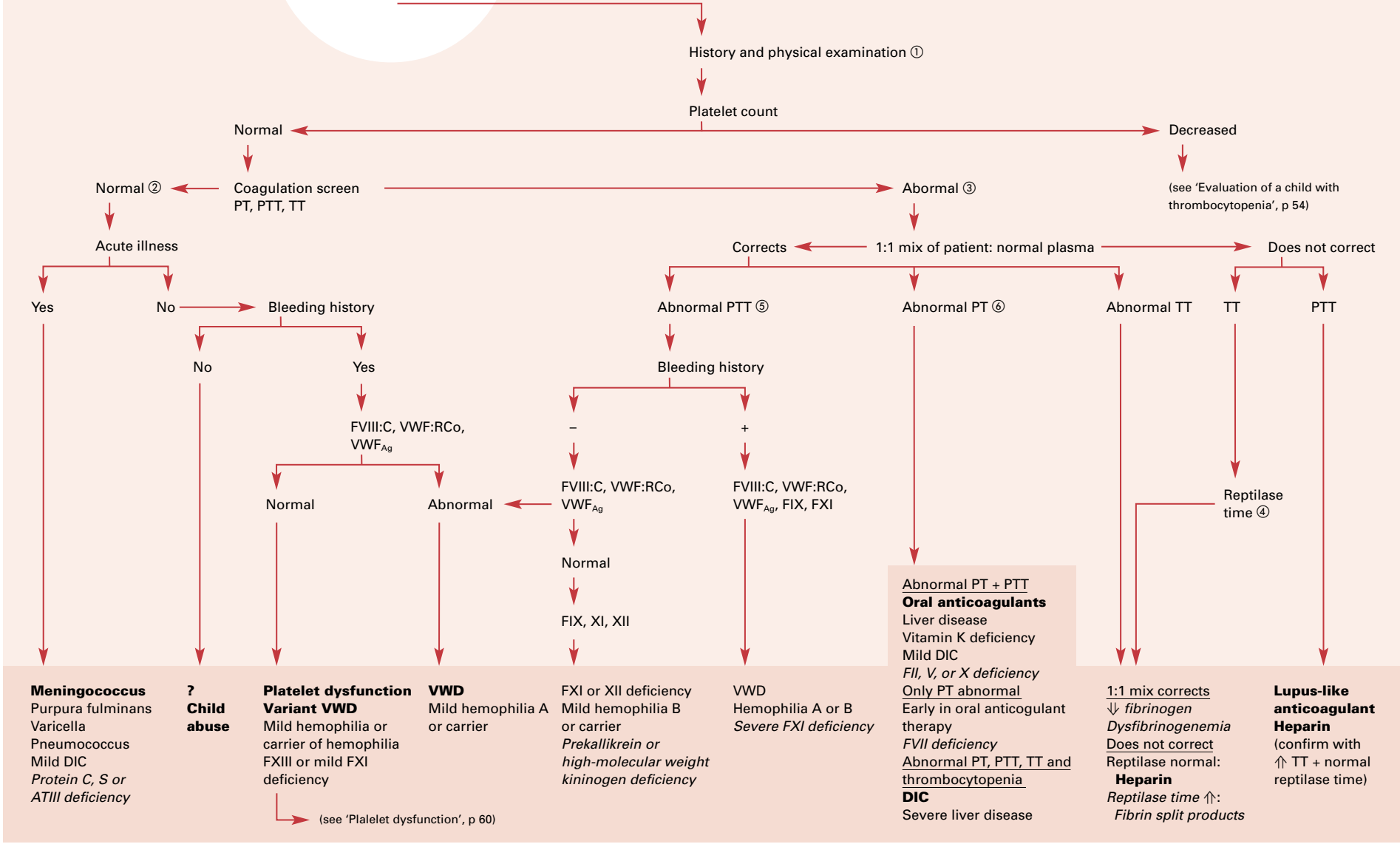
Evaluation of a child with bleeding or abnormal coagulation screening tests



① — Bleeding in a child can present as petechiae, purpura, epistaxis/mucosal bleeding, hematomas, gastrointestinal and genitourinary bleeding, excessive bleeding with procedures and surgery, as well as intracranial hemorrhage. Other children present with an incidental abnormal coagulation screen, often during presurgical screening, in the absence of clinical bleeding. Consider a platelet or vascular disorder if the bleeding is mucosal in nature or a clotting factor deficiency if it consists of deep-seated hematomas or hemarthroses. Nosebleeds and menorrhagia are the most common manifestations of von Willebrand disease (VWD). A family history of bleeding in only males suggests hemophilia A or B. A palpable, purpuric rash with the typical lower extremity predominance suggest the vasculitis of Henoch-Schönlein purpura. Less well localized rashes are often seen in viral illnesses, but an acutely ill child with a purpuric rash should be assumed to have meningococcemia or other bacterial septicemia until proven otherwise; although these children may develop DIC with low platelets and abnormal coagulation screen this often is not the case. A purpuric rash which becomes necrotic suggests purpura fulminans due to viral or bacterial infection, or a deficiency of a natural anticoagulant (protein C, S or antithrombin). Organomegaly suggests an infiltrative process: either malignancy or a storage disease.

② — A normal platelet count and normal coagulation screen suggests several disorders. If there is an acute illness consider purpura fulminans or mild DIC with infection. If the bleeding history is negative and the child is healthy consider the possibility of a bruising in a normal, active child, or the possibility of child abuse; the appearance of linear bruises or burns is strongly suspicious of abuse. If there is a past history of bleeding consider VWD and obtain factor VIII coagulant (FVIII:C), ristocetin co-factor which is the functional von Willebrand factor assay (VWF:RCo), and von Willebrand antigen (VWF_{Ag}) activities. FA100 closure time, if available, may provide an indicator of VWD and other platelet dysfunctions that is more accurate than the bleeding time (see *'Platelet dysfunction'*, p 60). Mild hemophilia or a hemophiliac carrier may present with normal coagulation studies and a positive history; the PTT may not prolong until the factor level is <30% (normal ~50–150%) so mild deficiencies may be missed. Factor XIII deficiency is a rare coagulation disorder that presents with umbilical stump hemorrhage, soft tissue hematomas and poor wound healing, but normal coagulation screen; a specific assay is required for this diagnosis. Vascular disorders causing purpura include Henoch-Schönlein purpura, infections, collagen vascular diseases, and collagen deficiencies (Ehlers-Danlos syndrome and Marfan syndrome).

③ — Normal platelet count and abnormal coagulation screen suggests a clotting factor deficiency or an anticoagulant. Repeating the abnormal test with a mixture of 1 part of patient plasma with 1 part normal plasma will normalize the test when a deficiency of a factor is present, but the screening test will remain abnormal after mixing if an anticoagulant is present. Lupus-like anticoagulants in children are frequent and transient postviral asymptomatic autoimmune reactions. Rarely, they cause thromboembolic disease and even less often bleeding problems. Lupus-like anticoagulants usually prolong the PTT. In the rare child in whom the anticoagulant results in acquired prothrombin deficiency, a bleeding tendency occurs and the PT is prolonged. The presence of a lupus-like anticoagulant should be confirmed by other phospholipid correction studies, including the platelet neutralization test and the Russell Viper venom test (RVVT). Heparin in the patient, or more often simply contaminating the sample, is frequent in the hospital setting.

④ — If heparin is present in the patient (or simply the laboratory sample), the TT will always be prolonged if the PTT is (the PT may be but is less sensitive to heparin). The reptilase (or Ancrod) time utilizes a snake enzyme which performs exactly like thrombin except that it is not inhibited by heparin. Therefore, a prolonged TT and a normal reptilase time confirm the presence of heparin. Prolongation of both the TT and reptilase times are consistent with a fibrinogen defect or increased FSP.

⑤ — If the coagulation screening test corrects with a 1:1 mix of patient and normal plasma, there is a factor deficiency. A markedly abnormal PTT with no history of bleeding suggests factor XII deficiency. Mild abnormalities of the PTT alone are most often due to vWD, given the 1% incidence of this disorder in the general population, but can also be due to mild factor deficiencies in mild hemophilia A or B or in carriers, or due to factor XI deficiency. Severe prolongations of the PTT due to factor deficiencies are usually due to hemophilia, but consider DIC in acutely ill patients.

⑥ — A prolonged PT is usually associated with a prolonged PTT, most often due to oral anticoagulants, liver disease, and vitamin K deficiency, and rarely to isolated deficiencies of factors II, V or X. The TT will be normal with oral anticoagulants and vitamin K deficiency, but may be abnormal in liver disease because of hypofibrinogenemia and/or elevated FSP. Rare isolated factor VII deficiency can cause an isolated prolongation of the PT, but this is usually seen at the beginning of oral anticoagulation therapy or vitamin K deficiency; FVII, which is only measured by the PT, falls much faster (half-life 3–6 h) than the other vitamin K- and hepatic-dependent factors. Prolongation of the PTT should be noted within 24–48 h. An abnormal TT suggests heparin effect or fibrinogen defects.

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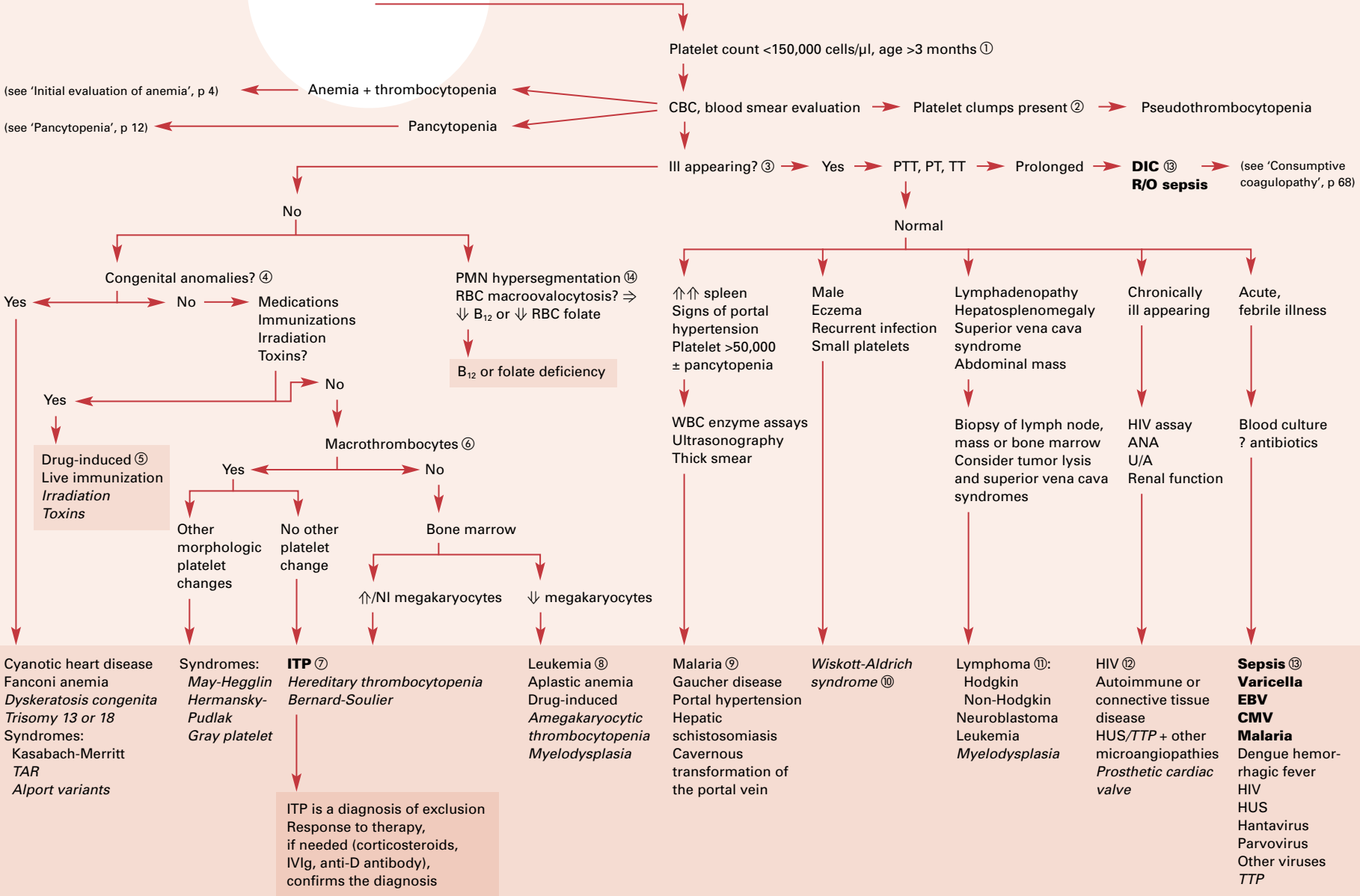
Evaluation of a child with thrombocytopenia



① — For infants <3 months of age, see *'Thrombocytopenia in the well neonate'* (p 56). Assess bleeding manifestations including bruising, petechiae, epistaxis, and menorrhagia, as well as travel, immunizations, HIV risk factors, diet and medications. Extensive petechiae and mucosal bleeding are indicators of greater hemorrhagic risk. Look for congenital malformations, joint or skin changes, adenopathy, and hepatosplenomegaly.

② — Spurious thrombocytopenia (TP) is usually caused by in vitro platelet clumping in anticoagulant and occurs in about 1/1,000 samples. Platelet clumps are noted on blood smear. Spurious results also occur if platelets aggregate in the syringe before reaching the anticoagulant, especially with difficulty obtaining the specimen. If suspected, obtain a new sample.

③ — It remains difficult to easily distinguish disorders of platelet destruction and production. Newer studies, such as reticulated platelets may be helpful, but are not widely available. Bone marrow examination may still be difficult to interpret. Practically, it is more helpful to simply consider whether the child appears ill or well.

④ — Several disorders, mostly rare, are associated with congenital anomalies. Children with *congenital cyanotic heart disease* may have moderate TP. *Kasabach-Merritt syndrome* is consumptive coagulopathy in a cavernous hemangioma. Although the hemangioma is usually obvious, it may be hidden in the viscera. Hemangiomas can resolve spontaneously, but corticosteroids and interferon may hasten involution. Radiation therapy is rarely used because of growth impairment and disfigurement. Compression or excision may be associated with uncontrollable hemorrhage. *Fanconi anemia* is a rare autosomal-recessive disorder usually associated with multiple physical anomalies. Mild-to-moderate TP or leukopenia as well as macrocytosis often precedes the eventual pancytopenia. *TAR* (thrombocytopenia and absent radii) is an autosomal-recessive syndrome with extremity deformity. *Dyskeratosis congenita* is a rare disorder with multiple anomalies (e.g. nail dystrophy, skin pigmentation, leukoplakia, eyes and teeth) in which TP or anemia precedes what ultimately becomes pancytopenia.

⑤ — Drug-induced TPs are most often due to quinine, quinidine, sulfa drugs, heparin and anticonvulsants. Attenuated vaccines, particularly measles and varicella, can cause mild-to-moderate thrombocytopenia.

⑥ — Macrothrombocytes are large platelets whose mean platelet volume (MPV) exceed the normal 7–11 fl. Young platelets resulting from rapid turnover are larger, but abnormally large platelets unrelated to platelet age occur in several rare platelet disorders.

⑦ — ITP is the most common childhood TP. The usual presentation is acute onset of petechiae and bruising in an otherwise well child, often related to a recent viral infection. CBC shows isolated, marked TP and smear reveals giant platelets. Although it is a diagnosis of exclusion, a well-appearing child who abruptly develops profound TP with an otherwise normal CBC almost always has ITP. Bone marrow studies are not necessary unless the diagnosis is in question or possibly before starting corticosteroids, but would show increased or normal megakaryocytes. Most children have acute, self-limited disease; 90% regain normal platelet counts within 9–12 months. The most serious complication is intracranial hemorrhage (<<1%). Mild-to-moderate disease usually requires no specific therapy. If necessary, treatment options are: IVIG, Rh_o (D) immune globulin (only if the child is Rh+), corticosteroids, and splenectomy. The latter is used only for life-threatening bleeding in acute ITP, but may be used in severe chronic ITP. Platelets are administered only for life-threatening hemorrhage. Most children with chronic ITP ultimately do recover. A minority of children with chronic ITP have an underlying abnormality, such as SLE or HIV. The combination of ITP and autoimmune hemolytic anemia (Evan syndrome) is a much more serious disorder, and is identified by a positive direct Coombs test. ITP often precedes AIHA by months or years. Treatment is often necessary.

⑧ — Bone marrow examination is indicated when no etiology is apparent. If ITP is likely, a marrow aspirate is often sufficient. If marrow involvement is suspected, a marrow biopsy should also be done. Infiltrative marrow disorders commonly present with lethargy, fever, infection, and bone pain; a leukocytosis with blast cells on smear or pancytopenia is usually present. Replacement of normal marrow with blasts confirms the diagnosis, usually leukemia but occasionally a solid tumor. Marrow examination also identifies bone marrow failure; aplastic anemia usually presents with pancytopenia but may initially demonstrate only TP. Rarely, pure megakaryocytic hypoplasia, with isolated TP, occurs due to congenital disease or drugs. Hereditary TP, usually with autosomal-dominant inheritance, often presents with normal-sized platelets and normal numbers of megakaryocytes in the marrow.

⑨ — The most common etiologies of hypersplenism (and the appropriate initial studies) include cavernous transformation of the portal vein, cirrhosis, and hepatic schistosomiasis (ultrasonography), malaria (thick smears) and Gaucher disease (leukocyte enzyme assay).

⑩ — Wiskott-Aldrich syndrome is a rare X-linked recessive immunodeficiency. Splenectomy can improve the TP, but is often followed by overwhelming sepsis and death.

⑪ — These malignancies may present primarily with lymphadenopathy or masses. Pancytopenia is more common but isolated TP occurs.

⑫ — TP occurs in 5–10% of patients with HIV infection and may be the presenting symptom. The TP may respond to antiviral therapy as well as steroids, IVIG, and splenectomy; the TP can remit spontaneously.

⑬ — Septicemia can cause moderate TP in the absence of DIC. Other infections, particularly viral, cause TP. During acute *Plasmodium falciparum* attacks, the platelet count can fall as low as 10,000–20,000/µl.

⑭ — Vitamin B_{12} or folate deficiency can present with TP, but PMN hypersegmentation, RBC macroovalocytosis or macrocytosis anemia are almost always present (see *'Macrocytic anemia'*, p 10). TP occurs in Fe deficiency when the microcytic anemia is usually obvious.

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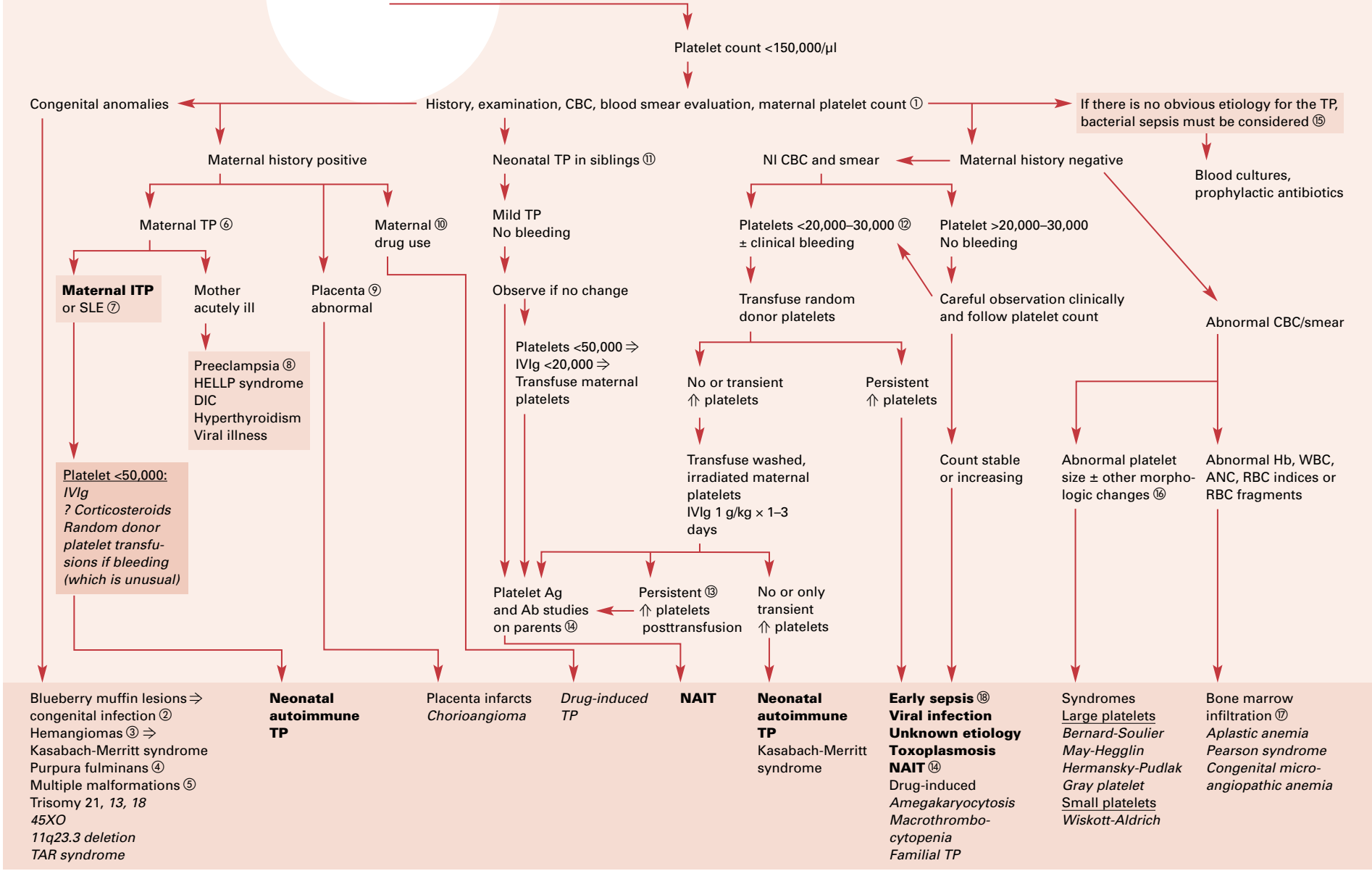
Thrombocytopenia in the well neonate



① — Thrombocytopenia (TP) occurs in 0.5–0.9% of all newborns.

② — 'Blueberry muffin' lesions are palpable blue skin nodules due to congenital infection (e.g. toxoplasmosis, rubella, CMV) and, rarely, congenital leukemia or hemolytic disease.

③ — Kasabach-Merritt syndrome is localized consumptive coagulopathy within a cavernous hemangioma. The hemangioma is usually visible, but can be occult especially within the liver. Bruit may be heard over the site of the lesion.

④ — Purpura fulminans with DIC may be primary due to congenital, severe deficiency of protein C or protein S, or secondary to infection.

⑤ — Seven percent of neonates with Down syndrome have TP; this is usually an isolated hematologic abnormality but can be associated with the transient myeloproliferative disorder, acute leukemia or polycythemia. In thrombocytopenia with absent radii (TAR) syndrome, platelets are typically decreased early in the first year of life, and then improve. Fanconi anemia rarely presents in the newborn with TP and absent or malformed thumbs.

⑥ — Gestational TP is mild (usually >70,000), asymptomatic, occurs in 5% of pregnant women and is not associated with neonatal TP. It can be confused with more concerning causes for maternal TP.

⑦ — Maternal ITP can cause neonatal autoimmune TP because of placental transfer of the maternal antibody directed against an antigen on both maternal and fetal platelets. It is among the more common causes of neonatal TP in well infants. The correlation between the maternal and fetal platelet counts is poor. Neonatal platelet counts are usually >50,000. The count often falls after birth to a nadir at days 1–3. Life-threatening hemorrhage is rare. Neither prenatal treatment nor Cesarean section is necessary. Maternal SLE or hyperthyroidism can cause similar autoimmune TP.

⑧ — HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome or DIC secondary to infection, amniotic fluid embolus, or peripartum hemorrhage in the mother can produce DIC in the infant. A current or past history of infection during the pregnancy may be a clue to TP due to viral or bacterial infection. It remains controversial whether maternal hypertension alone causes newborn TP.

⑨ — Chorioangioma or multiple placental infarcts can cause neonatal DIC and TP.

⑩ — Maternal drug use rarely causes neonatal TP, but causative drugs include anticonvulsants, quinidine, and antineoplastic agents.

⑪ — TP in siblings is suggestive of neonatal alloimmune thrombocytopenia (NAIT), autoimmune TP and the much less common familial forms of TP. If the maternal platelet count is normal, it is most likely due to NAIT. Parental studies (see *note 14*) will confirm the diagnosis.

⑫ — NAIT is the most common cause of severe TP in otherwise well infants, occurring in ~1/1,000–2,000 births. First pregnancies are affected as frequently as subsequent pregnancies. Antibody to the platelet antigen HPA-1 (PL^{A1}) is involved in 75% of cases involving European descent; 2% of this population does not express the antigen. In people of eastern Asian ancestry HPA-4b is the most frequently identified alloantigen. Approximately 15% of infants at risk (antigen-negative mother and antigen-positive father) develop the disease. Unlike autoimmune TP, the TP (usually <20,000) and clinical manifestations (~20% of these infants develop intracranial hemorrhage, half in utero) are severe. Cranial ultrasonography is used to determine if intracranial bleeding has occurred. TP worsens in the first days of life. Random donor platelets are usually positive for the responsible antigen so they usually survive very transiently. However, maternal platelets are antigen negative and survive normally; these platelets should be gently washed to remove excess antibody and irradiated to prevent GVHD. An alternative is known antigen-negative platelets from a donor other than the mother, but these are not usually readily available. Intravenous IgG is used alone for more moderate TP and, when necessary, along with random donor platelets until maternal platelets are hopefully available; it is not clear that corticosteroids are helpful. The natural history is resolution by 3–4 weeks of age.

⑬ — The diagnosis of NAIT is presumed if maternal platelets are effective after random donor platelets fail to maintain the platelet count posttransfusion; this is determined by measuring platelet counts 1 and 4 h after transfusion.

⑭ — Further testing is necessary for infants in whom NAIT is suspected but the TP was sufficiently mild that there was no test of the response to platelet transfusion. Parental platelet antigens are typed and the presence of maternal antiplatelet antibody directed against the father's platelets is evaluated. There is no need to study the infant. It can be determined if the father is homozygous or heterozygous for the offending antigen, delineating the potential risks for future children. If the father is heterozygous, the risk to future children is close to 50%. Given the risk of in utero intracranial hemorrhage, families at risk should be identified given the availability of prenatal diagnosis and in utero therapy. It is therefore critical to study families whose infants had unexplained thrombocytopenia, particularly in well, term infants.

⑮ — Thrombocytopenia may be the first and only initial sign of bacterial sepsis.

⑯ — The normal mean platelet volume is 6–10 fl; small or large platelet size can indicate different congenital syndromes, while large platelets can also reflect rapid platelet turnover. Size can also be estimated using the blood smear.

⑰ — Persistent TP, neutropenia and/or anemia may suggest bone marrow failure or infiltration (e.g. neuroblastoma, leukemia, Langerhans cell histiocytosis, osteopetrosis). Bone marrow examination may be necessary.

⑱ — The cause of TP is often not established, particularly if the platelet count is >50,000. Some may be due to infection, which is the most common of the established etiologies. Drug-induced TP can result from maternal or neonatal medications: the incidence of heparin-induced TP in neonates is unknown.

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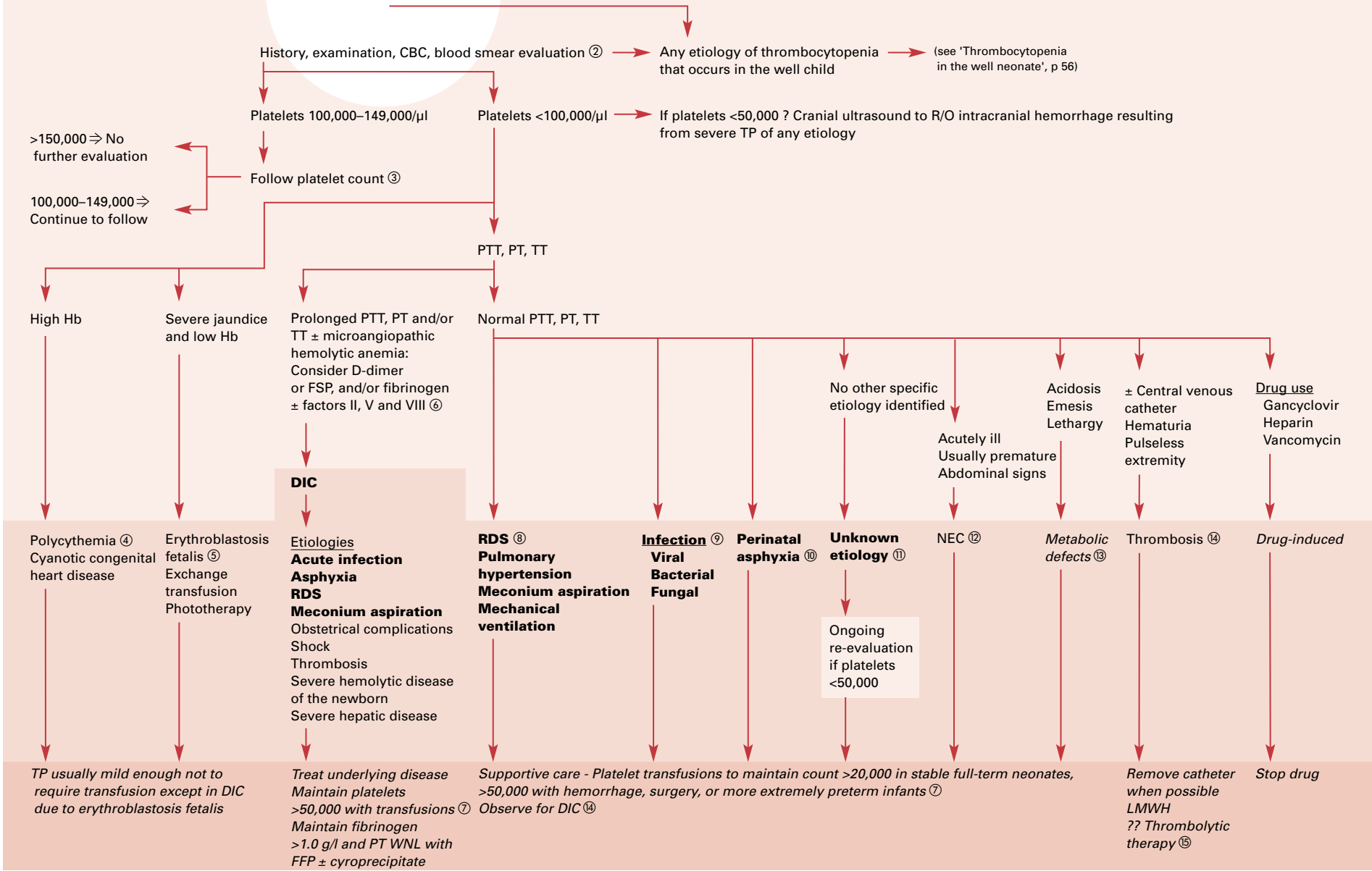
Thrombocytopenia in the ill neonate①



① — Thrombocytopenia (TP) is much more common in the ill neonate. Any disorder that affects a well neonate can also affect an ill neonate (such as neonatal alloimmune TP), but many other disorders are only likely to cause TP in a sick newborn. While 0.5–0.9% of all neonates have TP, it occurs in ~25% of neonates admitted to tertiary neonatal intensive care units, and in 20% of these the platelet count is below 50,000. The pattern of TP in ill neonates is often consistent; 75% have TP by day 2, the nadir is on day 4 and 86% are normal by day 10. The etiology of TP is not established in 60% of sick neonates.

② — The normal platelet count in premature infants is in the same general range as more mature infants, older children and adults (150,000–400,000/µl).

③ — The significance of platelet counts of 100,000–150,000 is unclear in this group; these babies are usually observed, but evaluated if the platelet count falls to <100,000. Depending on the clinical status of the infant, the count can be repeated daily if acutely ill or every few days if stable.

④ — Polycythemia alone or in association with cyanotic congenital heart disease causes TP.

⑤ — TP occurs with erythroblastosis fetalis (especially with concurrent hepatic dysfunction and/or DIC), due to washout effect during double volume exchange transfusions and from a mild thrombocytopenic effect of phototherapy.

⑥ — DIC is very likely with TP and prolongation of the PTT, PT and TT in a profoundly sick neonate. It is impossible to diagnose DIC without TP or at least a falling platelet count. A microangiopathic hemolytic anemia (which along with bleeding often causes substantial anemia) and/or elevated D-dimer helps confirm the diagnosis; given the frequent constraints on blood sampling in neonatal intensive care units, these studies are often used to establish a presumptive diagnosis of DIC. Other widely used confirmatory studies include fibrin split products, hypofibrinogenemia and decreased factors II, V and VIII. DIC is the second most common neonatal coagulopathy (after isolated TP); it is triggered by many disorders which cause tissue factor and cytokine release, resulting in excessive activation of coagulation factors and fibrinolysis, and ultimately a consumptive coagulopathy. The most common of those disorders are noted in the algorithm. Treatment of DIC depends on the ability to diagnosis and treat the underlying cause. It is not clear that hemostatic management alone improves the prognosis.

⑦ — There is no scientific evidence in neonates for a precise platelet number which necessitates platelet transfusion. A common approach is to transfuse to maintain a platelet count of 20,000 in all neonates in general, and a level of 50,000 in neonates with other hemostatic compromise, such as extreme prematurity, DIC, or hemostatic challenge, such as surgery. Random donor platelets which are ABO and Rh compatible are usually used, and it is reasonable to confirm a rise in platelet count an hour later (especially when the etiology of the TP is not clear and it is the first transfusion given). Transfusion of 0.2 units of platelets/kg of body weight should increase the platelet count 75,000–100,000; practically 10–15 ml/kg of standard platelet concentrates are given, and these transfused platelets should survive 3–5 days unless the TP is destructive in nature. If there is a question of survival of these platelets, check a count at 1 and 4 h and then daily. Platelet transfusions in the neonate are best irradiated (especially if from blood relatives), CMV safe and leukodepleted.

⑧ — TP occurs in association with these respiratory disorders and is frequent during mechanical ventilation. Although some of these infants have DIC, in most the mechanism of TP is not known.

⑨ — Infection is a very common cause of TP; 80% of neonates with proven infections develop TP. Bacterial sepsis usually causes leukocyte left shift followed by TP. 25% of septic neonates have TP at diagnosis and most have it within 36–48 h. Only a small minority have DIC, but when it occurs the platelets are more often <50,000. Fungal infections cause TP in almost three quarters of infants and it is the most consistent early laboratory finding. Viral infections often cause TP, but it is more frequent and severe with CMV. The platelet count is usually >20,000 in viral illness but TP may persist for up to 4 months. TP is rare in HIV infected neonates. Protozoan infections (toxoplasmosis and malaria) also cause TP.

⑩ — Perinatal asphyxia or intrauterine growth retardation often are associated with TP. The mechanism is not defined but may be part of a consumptive coagulopathy.

⑪ — Neonates with no identified etiology usually have platelet counts of 50,000–100,000 and are more often preterm. If the TP is severe, ongoing reevaluation is more likely to reveal an etiology.

⑫ — 80–90% of infants with necrotizing enterocolitis have TP although most do not have DIC.

⑬ — Several metabolic defects cause TP as well as lethargy, acidosis and failure to thrive, including isovaleric, propionic and methylmalonic acidemias as well as holocarboxylase synthetase deficiency.

⑭ — Large thrombi consume platelets and can cause TP. These are most commonly associated with central venous catheters and the renal veins, but can also involve the sagittal sinus. A pulseless extremity due to arterial thrombosis may initiate DIC.

⑮ — The treatment of thrombosis is complex. If a catheter is involved, it should be removed if possible. Low-molecular-weight heparin can be effective. The role of systemic thrombolytic therapy remains unclear.

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Platelet dysfunction ①

Document sites, duration and amount of bleeding especially epistaxis, menorrhagia, mucosal bleeding, history of systemic illness, medications, family history.
Examination documents bleeding and signs of systemic disease ②

CBC and examination of smear, PTT, PT, TT ③

- Normal platelet count and morphology
  - New onset bleeding ④
    - Platelet-inhibiting drugs
      - Yes → **Drug-induced** Underlying platelet dysfunction → *Stop drug if possible*
      - No → Liver and renal function tests
        - Abnormal → Uremia, Liver disease → *Manage underlying disease*
        - Normal → Abnormal CBC and blood smear → *MDS* → *BMA, BMB*
  - Lifelong bleeding
    - PTT, FVIII:C, VWF_{Ag}, VWF:RCo
      - Normal → Repeat → Normal upon repeat testing → Platelet aggregation studies ⑤ → Abnormal → **Intrinsic platelet dysfunction** *Glanzmann* → *DDAVP, Rarely platelet transfusion*
      - Abnormal → **von Willebrand disease** ⑥ → VW multimer assay
        - Normal → *Type I VWD ⇒ DDAVP challenge*
        - Abnormal → *Type 2A, 2B, 3, platelet-type ⇒ VWF replacement, Platelet transfusion for latter*
- Normal to slightly low platelet count and small platelet size ⑦
  - Recurrent infections, eczema, lymphoreticular malignancies, males
    - No → *X-linked thrombocytopenia, Amegakaryocytosis*
    - Yes → Wiskott-Aldrich → *Splenectomy may ⇓ bleeding, BMT*
- Normal to slightly low platelet count and large platelet size ⑧
  - Specific morphologic abnormality
    - Yes → Some very large platelets + abnormal ristocetin platelet aggregation ⇒ *Bernard-Soulier*; Large, pale, ghost-like platelets ⇒ *gray platelet syndrome*; Large platelet, PMN Dohle bodies ⇒ May-Hegglin anomaly; *Other macrothrombocytopenias* → *DDAVP may ⇓ bleeding, Platelet transfusions rarely needed*
    - No → **ITP** *Other macrothrombocytopenias* → *Platelet dysfunction can be seen in ITP but ⇓ platelets more important*

① — Consider platelet dysfunction in patients with bleeding symptoms and normal platelet counts, PTT, PT and TT. They should also be considered in occasional patients with mild thrombocytopenia who have bleeding symptoms disproportional in severity to the degree of thrombocytopenia. Whether acquired or inherited, these disorders are usually mild in severity and may not require any therapy. Bleeding is generally mucocutaneous in nature and not life threatening except in severe trauma, major surgery, the rare CNS hemorrhage or a concomitant coagulation defect. Clinically significant platelet dysfunction very rarely presents in the newborn.

② — Document the site and amount of bleeding and the duration of symptoms. Bleeding symptoms are most often epistaxis, oral bleeding, bruising, and menorrhagia; GI bleeding and CNS bleeding may occur, particularly in severe but rare disorders like Glanzmann thrombasthenia. Platelet dysfunction should not cause deep muscle hematomas or joint hemarthroses. Distinguish new onset from lifelong bleeding symptoms to discern whether the defect is likely acquired or hereditary. Review of systems should consider renal, liver, and myeloproliferative disorders. Family history should include gender of affected members, site and duration of bleeding and therapies instituted. Medication history should identify any agents which can cause platelet dysfunction (e.g. NSAIDs, penicillins, cephalosporins, antiplatelet agents). Physical examination should document sites of bleeding. Platelet disorders are not generally associated with splenomegaly or lymphadenopathy (except in the case of ITP and Wiskott-Aldrich syndrome). Eczema occurs in Wiskott-Aldrich.

③ — Examination of the blood smear and a CBC are essential. Platelet size measured by automated cell counts as the mean platelet volume (MPV) is now more widely available. Normal platelet size during childhood ranges from 7 to 11 fl. Normal platelet counts are similar in children and adults ranging from 150,000/mm^3 to 400,000/mm^3. PT, PTT and thrombin time (TT) should be normal unless von Willebrand disease (VWD) is prolonging the PTT (which it does not in most cases) or there is associated liver disease.

④ — Normal platelet counts and morphology occur with acquired defects such as medication-induced platelet dysfunction, uremia and liver disease. The platelet dysfunction in uremia is complex but is likely related to serum accumulation of guanidinosuccinic acid and nitric oxide, which inhibit platelet aggregation. Dialysis removes these toxins and improves platelet function. DDAVP can improve platelet function.

⑤ — In the presence of platelet-type bleeding symptoms and the absence of drugs, systemic disease or VWD, further testing for intrinsic platelet defects should be done. Bleeding times are too unreliable to be useful in most situations. PFA-100 analysis is a newer diagnostic test that is finding more utility than bleeding times, but is not widely available. Platelet aggregation studies can identify intrinsic platelet defects (as opposed to extrinsic defects like VWD where a plasma defect is not 'intrinsic' to the platelet). A heterogeneous group of inherited defects in platelet secretion and signal transduction constitute the most common intrinsic platelet dysfunction disorders. They are usually identified by abnormal platelet aggregation in response to epinephrine, collagen, ADP, or arachidonic acid. These disorders are generally very mild and respond to DDAVP therapy. Other rare disorders, such as Glanzmann thrombasthenia, and Bernard-Soulier, are much more severe and can cause life-threatening bleeding. Glanzmann thrombasthenia is associated with abnormal platelet aggregation to epinephrine, ADP and collagen (but is normal with ristocetin) and a defect in the glycoprotein IIb-IIIa complex. These more severe disorders may require platelet transfusion. Platelet dysfunction due to diminished storage pools in platelet granules is associated with a distinct abnormality of ADP-induced aggregation. These disorders tend to be milder and include gray platelet, Hermansky-Pudlak, and Chediak-Higashi syndromes.

⑥ — Platelet counts and morphology are normal in VWD. Affecting approximately 1% of the population, VWD is the most common bleeding disorder and should be excluded prior to further investigation in patients with bleeding symptoms, and normal platelet count and morphology. The diagnosis can be made by the coagulation tests outlined. There is considerable overlap of the normal range and the range of factor levels in patients with VWD. Blood type, hormones, stress and other factors may affect the vWF levels. Therefore, a single set of normal studies, particularly if the values are below the mean, do not exclude VWD; repeat assays, and even family studies, may be indicated to prove or exclude this diagnosis. If the screening tests suggest VWD, then multimer analysis should be done to subtype the disease. Types 1 and 2A can generally be treated with DDAVP, while type 2B will be worsened by DDAVP therapy. Types 2B and 3 generally require replacement with human factor VIII concentrates that also contain vWf. The rare platelet-type VWD requires platelet transfusion for treatment of bleeding episodes.

⑦ — Small platelet size is associated with X-linked recessive Wiskott-Aldrich syndrome and a less severe variant X-linked thrombocytopenia. Wiskott-Aldrich is characterized by immunodeficiency, eczema and thrombocytopenia. Small platelet size is also associated with poor marrow production as seen in congenital amegakaryocytosis; these patients exhibit varying degrees of thrombocytopenia.

⑧ — Large platelets are seen in Bernard-Soulier syndrome, with variable thrombocytopenia. Ristocetin-induced platelet aggregation is abnormal. A defective glycoprotein Ib-IX-V complex is responsible for impaired platelet adhesion to vascular endothelium via the von Willebrand factor (vWf). Large platelets can also be seen in other disorders. In gray platelet syndrome, the large platelets appear gray on smear and lack α-granules. May-Hegglin anomaly is characterized by large platelets, variable thrombocytopenia and Döhle inclusion bodies in neutrophils. There are other rare macrothrombocytopenias that may have mild platelet dysfunction. In ITP platelets are large due to increased platelet turnover; in addition to the thrombocytopenia, there may be some degree of platelet dysfunction due to the anti-platelet antibody.

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Thrombocytosis①

History, physical examination ②
CBC, smear evaluation,
reticulocyte count ③

→ Smear reveals RBC or WBC fragments ⑬ → Spurious thrombocytosis

Reactive or secondary thrombocytosis
Usually evidence of an underlying disorder
No increased risk of thrombosis

Normal CBC or mild-moderate leukocytosis ± shift to the left ④

- Acute febrile illness
  - **Acute infection**
    Kawasaki syndrome ⑤
    Acute rheumatic fever
- Chronic illness, usually afebrile
  - **Preterm infant**
    Autoimmune and connective tissue disorders
    Crohn disease
    Ulcerative colitis
    Tuberculosis
    Chronic hepatitis
    Nephrotic syndrome
    Langerhans cell histiocytosis
    Chronic osteomyelitis
    Celiac sprue
    Congenital adrenal hyperplasia
    Caffey syndrome
    Sarcoidosis
    GvHD

Anemia
Recovery from thrombocytopenia

RBC indices ⑥
Hypersegmented PMN
± macroovalocytosis
Blood loss
Stool for occult blood

- **Fe deficiency**
  Hemorrhage
  Rebound thrombocytopenia
  Hemolysis
  Megaloblastic anemia
  Vitamin E deficiency

Lymphadenopathy
Palpable mass
Superior vena cava syndrome

- Lymphomas
  Non-Hodgkin lymphoma
  Hodgkin disease
  Neuroblastoma
  Hepatoblastoma
  Other solid tumors

Stress and/or drugs ⑦

- **Exercise**
  Surgery
  Child birth
  Epinephrine
  Corticosteroids
  Fracture
  Neonatal methadone withdrawal
  Vincristine
  Vinblastine

Surgical or functional asplenia
Howell-Jolly bodies on smear ⑧

- Sickle cell disease or other causes functional asplenia
  Post-splenectomy
  Congenital asplenia

No evidence of underlying disorder causing reactive thrombocytosis

- Trisomy 21
  Trisomy 21
  Platelet count often ↑ in 1st year of life ⑨
  Transient myelopro-liferative disorder
  M7-AML

Primary thrombocytosis
Rare in children
Increased risk of thrombosis ⑩

Persistent thrombocytosis
Large, pale, hypogranular platelets
Splenomegaly
± Thromboses and/or hemorrhage
Hb ≤ 13 g/dl ⑪
Rarely + family history

- *Essential thrombocytosis*
  Familial essential thrombocytosis

WBC >100,000
↑↑ shift to left
or Polycythemia
± symptoms ⑫

- *CML*
  Polycythemia vera
  M7-AML

① — Thrombocytosis in children is almost always a reactive response secondary to an underlying process, most often infectious or inflammatory. Elaboration of cytokines such as interleukin-6 and C-reactive protein likely play a role in stimulating platelet production. The severity of the thrombocytosis parallels the disease activity of the underlying process, and is, in effect, an acute-phase reactant like the erythrocyte sedimentation rate. The thrombocytosis resolves when the underlying process does, and complicating thromboses probably do not occur. Therefore, therapy to reduce the platelet count or prevent thrombosis is not indicated in reactive thrombocytosis. Thrombocytosis is no more specific in the neonate, but mild thrombocytosis is very common in preterm infants.

② — History should focus on concurrent chronic disease, infection, complicating hemorrhage or thrombosis, anemia or icterus, rash, lymphadenopathy, polyuria/polydipsia, diet, medications, prior surgery and trauma. Physical examination should consider growth and development, rash, inflammation, lymphadenopathy, organomegaly, masses, conjunctivitis, and surgical scars.

③ — If a transient thrombocytosis due to a benign intercurrent infection is suspected, simply repeat the platelet count in 3–4 weeks. If there is a serious concern, laboratory studies at a minimum should include CBC, reticulocyte count, and peripheral smear. ESR, PPD, hepatic function studies, chest X-ray, bone X-rays, ANA, ASO, urinalysis, cultures, bone marrow aspirate and biopsy, as well as levels of vitamin B_{12} and E and folic acid may be indicated depending on the clinical evaluation. If there is a likely underlying disorder, laboratory studies should investigate that diagnosis and not the thrombocytosis.

④ — The most common cause of thrombocytosis is acute infection, in which the CBC may be normal or may demonstrate a mild leukocytosis, less often a leukopenia and often a normal blood count. Mild anemia may represent the anemia of acute or chronic infection/inflammation. Further evaluation is based upon the specific presentation of the patient.

⑤ — In Kawasaki syndrome, the platelet count may exceed 1,000,000 cells/µl. Diagnostic criteria include fever for at least 5 days and at least four of the following five signs: bilateral bulbar conjunctival injection, oropharyngeal changes, skin changes in the peripheral extremities, primarily truncal rash and cervical adenopathy. Treat with intravenous gammaglobulin and high-dose aspirin as soon as possible after diagnosis.

⑥ — A variety of hematologic conditions cause thrombocytosis; iron deficiency either at diagnosis or during therapy, hemorrhage, hemolysis and rebound from any thrombocytopenia (particularly common with chemotherapy). Thrombocytosis may persist in chronic conditions such as hemoglobinopathies. Megaloblastic anemia, usually presenting with macrocytosis and macro-ovalocytosis, may have an associated thrombocytosis. With newer infant formulas, vitamin E deficiency is uncommon.

⑦ — The simple stress of exercise, surgery, childbirth, as well as several drugs, all commonly cause thrombocytosis.

⑧ — One-third of the circulating platelets are normally sequestered within the spleen. Congenital or surgical asplenia shifts these platelets into the circulating pool, often causing a relative thrombocytosis. Although surgical asplenia is usually obvious, congenital or functional asplenia may not be. Howell-Jolly bodies in red blood cells are a clue to underlying asplenia. The sickle hemoglobinopathies are the most common cause of functional asplenia. After splenectomy platelet counts > 1,000,000 are not uncommon and the thrombocytosis may persist for years.

⑨ — In Down syndrome, thrombocytosis is very common by the second month of life and often persists in the first year without other hematologic abnormalities. Less commonly, neonates with Down syndrome have thrombocytosis as a manifestation of the transient myeloproliferative disorder which occurs in these infants. Children with Down syndrome are at increased risk for acute megakaryoblastic leukemia (M7 variant of AML), of which thrombocytosis is rarely a presenting sign.

⑩ — While reactive thrombocytosis is extremely common in children, primary thrombocytosis is very rare; it represents unregulated and excessive platelet production caused by a myeloproliferative disorder in the bone marrow. Cytokines like interleukin-6 and C-reactive protein, elevated in reactive disorders, are usually low in myeloproliferative syndromes.

⑪ — Essential thrombocytosis is also very rare in children and usually difficult to recognize. It remains a diagnosis of exclusion; adult diagnostic criteria help primarily to distinguish it from other myeloproliferative disorders (e.g. CML, polycythemia vera, and myeloid metaplasia), but in children the diagnostic dilemma is to identify this very rare disorder and differentiate it from the so much more common chronic, reactive conditions. The presence of large, hypogranular platelets is helpful but not diagnostic. Splenomegaly is usually present, but is nonspecific. Complicating thromboses occur in approximately one-quarter of patients, may be very serious (intracerebral, peripheral arterial, deep vein thromboses) and their occurrence is a very strong indication of essential thrombocytosis. Hemorrhage also can occur. In most children, who are asymptomatic, it is persistence of the thrombocytosis (usually at least 600,000 and often > 1,000,000) over months or years without any other etiology apparent which eventually leads to the diagnosis by exclusion. Therapies are available although children without thrombotic complications may not merit intervention. Families with an autosomal-dominant form of the disease have been identified.

⑫ — Chronic myelogenous leukemia and polycythemia vera are both myeloproliferative disorders associated with thrombocytosis. In the former, a severe leukocytosis (averaging more than 300,000 cells/µl and almost always > 100,000 in children) and shift to the left (including metamyelocytes, myelocytes and promyelocytes in peripheral blood) readily identifies this disorder. Polycythemia vera is extremely rare in children and when it occurs the polycythemia is usually the predominant concern; plethora, weakness, headache, hypertension and splenomegaly are usually noted. The M7 variant of AML rarely presents with thrombocytosis.

⑬ — Red cell or white cell fragments, as found in microangiopathic hemolytic anemia, hemoglobin H disease and leukemias , can be mistaken for platelets in automated cell counters, which rely on cell size for identification. Peripheral smear review confirms this pseudothrombocytosis.

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Treatment of bleeding in children with hemophilia ①

Collaborate with Hemophilia Treatment Center ②

Mild or moderate hemophilia ⑩

Severe hemophilia

Life-threatening

- Suspected CNS bleed ③
  - Factor replacement prior to CNS imaging or LP
- Impending airway compromise
  Tongue bleed
  Neck trauma
  Dental anesthesia
  without factor ④
- Surgery ⑤
  Major trauma
  GI hemorrhage
  Retroperitoneal or large muscle hemorrhage

Obtain inhibitor level (always prior to elective surgery)
Infuse factor to 100% level with i.v. bolus dose
Initiate continuous infusion to *maintain* 80–100% level
or bolus therapy *maintaining* a trough level of >50%

If neurovascular compromise, Rx as life-threatening bleed,
Obtain neurology + surgical consult ⑥

Measure levels to ensure adequacy of Rx
Continuous or bolus therapy at minimum 50% level until wound healing begins and then ⇓ to minimum 30% level for 7–14 days depending on type of bleeding

May need 30–50% level for physical therapy or other procedures in healing phase
May use prophylaxis for 6–12 weeks after CNS bleed to prevent early recurrence

Non-life-threatening

Muscle bleed

50–100% level *via single i.v.* bolus q.d. or q.o.d. until improved, then q.o.d. until resolved
May need 30–50% doses with physical therapy to prevent rebleeding

Fails to improve

Orthopedic evaluation
Consider X-ray, US, MRI

Hemarthrosis ⑦

40–80% bolus dose then 40% at 24 and 72 h, and q.o.d. until resolved
Initially rest + immobilize then physical therapy

Recurrent bleeding

Consider prophylaxis regimen for recurrent hemarthroses ⑦

Evaluate for radio-isotopic or surgical synovectomy ⑦

Mucosal bleed

- Epistaxis, oral mucosal oozing, or GI bleeding
  - *50–100% dose depending on severity*
  - *Antifibrinolytics for 3–5 days ⑧*
  - Persistent, recurrent bleeding
  - *30–50% dose q.o.d. up to 1 week*
  - *Epistaxis: refer to otolaryngology for possible nasal packing or cautery*
- Hematuria
  - Bed rest ⑨
    Hydration
  - *Persistent or recurrent bleeding 30–50% dose q.d. × 5*
    No antifibrinolytics ⑧
  - Persistent, recurrent bleeding
  - *Redose to 100%*
    Prednisone 1–2 mg/kg/day × 1–2 weeks
    GU evaluation

(for any child failing Rx, see 'Evaluation of a child with hemophilia who fails infusion therapy', p 66)

① — Hemophilia A (factor VIII deficiency) and B (factor IX deficiency) affect all racial groups worldwide, with hemophilia A responsible for ~85% of cases. Disease severity is defined by the plasma level of deficient factor; severe disease <1% (0.01 IU/ml), moderate 1–5%, and mild >5%, compared to NI = 100%. Most patients have severe disease. Primary treatment is factor replacement of either factor VIII or factor IX using either monoclonal antibody purified factor concentrates derived from human plasma or recombinant protein products. Viral screening of blood donors and viral inactivation processes have made plasma-derived products much safer, but children should be treated with recombinant products whenever possible. If neither product is available, cryoprecipitate is a source of factor VIII and fresh-frozen plasma a source of factor IX, but *both should be avoided if at all possible* because of the risk of viral transmission in these untreated plasma products. Factor dosage is measured in units which are equivalent to the amount of factor in a milliliter of 'normal' plasma. To replace factor VIII with either monoclonal or recombinant factor, 1 U/kg increases the plasma factor VIII level by 2%; if a level of 100% is required, give 50 U/kg. In the algorithm treatment is defined as the percent level of factor desired to treat different hemorrhages. Except as noted, this is the peak level from a single bolus of intravenous factor. For factor IX, 1 U/kg of factor IX with monoclonal concentrates increases the plasma level by 1% while the same dose of recombinant product produces a 0.4–0.8% increase. Because of this variability, recovery studies (factor levels before and $^1/_4$–$^1/_2$, 1, 2–4, 8–12 and 24 h after infusion, or at least a level 1 h postinfusion) should be performed on patients with hemophilia B to determine dosing. The NI $T^1/_2$ of factors VIII and IX are, respectively, ~12 and 24 h; the longer $T^1/_2$ of factor IX allows for less frequent dosing than factor VIII. Because infants and young children have a higher volume of distribution and clearance of factors, dose and frequency may be higher in younger patients. After calculating the dose, use the number of whole factor vials to bring you closest to that dose; do not waste parts of a vial. Factor is very expensive (USD >$1/unit for recombinant and ~1/3 less for plasma-derived factor concentrates).

② — Rx should be provided in collaboration with a comprehensive hemophilia treatment center because this approach leads to lower morbidity and mortality. If patients cannot travel to centers, physician consultation with the center is critical.

③ — CNS hemorrhage is the most serious complication with prevalence and recurrence rates of ~10%. Symptoms may be delayed for days after trauma and often no trauma is recognized. A suspected CNS bleed must be treated urgently with factor prior to CNS imaging since function can rapidly deteriorate. Factor replacement must also precede lumbar puncture to prevent an epidural or subdural spinal hematoma.

④ — Dental block anesthesia without prior factor replacement can result in dissecting hematomas, which can cause potentially fatal airway obstruction.

⑤ — Surgery without factor replacement is extremely dangerous. Prophylaxis for surgery or Rx of any life-threatening bleeding requires monitoring factor levels frequently to assure safe levels are maintained. Continuous infusions of factor are more effective, safe and cost effective in managing these serious complications (typical starting dose of factor VIII = 50 U/kg followed by ~4 U/kg/h). Inhibitor development is a critical complication (see '*Evaluation of a child with hemophilia who fails infusion therapy*', p 66). Inhibitor assays are performed prior to elective procedures, during life-threatening events and annually as part of routine care. Serious blood loss can accompany mucosal, GI, retroperitoneal, and large muscle (iliopsoas, quadriceps and hamstring) hemorrhage. Iliopsoas bleeds can present with upward flexion of the thigh, lower quadrant tenderness, or paresthesias in the femoral nerve distribution. These major muscle hemorrhages require 10–14 days of factor replacement for full recovery and to prevent recurrence.

⑥ — Compartment syndrome may result from bleeding into flexor muscle groups (e.g. forearm or calf). Impaired blood flow and peripheral nerve damage can be serious and deficits can be permanent. Factor replacement is imperative. Fasciotomy is rarely required.

⑦ — Hemarthrosis is the most common debilitating complication of hemophilia and may occur without recognized trauma. Joint hemorrhage causes synovial thickening and friability, triggering chronic inflammation. This results in a 'target joint', prone to chronic arthritis, loss of mobility and recurrent hemorrhage. Prophylactic factor regimens are instituted, either following a small number of hemarthroses (1–3 in a single joint), or following the development of a 'target joint' either clinically or via evidence of synovitis radiologically. Hemophilia specialists should be consulted to choose the regimen and when to institute it. Factor is usually infused 2–3 times weekly to prevent factor levels <1%. Prophylaxis can drastically improve quality of life by markedly reducing bleeding, but it is very costly. Target joints may also benefit from surgical synovectomy or radioisotopic synovectomy (using injection of the radioisotope [e.g., ^{32}P] into the joint) to control synovial inflammation. Hip hemorrhage can result in aseptic necrosis of the joint; both hip and shoulder hemarthroses are corrected to 100% immediately and managed aggressively until resolution.

⑧ — Antifibrinolytics may be helpful for oral mucosal bleeding but are generally contraindicated in patients with hematuria. For oral mucosal bleeding (i.e. dental extractions), use ϵ-aminocaproic acid (75–100 mg/kg/dose every 6 h p.o. or i.v.) or tranexamic acid (10 mg/kg/dose i.v. or 25 mg/kg/ dose p.o.).

⑨ — 10% of patients experience hematuria, which is seldom of medical significance. Factor replacement is often not helpful. Bed rest and hydration are first-line therapy, but steroids are occasionally useful.

⑩ — Treatment of children with mild and moderate hemophilia is very similar to that of severe disease but may be modified. Life-threatening or serious (e.g. hemarthrosis) bleeding are treated identically, but somewhat lower and less frequent factor dosing may be adequate. In mild and occasionally moderate hemophilia A, i.v. or nasal DDAVP increases factor VIII levels and in some situations obviates the need for factor. DDAVP is ineffective in hemophilia B.

Selected reading

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Evaluation of a child with hemophilia who fails infusion therapy

Child with hemophilia who manifests bleeding events that have become more frequent, more spontaneous or are unresponsive to standard therapy

Assess adherence to current treatment regimen, compliance with home Rx (product used, dosage, storage, and reconstitution), concurrent medications/treatments/exercise/physical therapy, prior inhibitor, new medical problems ①

Incorrect therapy
Poor compliance

Adjust Rx
Work with family

Confirm Dx if not certain based on Hx and records ②

FVIII:C, VWF:RCo, VWF_{Ag}
FIX levels

<u>VIII + IX NI</u>
Repeat complete bleeding evaluation

<u>Incorrect type of hemophilia or VWD</u>
Educate family

<u>Dx of hemophilia correct</u>
Inhibitor assay

Factor VIII (or IX) inhibitor using Bethesda assay (BU) ③

Inhibitor + ④

Factor inhibitor

Rx of inhibitors is complex – Consult with specialist

Treatment of acute bleeding ⑤

<u>Standard therapies</u>
Factor replacement to overcome inhibitor
Recombinant FVIIa
Activated PCCs
<u>Non-standard therapies</u>
Porcine factor VIII (hemophilia A only)
Possible plasmapheresis + factor replacement

Consider immune tolerance induction (ITI) for long-term management

<u>>5 U: high titer inhibitor ⑥</u>
<10 BU: begin ITI immediately
>10 BU: begin ITI when titer is <10;
***or** if need is emergent, reduce titer with plasmapheresis and begin ITI;*
***or** begin ITI at >10 BU*

<u><5 BU: low titer inhibitor ⑦</u>
May begin immune tolerance induction (ITI)
***or** treat with higher doses of factor VIII prn*
Monitor at least monthly

The specific immune tolerance regimen should be chosen in consultation with a hemophilia specialist given the complex and rapidly changing nature of this therapy

Inhibitor – → Determine factor recovery and $T^1/_2$ ⑧

<u>Low factor recovery (⇩$T^1/_2$)</u>
Adjust factor dosage and frequency to reflect individual variation

Continued frequent bleeding events

Initiate prophylaxis and titrate dose

Isolated hemarthroses
US and/or MRI to confirm synovitis

Initiate prophylaxis
Consider radiosynovectomy or surgical synovectomy

<u>NI factor recovery and $T^1/_2$</u>
2nd bleeding disorder
VWD
Drug-induced
Thrombocytopenia
Hepatitis/liver dysfunction
Other bleeding disorder
Hemarthroses only
Synovitis
Unrelated joint disease

Hemostatic evaluation
CBC, PT, PTT, TT
FVIII:C, VWF:RCo, VWF_{Ag}
Platelet function
Clinical evaluation to R/O other joint disease

① — Ensure that the treatment plan is correct. For home therapy, assess if factor storage is appropriate to maintain potency and observe family administering the factor. It may be necessary to stop home therapy or provide more home supervision. Assess all medications, including NSAIDs, as a possible cause of treatment failure.

② — Ensure the diagnosis is hemophilia and the correct type. This is rarely a problem if the family is well known to the provider, but occurs with new families if decisions are based solely on history. Parents may confuse hemophilia A and B, VWD or another bleeding disorder, and rarely there is no bleeding disorder (Munchausen syndrome by proxy). If there is a question, FVIII:C, VWF:RCo, VWF_{Ag} and FIX assays to distinguish hemophilia A, B and VWD. The factor concentrates only contain the individual factor (e.g. factor VIII will not work in hemophilia B and even in VWD if the concentrate contains FVIII:C but not VWF it may fail).

③ — Development of an anti-factor VIII inhibitor complicates factor replacement in 5–10% of all patients with hemophilia A, but ≥20% of those with severe disease. The incidence of anti-factor IX antibodies is lower in hemophilia B at 3%. Inhibitors are IgG antibodies which develop after an average 10 days of exposure to factor replacement. Inhibitors are documented and quantitated with the Bethesda assay using timed incubations of normal and patient plasma; 1 Bethesda unit neutralizes 50% of the normal factor in the sample. If the assay is not readily available, an inhibitor is likely if the PTT of a mixture of both normal and patient plasma remains prolonged after 1–2 h of incubation at 37°C. These findings must be confirmed with the Bethesda assay as soon as possible.

④ — Positive results should be confirmed. It is then critical to determine if the patient is a low responder (1/4 of patients who have 3–5 BU level titers and whose titers do not rise with additional treatment) or a high responder (3/4 of patients with >5 BU and an anamnestic response to additional factor therapy).

⑤ — Management of acute bleeding in inhibitor patients is complex, extremely costly and produces inconsistent results. Simple factor replacement, often in high doses, may overcome modest inhibitors. More severe inhibitors are usually treated with recombinant activated factor VII (rVIIa – usual dosage 90–120 µg/kg) or activated prothrombin complex concentrates (PCC, usual dosage 75–100 IU/kg) both of which bypass the need for factors VIII or IX. Bleeding can be treated in many patients with porcine factor VIII. Plasma exchange and high-dose factor replacement is also an option with serious bleeding. The very high cost of these products may limit their use in many areas.

⑥ — High titer inhibitors are serious complications which do not increase the frequency of hemorrhage but greatly complicate its treatment. High titer inhibitors can render factor therapy ineffective. The long-term approach is to institute immune tolerance induction (ITI) to suppress inhibitor production. It is very costly but in ~70–80% of patients the inhibitor can be eradicated over a period of months. A variety of regimens have been tried; most use ≥100 U/kg/day of factor daily for weeks to years until the inhibitor disappears. Immunomodulatory therapy (low-dose cyclophosphamide, IVIG, prednisone) has been added but is often avoided in children. Success is improved if ITI is begun early when the inhibitor is <10 BU. If the titer is >10 BU, it is not clear if it is better to start ITI immediately, wait until the titer falls to <10 BU and then start, or if urgent bleeding occurs to treat reduce the inhibitor titer with plasmapheresis and then begin ITI. Ongoing studies should soon define the best approach. Factor IX antibodies are somewhat less responsive (50%) with analogous regimens using factor IX, but anaphylactic reactions have been reported. Consultation with a hemophilia specialist is critical for the management of all children with hemophilia and inhibitors.

⑦ — Low titer inhibitors can be transient (1/3 of patients), may persist but not increase over time, or may develop into high titer inhibitors. If the inhibitor is <5 BU ITI can be started, but it is reasonable to monitor the inhibitor and to treat bleeding, if necessary, with higher doses of factor to overcome the inhibitor; if the inhibitor is transient and resolves, no therapy is necessary. If it becomes anamnestic or persists at low titer, ITI is started.

⑧ — If there is no inhibitor, determine recovery (R) and half-life ($T^1/_2$) of infused factor. Obtain baseline level, infuse factor and measure factor levels at 1/4–1/2, 1, 2–4, 8–12 and 24 h. If R or $T^1/_2$ is reduced, that patient may require higher or more frequent doses of factor; if bleeding persists, ongoing prophylactic factor therapy may be indicated (titrating the dose to the $T^1/_2$) and a hemophilia specialist should be consulted. If $T^1/_2$ is normal, joint bleeding may be due to synovitis or other joint disease and not ongoing hemorrhage. This can be confirmed by ultrasound and, if necessary, MRI. Recurrent hemarthroses ± synovitis are an indication for prophylactic factor infusion and specialty consultation. Either radio- or surgical synovectomy may be indicated. If there is no other joint disease, or the recurrent bleeding is not in the joint, consider again if the diagnosis or correct or if there is a concomitant second bleeding disorder. Given that VWD occurs in 1% of the population, it may be mistaken for hemophilia A or may be a concomitant disorder with either form of hemophilia; factor VIII studies in the patient and family should be performed. Check for disorders potentially associated with hemophilia, such as HIV-induced TP or hepatitis-induced coagulopathy, as well as the much less likely possibility of some other coincidental bleeding disorder.

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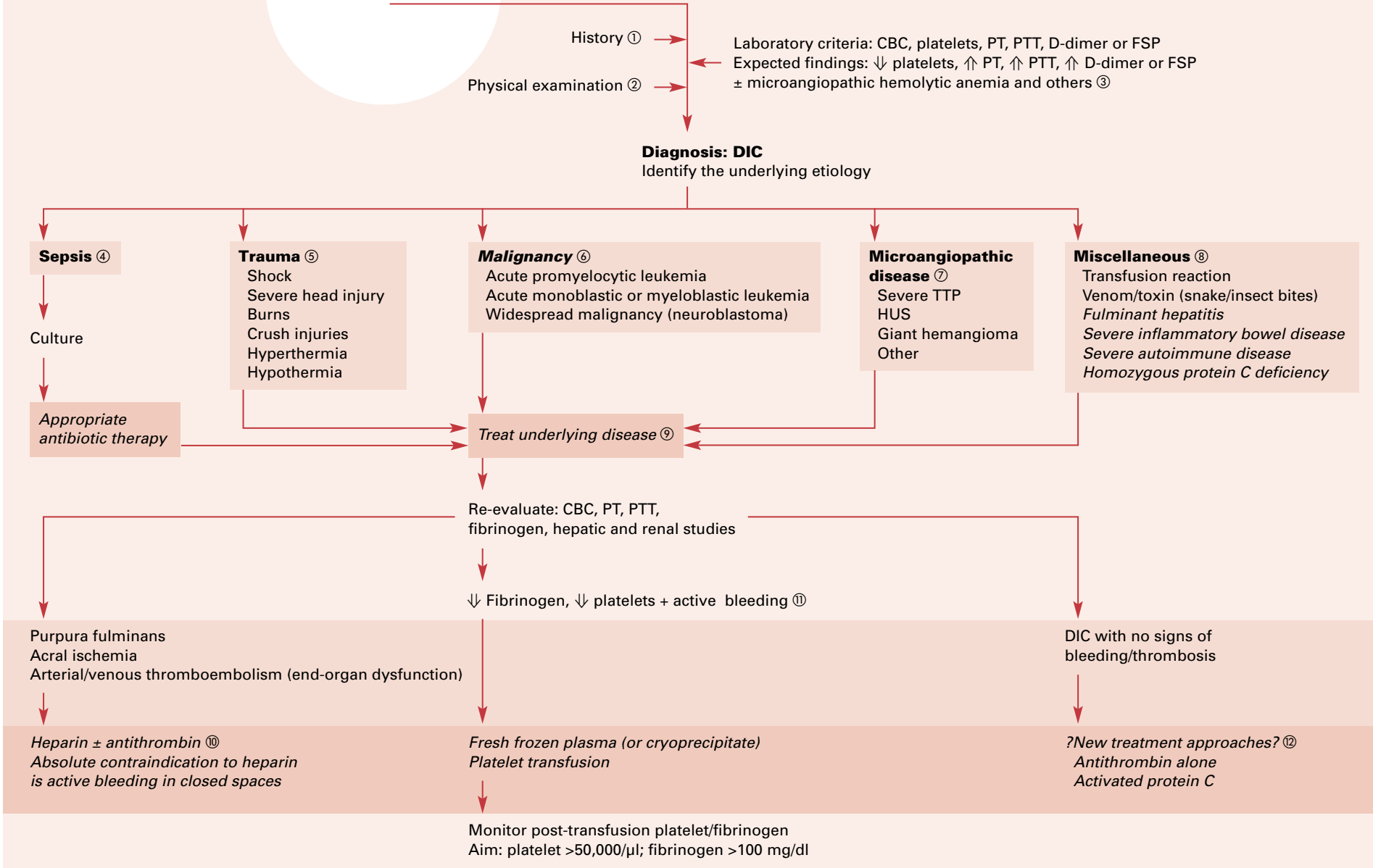
Consumptive coagulopathy



① — DIC can be induced by direct endothelial damage, antigen-antibody complexes, direct platelet activation and vascular stasis. Note predisposing factors in history of present illness and past medical history, such as infection, trauma, prior transfusion, and chronic disease (e.g. autoimmune or malignant systemic disease).

② — Note signs of trauma, hypothermia, and fever. Note signs of coagulopathy (e.g. petechiae, purpura or oozing from wounds) and, less commonly, signs of thrombosis (e.g. cutaneous infarction or acral gangrene). Evaluate cardiocirculatory status, note hypotension, signs of decreased microcirculation, and signs of organ dysfunction (e.g. CNS, pulmonary, or renal).

③ — The laboratory abnormalities of DIC reflect excessive thrombosis which results in depletion of platelets and coagulation factors as well as fibrinolysis. While there is no specific test to diagnose DIC, the classic and usually obvious findings are a prolonged PT and PTT in a thrombocytopenic patient, who has an obvious underlying cause of consumptive coagulopathy. Evidence of accompanying fibrinolysis (e.g. elevated D-dimer or fibrin degradation products [FSP]) confirms the diagnosis. Other abnormalities are frequently found but may not be necessary to establish a diagnosis. These include decreased levels of antithrombin III, protein C and S, and factors VIII:C, and V. Fibrinogen is often decreased, but as an acute phase reactant can be normal or increased. A microangiopathic hemolytic anemia can occur as the result of shearing effect on RBCs by the damaged vascular surfaces and by fibrin deposition; it is manifested by fragmented red cells (schistocytes) and helmet cells.

④ — Sepsis is a common cause of DIC. Sepsis-related DIC usually is a fulminant process with hemorrhage as the predominant manifestation. Gram-negative bacterial infections associated with endotoxin release are typical. Any sepsis syndrome, however, can lead to DIC.

⑤ — Trauma, especially severe head injury, burns and crush injury, are associated with DIC due to release of tissue thromboplastin or as a consequence of hypotension.

⑥ — Systemic malignancy may also induce DIC. This is a very frequent complication of acute promyelocytic leukemia, but also occurs in acute monoblastic or myelocytic leukemia. Coagulopathy is less common in ALL. DIC can also complicate other widespread malignant disorders such as neuroblastoma.

⑦ — Microangiopathic disorders such as HUS or TTP may lead to DIC following endothelial damage and/or direct platelet activation. In the Kasabach-Merritt syndrome, consumption of coagulation factors occurs within a giant hemangioma. Consider that the hemangioma may not always be evident on physical examination. Other disorders associated with microangiopathy include preeclampsia, HELLP syndrome, abruptio placentae, drugs (mostly chemotherapeutic agents), prosthetic cardiac valves or patches, and liver or kidney transplantation. Some patients with microangiopathy only manifest a microangiopathic hemolytic anemia and/or thrombocytopenia, while others also consume fibrinogen and develop DIC.

⑧ — Other causes for DIC include transfusion reactions, snake or insect bites, hereditary protein C deficiency (homozygous) and any severe inflammatory disorder.

⑨ — The most effective therapy in DIC is treating the underlying disease and thereby eliminating activators of intravascular coagulation. The effectiveness of hemostatic therapy remains controversial and may not be effective if the underlying disease process cannot be successfully managed.

⑩ — With purpura fulminans, acral ischemia and arterial or venous thromboembolism, treatment with heparin is recommended (± antithrombin). Heparin is usually given as a continuous infusion at 15–25 U/kg/h after an initial bolus of 50–75 U/kg or in a dose of 75–100 U/kg every 4 h. Antithrombin can be administered at doses ranging from 30 to 150 IU/kg/day, in order to attain normal antithrombin levels. Heparin is contraindicated when signs of active bleeding in closed spaces (e.g. intraspinal, intracranial) are present.

⑪ — In severe DIC with active bleeding, FFP and platelets are given. Any volume loss is substituted with FFP. At least 10–15 ml FFP/kg are infused. Alternatively, cryoprecipitate can be given to provide FVIII:C and fibrinogen. Monitor posttransfusion platelet counts and coagulation parameters. Reasonable goals are platelet levels >50,000/µl and fibrinogen levels >100 mg/dl (1 g/l).

⑫ — In severe sepsis, newer treatment approaches have been evaluated for patients at risk for or in early phase of DIC. In adults, activated protein C has been shown to reverse the procoagulant and inflammatory effects of sepsis and to increase survival. Early substitution of antithrombin without additional heparin has also been shown to successfully treat consumptive coagulopathy with sepsis in childhood.

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Thrombophilia evaluation in a newborn infant with thrombosis①

Infants (<28 days old) with arterial or venous thrombosis, confirmed with Doppler ultrasound or appropriate imaging technique
Signs of stroke; altered level of consciousness, seizures, hemiparesis, or abnormal neurologic examinations ②

CBC, smear, PT, PTT, fibrinogen, D-dimer ③ → Risk factor assessment ④

High risk	Moderate risk	Low risk	Lowest risk
Known thrombophilia in either parent Purpura fulminans or DIC Progressive or recurrent thrombosis Prior fetal/neonatal loss, PE	Multiple thromboses *or* unprovoked thrombosis	Static thrombosis Maternal diabetes, cocaine use Neonatal dehydration, poor feeding, vomiting, diarrhea, placental abruption, demise of fetal twin	Preterm infant with catheter-related thrombosis ⑧
Thrombosis evaluation at diagnosis Consider protein replacement and/or anticoagulation Expectant observation for recurrent thrombosis	Thrombosis evaluation at diagnosis or at age 6 months and expectant observation for recurrent thrombosis	Thrombosis evaluation at age 6 months *or* expectant observation for recurrent thrombosis	

Observe

Thrombosis recurs

Initial evaluation for underlying thrombophilia ⑤
Maternal assay for LA and ACA ⑥
Antithrombin functional assay
Protein C functional/chromogenic assay
Protein S (free antigen)
Activated protein C resistance (APCR)
DNA: prothrombin 20210; factor V Leiden if APCR abnormal (rare in African or Asian populations)

Protein C, S or AT deficiency
Doubly heterozygous deficiency

If functional protein <10% of normal adult, repeat urgently and assay parents for carrier status
If milder deficiency repeat at 6 months or study parents

Evaluation negative

Thrombosis recurs

No recurrent thrombosis

Strong family history ⑩

Yes

No

Observe for recurrent thrombosis

Diagnosis based on above studies: consider risk of doubly heterozygous deficiency

Repeat evaluation may be necessary at 3–6 months

Further evaluation ⑨
Plasma homocysteine
Lipoprotein (a)
Dysfibrinogenemia
Fibrinogen clotting and Ag, thrombin and reptilase times
Heparin co-factor II
FVIII:C

Thrombosis

Rx ⑦
Controversial with no controlled studies
LMWH and standard heparin are used widely
Larger doses are generally required in neonates due to ↑↑ distribution and ↑↑ clearance
Generally 1.5–2× adult dose for term infants
Neonates rarely require long-term anticoagulation: 10–14 days for arterial lesions, 4–6 weeks for venous
Thrombolytic agents are usually limited to thrombosis with organ or limb viability compromised; intracranial hemorrhage is a contraindication and complication of thrombolytic agents

① — The risk of thrombosis is greatest in the neonatal period, at which time the pattern of thrombosis is different compared to older children. Thromboses are most common in the premature and other high-risk infants, have a predilection for arteries and the major vessels and are often related to umbilical catheters. Unprovoked thromboses occur and involve the inferior vena cava, renal veins and the cerebral venous sinuses as well as the aortic, femoral, renal and middle cerebral arteries. Thrombosis occurs in 2.4/1,000 neonatal intensive care admissions, but are very rare in healthy term infants. The probability of genetic thrombophilia in neonates with thrombosis has not yet been defined, but thrombosis does occur more frequently in the presence of several prothrombotic mutations.

② — Clinical signs are often evident at delivery or within 24 h. A white pulseless extremity suggests a recent occlusion while a black, necrotic extremity reflects an earlier event. Circatricial amniotic bands may be noted. Enlarged kidneys and hematuria suggest a renal vein thrombosis. Stroke in term infants often presents with seizures and altered neurologic status in the first day of life but the signs may be subtle. Venous thrombosis, particularly involving the renal vein, is common while massive aortic thrombosis occurs in asphyxiated preterm infants with a UAC and pulseless, pale extremities and evidence of DIC. SVC thromboses present as edema of the arms and head, whereas IVC thrombosis cause swelling of the lower body and legs, usually associated with CVLs. Doppler ultrasound is the preferred diagnostic tool, except for CNS events which are best evaluated by MRI. Angiography can be performed through a CVL, particularly if ultrasound is negative but the clinical suspicion of thrombosis is high.

③ — These studies define DIC and other unexpected abnormalities. Thrombocytopenia often occurs with large thromboses, and with hematuria suggests renal vein thrombosis. Subtle DIC and fibrinolysis are so common in the sick neonate that markers such as AT and plasminogen are not very helpful.

④ — Several risk factors for thrombosis have been recognized. The most important maternal factor is diabetes mellitus, which is commonly associated with renal vein thrombosis; others include APLA syndrome, family history of thromboses suggestive of familial thrombophilia and maternal factors resulting in IUGR. The prime neonatal risk factor is a catheter (present in ~90% of cases); others are systemic infection, congenital heart disease, dehydration and asphyxia, IUGR and polycythemia. Inherited thrombophilia, such as homozygous or heterozygous protein C, homozygous protein S, both heterozygous and the rare homozygous AT deficiency, factor V Leiden and prothrombin G20210A, have been associated with neonatal thrombosis. Purpura fulminans occurring within hours to days of birth is the classic presentation of homozygous protein C deficiency, but also occurs with severe protein S, AT deficiency or combined C and S deficiencies. Factor V Leiden has been reported in neonates with CNS arterial thrombi; other thrombophilias, such as methyltetrahydrofolate reductase deficiency and increased Lp(a) lipoprotein may be risk factors for thrombosis but have not been adequately studied. Overall, the role of inherited thrombophilia in neonates with thrombosis remains a concern but needs to be better defined.

⑤ — Consider age-appropriate normals, but also the potential effects of consumption within thromboses, DIC and the depressing effect of intercurrent illnesses such as infection; protein C, S and AT generally require repetition at 3–6 months of age or by studying the parents. Tests for the DNA defects factor V Leiden and prothrombin G20210A need not be repeated, but note that these are very rare in individuals of African or Asian descent. There is no role for screening asymptomatic infants for hereditary thrombophilia.

⑥ — Maternal antiphospholipid antibody can cause neonatal thrombosis due to transplacental transfer. Additional details in *'Thrombophilia evaluation in a child with thrombosis'* (p 72).

⑦ — There are no controlled therapeutic trials so treatment is controversial. Heparin has been used, but the greater predictability, safety, twice daily dosing, and subcutaneous administration of LMWH has led to its increased use. Since neonatal thrombosis does not usually recur after initial therapy is stopped, long-term coagulation is rarely needed. Extremely preterm infants with limited subcutaneous tissue or a history of bleeding within 72 h may be treated with standard heparin as it can be given intravenously and is cleared rapidly if bleeding necessitates premature discontinuation. Oral anticoagulation is much more difficult to dose and monitor, and carries a much greater risk of hemorrhage; it is fortunate it is rarely needed except in rare homozygous prothrombotic conditions (e.g. homozygous protein C deficiency). LMWH is often used if several weeks or a few months of therapy are necessary. Thrombolytic therapy is reserved for recent thrombotic lesions that compromise perfusion in vital areas; intracranial hemorrhage in the prior 10 days is a contraindication and cranial US should ensure it has not occurred. Intracranial bleeding is also a serious risk of this therapy.

⑧ — Catheter-related thrombosis, usually involving umbilical arterial or venous catheter, are symptomatic in ~1% of infants with catheters, but asymptomatic thrombosis likely occurs in 20–30%. Serious complications (hypertension, endocarditis, organ infarction, death) are uncommon. Thromboses of the aorta, right atrium and SVC are associated with the highest mortality. Evaluate with ultrasound, but an angiogram through the catheter may be helpful.

⑨ — The role of these prothrombotic defects in neonatal thrombosis remains undefined; therefore these studies are often reserved for children with recurrent thrombosis.

⑩ — A family history of thrombosis, particularly in first-degree relatives before age 40 years or in unusual sites, merits evaluation. Management of recurrent thrombosis beyond the neonatal is addressed in *'Thrombophilia evaluation in a child with thrombosis'* (p 72).

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Thrombophilia evaluation in a child with thrombosis

Venous or arterial thrombosis: DVT and PE most but unusual thromboses are seen ①

→ Routine screening of well children without thrombosis is *not* recommended given their very low risk of thrombosis

Medical and family history ②
Catheters and other risk factors for thrombosis ①
Signs of underlying medical conditions or old thrombosis

→ Routine screening may not be indicated with localized thrombosis at site of CVL or femoral catheter ③

Perform level I evaluation (at time of thrombosis) ④

CBC, blood smear, liver and renal function, PT, PTT, ESR, C-reactive protein, FVIII:C
Lupus anticoagulant and anticardiolipin antibody ⑤
Antithrombin (functional assay) ⑥
Protein C (functional assay) ⑦
Protein S (free antigen)
Factor V Leiden PCR or functional APCR ⑧
Prothrombin G20210A (PCR)
Homocysteine level ⑨
Sickle cell screen

← Positive level I evaluation

- 1–2 defects: Treat 1–2 years after thrombotic event and observe with prophylactic heparin around high-risk events ⑩
- >2 defects: Consider long-term (indefinite) anticoagulation

→ Negative level I evaluation → Normal studies and underlying predisposing medical condition or provoking factor: Anticoagulation for 3 months or until the predisposing condition resolves

Recurrent or progressive thrombosis
Positive family history

Recurrent or progressive thrombosis

If positive family history, family studies may be very helpful

Perform level II evaluation ⑪

Fibrinolytic evaluation: euglobulin clot lysis time, plasminogen, plasminogen activator inhibitor
Dysfibrinogenemia evaluation: fibrinogen activity and antigen, thrombin time, reptilase time, fibrin degradation products, consider crossed immunoelectrophoresis
Heparin cofactor II
Paroxysmal nocturnal hemoglobinuria (flow cytometry for CD 55 and 59)
Lipoprotein(a)
If not previously performed
Functional activated protein C resistance (modified functional assay)
Hemoglobin electrophoresis

No abnormality identified with level I or II testing

- *1–2 defects: treat 1–2 years after thrombotic event and observe with prophylactic heparin around high-risk events*
- *>2 defects: consider long-term (indefinite) anticoagulation*

Consider further testing depending on strength of patient and family history

Factors under investigation as potential etiologies of thrombophilia ⑫
Factor VIII
Factor XII
Factor XI
von Willebrand factor level and multimers
Spontaneous platelet aggregation
Platelet receptor polymorphisms
TPA (tissue plasminogen activator)
TFPI (tissue factor pathway inhibitor)
Thrombomodulin

① — Childhood thrombotic events, although rare, are increasingly being recognized in tertiary care. The rarity of thromboses in children requires some extrapolation from adult data, but there are important differences. Pediatric thromboses are most common in the first months of life or in adolescence. They are most often related to CVLs but there are many other risk factors. Several inherited prothrombotic defects are associated with thrombosis, but usually with multiple thrombophilic genes or acquired risk factors (e.g. indwelling catheter, malignancy [most often leukemias], congenital heart disease, trauma/surgery/immobilization, total parenteral nutrition, pregnancy and puerperium, medications [most importantly oral contraceptives], infection, nephrotic syndrome, SLE, sickle cell disease, polycythemia and liver failure). Most children already have an apparent underlying disease. Thromboses are often unusual: ischemic strokes, peripheral arterial disease (most often related to catheterization), and sagittal sinus, mesenteric, renal, or hepatic venous thrombosis. 20% of children have recurrent thromboses. A spontaneous thrombosis or stroke in an otherwise healthy child suggests a hereditary deficiency or an APLA. However, most children with inherited prothrombotic defects do not develop thrombosis so routine screening is not indicated. Also note that many of the factors decreased by congenital defects may also be decreased by some acquired conditions.

② — In addition to risk factor assessment, consider possible past thromboses (which are often clinically silent in children), other medical problems and medications and family history (particularly if ≥1 first-degree relative had thrombosis). Examination should evaluate signs of old thrombosis including limb swelling, dilated veins and skin changes.

③ — Approximately one-third of children with CVLs develop thrombosis; this is so common that routine screening for prothrombotic defects is not necessary.

④ — This initial evaluation is performed even if there is a family history of an inherited procoagulant defect, because the risk of a second defect in a child with a thrombosis justifies the additional evaluation. Acute-phase reactants and other general studies help to recognize underlying acquired risk defects. Elevated factor VIII coagulant (FVIII:C) activity is now known to be a specific risk factor for thrombophilia.

⑤ — Antiphospholipid antibodies (including lupus anticoagulants and anticardiolipin antibodies) are strong acquired risk factors for thrombosis. Most children do not have SLE. Confirming the diagnosis is complex, requiring at least two abnormal phospholipid- based assays (e.g. PTT), an inhibitory effect (failure to correct upon dilution with normal plasma) and correction of the abnormality with excessive phospholipid (hexagonal phospholipid assay). Anticardiolipin antibody and anti-β GP1 antibodies are assayed. Abnormalities that persist for 2–4 months constitute an anti-phospholipid antibody syndrome. More often these findings are transient and benign in children.

⑥ — Antithrombin deficiency has a higher risk of thrombosis than the other common congenital disorders; its odds ratio in adults (increased risk of thrombosis compared to the general population) is 10–20:1. Its population incidence is 1/250–500. Most childhood thromboses are deep venous and are postpubertal. Rare homozygotes can have arterial thrombosis.

⑦ — Protein C deficiency occurs in 0.2–0.4% of the population with an odds ratio for venous thrombosis of 6.5–8 in adults; oral anticoagulant use can induce skin necrosis. Protein S deficiency is less common but similar clinically except that arterial thromboses are more frequent. Normally 40% of the protein is both free and active. Both proteins C and S are vitamin K dependent and are reduced in infants and by oral anticoagulants; delay testing until the latter are stopped for 10 days. Both autosomal-dominant genes cause venous thrombosis but homozygotes have life-threatening purpura fulminans.

⑧ — APCR, due to the factor V Leiden mutation in >95% of cases, occurs in 3–12% of Caucasians but is rare in other groups. There is a functional assay for APCR as well as DNA testing for V Leiden. The odds ratio for adult thrombosis is 3–7:1, but increases to 48:1 with oral contraceptive use. Thromboses usually follow puberty, but occur earlier with other risk factors. Prothrombin mutation G20210A occurs in 1–2% of European and Middle Eastern but is rare among Asian and African populations; the odds ratio for thrombosis in adults is 2–5:1. It is associated with an increased risk of both arterial and venous CNS thrombosis in children.

⑨ — Hyperhomocysteinemia increases the risk of arterial stroke and venous thrombosis in children and adults, with an odds ratio of 2–5:1 and may be due to congenital or acquired factors. It can occur in as high as 5–10% of the population. Rare homozygotes for cystathionine β-synthetase deficiency are at much higher risk. Blood samples should be obtained fasting, kept cold and centrifuged quickly. Deficiencies of vitamin B_{12}, B_6 or folate can cause it but whether treatment decreases thrombosis is not known. Elevated lipoprotein(a), a low-density lipoprotein, is a risk factor for stroke in young adults. Sickle cell disease is a risk factor for stroke; a negative screen makes it unlikely but a positive screen is more often due only to sickle cell trait.

⑩ — Treat 1–2 years with oral anticoagulants and then prophylactic LMWH or unfractionated heparin at time of high risk events (see ①). Although LMWH is an attractive option to oral anticoagulants, its long-term toxicity has not yet been evaluated. Its better therapeutic/safety record in the short run will make it attractive if longer-term follow-up confirms its safety, but it is much more expensive.

⑪ — The level II evaluation examines less common procoagulant conditions, including abnormalities of fibrinolysis (as determined by a long euglobulin clot lysis time, low plasminogen, increased plasminogen activator inhibitor), dysfibrinogenemia, and low heparin cofactor II, and is used to exclude paroxysmal nocturnal hemoglobinuria and sickle cell disease.

⑫ — Some of these studies may be indicated especially as experience defines their role as risk factor for thrombosis.

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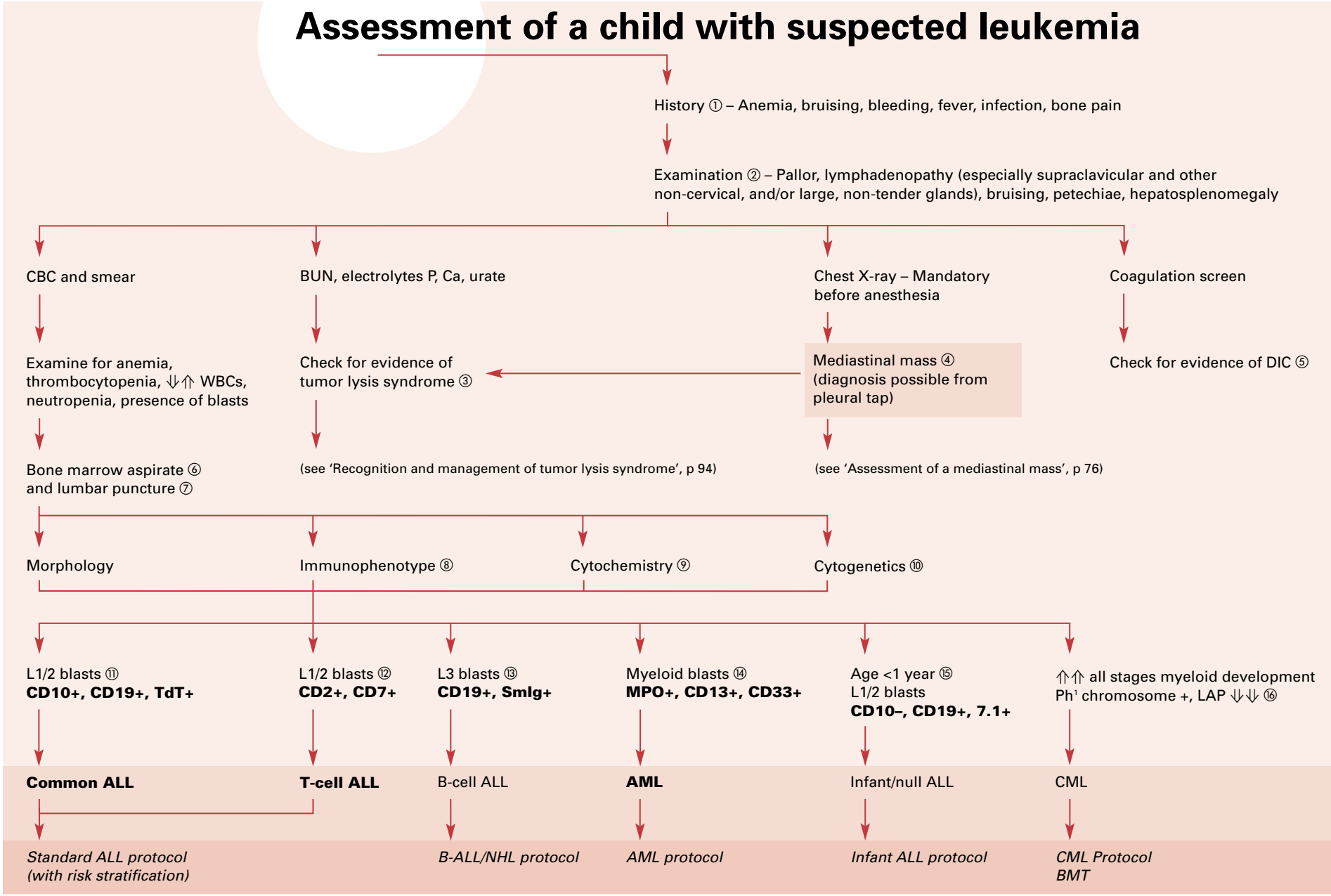
Assessment of a child with suspected leukemia



① — Among children with ALL at the time of diagnosis, approximately 60% have fever, 50% have bleeding, and over 20% have bone pain or limp. The symptoms are similar in children with AML although the proportion affected is somewhat less.

② — Bulky nontender nodes ± splenomegaly in an afebrile child are highly suggestive of a malignant process. Supraclavicular adenopathy is especially concerning.

③ — Critical management steps are outlined in the algorithm on *'Recognition and management of tumor lysis syndrome'* (p 94).

④ — The differential diagnosis of a mediastinal mass is discussed in the algorithm on this topic. The presence of an anterior mediastinal mass in a child with suspected leukemia is almost always associated with the presence of a T-cell ALL or non-Hodgkin lymphoma. Mediastinal masses can be a medical emergency. General anesthetic and sedation should be avoided as the muscle relaxation on the operating table allows the mass to fall posteriorly and compress the trachea deep within the mediastinum beyond the reach of a standard endotracheal tube. Often such cases are associated with pleural and/or pericardial effusion; a simple aspirate of the effusion usually yields adequate cells to allow a diagnosis to be reached and often enough to set up cytogenetic cultures. However, it is still important to perform a bone marrow aspirate to establish the degree of infiltration as soon as possible and certainly within 3 days of starting chemotherapy. Less than 20% blasts within the bone marrow would generally be called T cell-non-Hodgkin lymphoma, have a slightly better prognosis and less aggressive treatment.

⑤ — Most common with acute promyelocytic leukemia. Also found in monocytic leukemias and to a lesser extent in any subtype of leukemia. A partial thromboplastin time (PTT) and prothrombin time (PT) should be performed as a minimum coagulation screen.

⑥ — Even if the diagnosis of leukemia is not obvious at this stage, it is usual to aspirate sufficient marrow to allow all the investigations listed to be performed. Occasionally, the marrow can be fibrotic and insufficient marrow can be obtained by aspiration alone; a trephine bone marrow biopsy then becomes essential.

⑦ — If the diagnosis is clearly ALL on the blood film, then it is usual to give the first intrathecal chemotherapy at this juncture (assuming the coagulation screen is normal or has been corrected according to institutional guidelines). However, a clean tap must be obtained first as the presence of CNS blasts at diagnosis may infer a worse prognosis.

⑧ — Most laboratories have large standard panels of antibodies for flow cytometry that are performed in a designated order (according to morphology); only the characteristic antigens have been shown here. Terminology assigns a CD (cluster differentiation) number to identify most antigens. Flow cytometry has become a very powerful tool and enables the leukemic subtype to be confirmed within a few hours of the bone marrow aspirate. The most specific markers are noted in bolded text.

⑨ — Cytochemistry has largely been replaced by flow cytometry in the majority of laboratories, but can be useful in difficult cases when it is hard to separate ALL from AML.

⑩ — Chromosomal translocations are the most significant prognostic factor in AML. In ALL, translocations are less frequent and often of adverse prognostic significance (t(4;11), t(9;22)). However, standard G-banding techniques do not produce results for 14 days and can thus not be used in the initial assessment. The cytogenetics laboratory may also perform PCR to identify specific translocations and should store DNA and RNA for future studies.

⑪ — A homogeneous population of cells with a very high nuclear/cytoplasmic ratio and the absence of prominent nucleoli typify L1 morphology. L2 cells have more pale blue cytoplasm and nucleoli. Distinction between the two is not of prognostic significance, but they must be separated from L3 blasts. L3 blasts signify a different disease, which needs different treatment and responds poorly with standard ALL therapy.

⑫ — 'Hand-mirror' cells have been suggested to typify T-cell morphology, in which the nucleus of the cell forms the glass and the cytoplasm the handle. However, objective analysis of large numbers of cases does not support this view.

⑬ — L3 blasts are striking for their deep blue vacuolated cytoplasm. However, care still needs to be applied, as not all cases are as obvious as those in hematological atlases. Their immunophenotype is characterized by the presence of immunoglobulin on the surface of the cell, signifying a more mature cell of origin than that of common ALL. The risk of tumor lysis syndrome is very high.

⑭ — Myeloid blasts are typically larger and have more cytoplasm. Often the presence of myeloperoxidase positive granules or Auer rods confirms their lineage. However, it is not always possible to separate L2 ALL from AML and it is on this occasion where cytochemistry and extensive immunophenotyping become invaluable.

⑮ — Infant ALL is characterized by the presence of 11q23 chromosomal translocations and a much worse prognosis than childhood ALL. The '7.1' antibody recognizes a surface antigen which is only expressed by cells carrying the 11q23 translocation. An accurate same-day diagnosis can thus be achieved. This is important particularly for the child in the second year of life as there is increasing evidence that such children without 11q23 have a much better prognosis and do not need the aggressive and dangerous infant chemotherapy.

⑯ — CML is usually easily diagnosed. WBC averages 250,000 but few blasts are noted and platelets are ↑ or normal. ↑↑ blasts only occur with conversion from chronic to blast phase. Juvenile myelomonocytic leukemia ('juvenile CML') is a rare but distinct entity, occurs at <2 years of age, is Ph^{1} chromosome negative and associated with elevated fetal hemoglobin.

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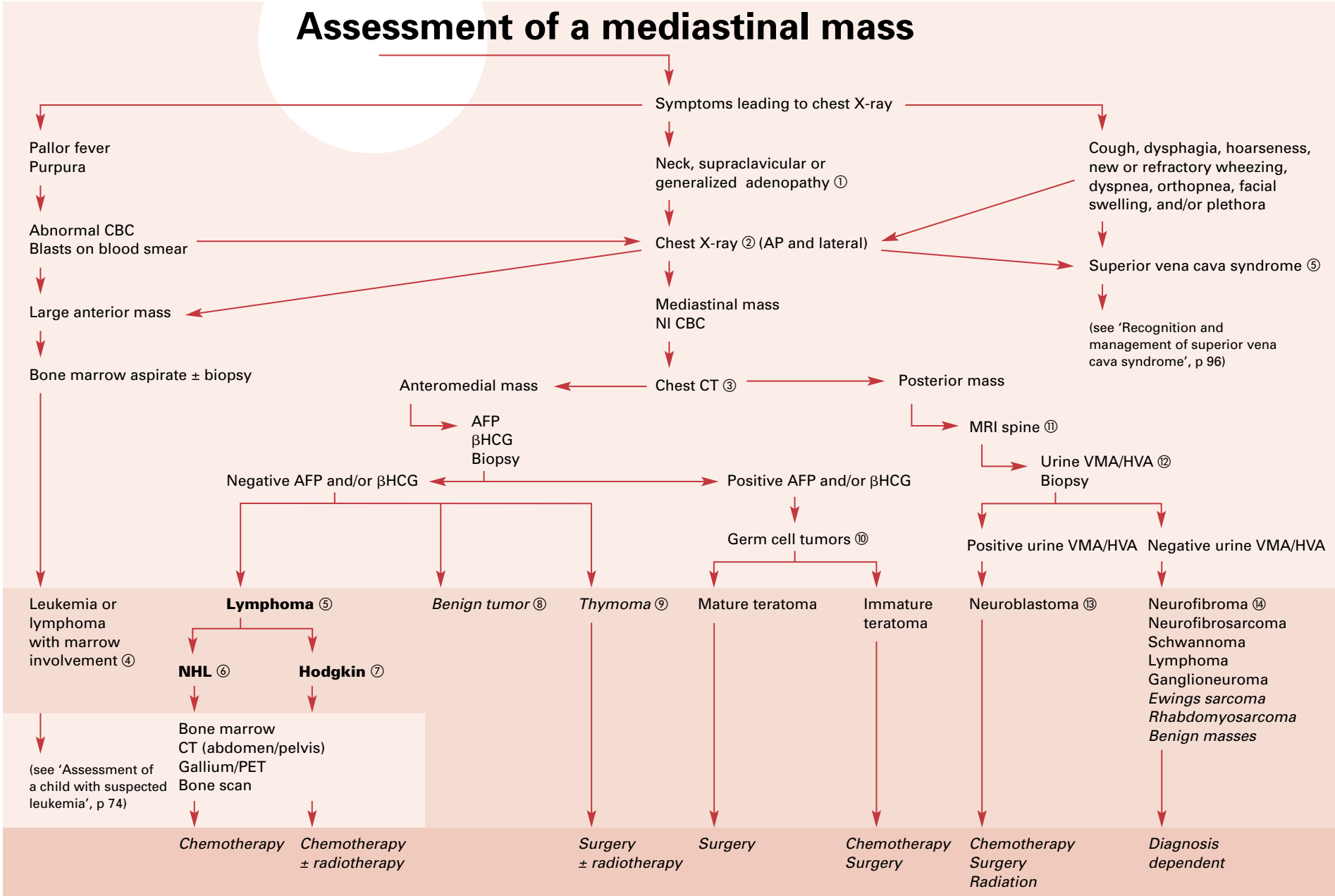
Assessment of a mediastinal mass



① — See algorithms on generalized and localized lymphadenopathy for additional details of clinical presentation. Cancerous nodes are generally very firm and fixed to underlying structures. It is often possible to discern several different nodes matted together. They are not warm, tender or fluctuant and do not respond to antibiotics. Supraclavicular adenopathy is most often associated with malignancy.

② — It is important to assess the airway with any anteromedial mediastinal mass – airway compression can be a life-threatening emergency. On plain chest X-ray the thymus may look like a mediastinal mass, but it has a characteristic shape and does not cause tracheal deviation. Presence of paratracheal and mediastinal adenopathy increases the suspicion of malignancy.

③ — Evaluation of chest masses by CT scan is usually sufficient, especially with the high resolution and thin sections of spiral CT when available. MRI is valuable in defining posterior mediastinal masses and potential spinal canal involvement, which is an oncologic emergency to preserve neural function.

④ — Diagnosis is confirmed by bone marrow examination. The arbitrary line between leukemia with adenopathy vs. lymphoma with marrow involvement is the percentage of blasts in the marrow. Greater than 25% blasts is defined as leukemia. T cell ALL is the leukemia most commonly associated with mediastinal masses, usually with a high WBC count.

⑤ — Emergency low-dose radiation is indicated when there is life-threatening airway compromise from tracheal compression. Tissue radiation can make the pathologic diagnosis difficult. Ideally, biopsy of the mass occurs before radiation or from a node outside the radiation field. Chemotherapy can also be used before a biopsy, but within 24–48 h all of the tumor will be affected and it may be difficult to impossible to make a pathologic diagnosis thereafter.

⑥ — Mediastinal non-Hodgkin lymphoma is most commonly of T cell phenotype. It is possible to make the diagnosis from pleural fluid or bone marrow if those tissues are involved. Evaluate the spinal fluid for malignant involvement. Except for emergency radiation for the airway, therapy is based on chemotherapy alone.

⑦ — 20–30% of children present with B symptoms (night sweats, weight loss of >10% body weight, and/or fevers >38°C). Nodes are generally not painful or tender but have a 'rubbery' firmness, and often have a variable growth rate. Gallium scan is positive in 40–60% of the cases and can be used to follow the disease response with treatment, but it is also positive in many nonmalignant inflammatory conditions. PET scanning is gaining favor as it is more specific to identification of lymphoma sites and as a marker of disease response is more highly predictive of cure.

⑧ — Benign tumors are usually located in the anteromedial mediastinum: bronchogenic cysts, goiter, lipoma, lymphangioma, and enteric cysts are the most frequent and are diagnosed by open biopsy. In the posterior mediastinum, neurenteric cysts are generally associated with congenital abnormalities of the thoracic spine. The CT findings will often suggest these diagnoses.

⑨ — Nearly one-half of these tumors are asymptomatic, but up to 30% of all patients, with or without symptoms, can have myasthenia gravis. The histologic diagnosis is made through open biopsy or mediastinoscopy. Treatment is surgical excision.

⑩ — These tumors are usually asymptomatic until they reach a considerable size and may produce tracheal and bronchial compression. Tumor markers such as α-fetoprotein (AFP) and human chorionic gonadotrophin (βHCG), both detected in serum, may be the only clues to diagnosis. Interpreting AFP in infants can be difficult as they normally have a high level at birth and a variable half-life. Mature teratomas are negative for these markers and, therefore, the presence of a positive marker indicates a malignant component within the mass. A biopsy, open or by mediastinoscopy, is necessary to differentiate the subtype of germ cell tumor although treatment is currently the same for all groups. Completely mature teratomas respond only to surgical resection.

⑪ — Posterior masses adjacent to the vertebra can invade the spinal cord. If the cord and clinical function are compromised it is possible to preserve neurologic function by immediate initiation of chemotherapy, spot radiation or surgical laminectomy with removal of tumor.

⑫ — Elevation of urinary HVA and/or VMA can be diagnostic of neuroblastoma. Minor elevations can be due to diet intake, as phenylalanine and tyrosine raise these levels. To be significant they should be 3 SD above the mean. VMA and HVA can be measured on spot urine samples by normalizing them against creatinine levels on the same sample.

⑬ — Neuroblastoma in the posterior mediastinum tends to be stage I–III with more histologic differentiation and a decreased rate of metastases. Surgical removal can be difficult because of adjacent vital structures. The posterior mediastinum is also the most common site of a fully mature ganglioneuroma (often VMA/HVA negative) as well as ganglioneuroblastoma.

⑭ — Neurofibroma, neurofibrosarcoma, and malignant schwannomas are all derived from the neural crest and are most commonly seen in patients with neurofibromatosis. Enteric cysts and thoracic meningoceles are very rare. Very rarely, Ewing and rhabdomyosarcoma occur in the posterior mediastinum.

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For chapters on non-Hodgkin lymphoma, Hodgkin disease, acute lymphoblastic leukemia and neuroblastoma see Emedicine Pediatric Medicine, E medicine, 2002 (http://emedicine.com).

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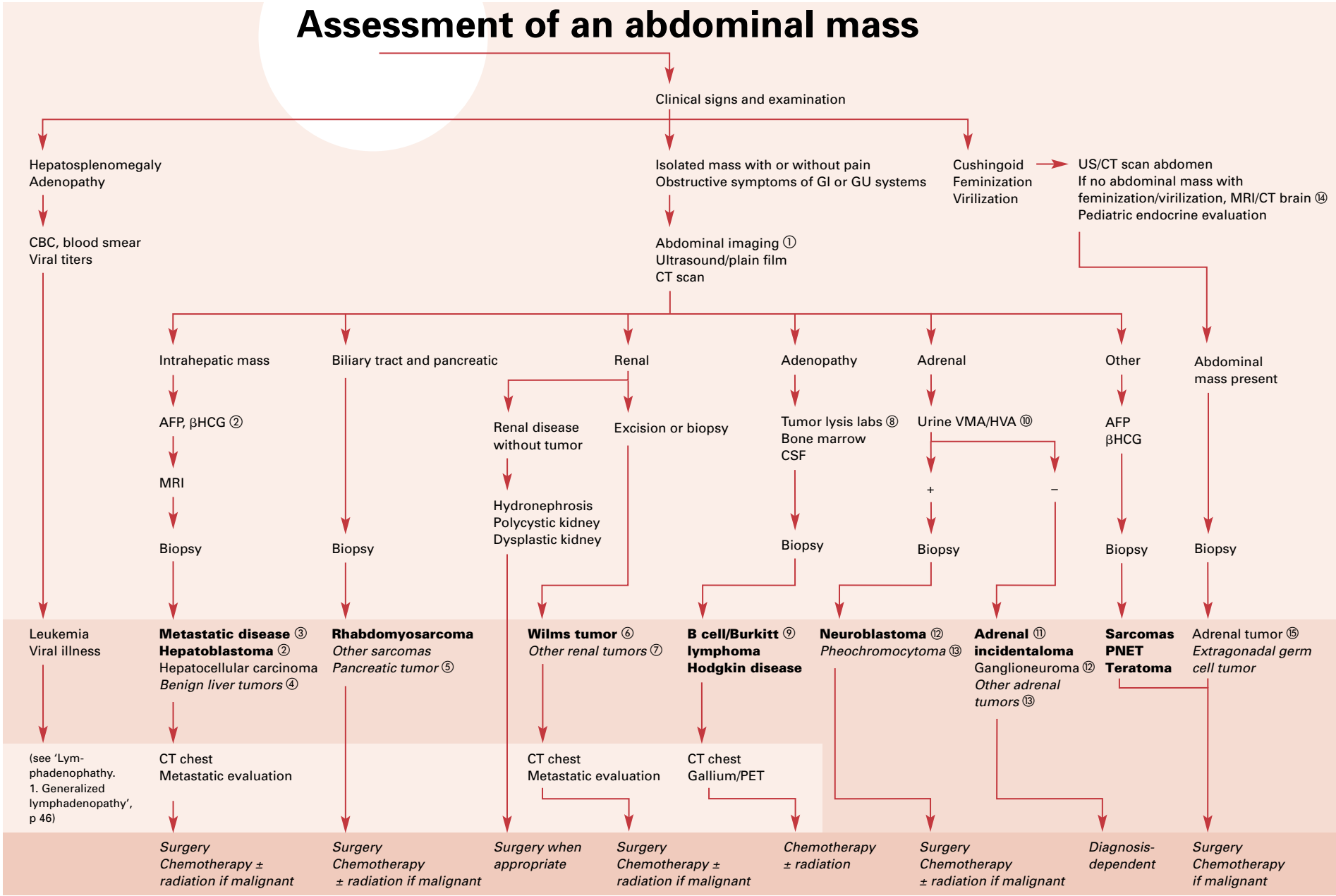
Assessment of an abdominal mass



① — Plain X-rays are most helpful to evaluate for GI obstruction or to rule out constipation as a cause of the 'mass'. US is more useful for rapid evaluation of abdominal masses. In neonates, cystic and fluid filled masses are generally benign but solid masses must be considered malignant until proven otherwise. More than 50% of flank masses in the newborn are non-malignant renal anomalies. In Wilms tumor US can often clarify whether tumor extends into the inferior vena cava. CT with oral and i.v. contrast can define the extent of the mass, helping the surgeon decide whether to attempt total resection or biopsy only. High resolution spiral CT or MRI better define the extent of hepatic lesions.

② — Hepatoblastoma is the most common pediatric liver tumor in most areas, but where chronic active hepatitis is common, hepatocellular carcinoma is more prevalent. Hepatoblastoma, an embryonal tumor, arises in normal liver, is most commonly unifocal and in the right lobe. However, it can be multifocal and involve the entire liver. Hepatocellular carcinoma is more frequent in older children, more likely involves both lobes at diagnosis, generally arises in already damaged liver tissue and is difficult to cure. Both present with hepatomegaly and abdominal pain and can have elevated AFP (in 90% of hepatoblastoma and 60% of hepatocellular carcinoma). Staging is dependent on site, vessel invasion, resectability and metastases. The combination of US, CT and MRI can define many of these issues, including vascular involvement.

③ — The tumors which most often metastasize to the liver are Wilms tumor, neuroblastoma and ovarian tumors.

④ — One third of primary liver tumors are benign and include hemangioendothelioma, mesenchymal hamartoma, focal nodular hyperplasia and adenoma.

⑤ — Pancreatic tumors are rare but include benign papillary-cystic tumors and hemangiomas. Malignant tumors are similar to those of adults.

⑥ — Most children are asymptomatic and diagnosed because a flank mass is felt by a family member or physician. The tumor is generally ballotable and smooth. Those with symptoms have abdominal pain, fever, anemia (from intratumor hemorrhage), hematuria (20%) and/or hypertension. While most children with Wilms tumor are otherwise normal, there is an increased incidence in children with Beckwith-Wiedemann syndrome, aniridia, hemihypertrophy and genitourinary anomalies. Anaplastic histology confers a worse prognosis. In Europe it is common to make the diagnosis by biopsy and then chemotherapy is delivered before definitive resection. In the United States total resection is attempted at diagnosis, followed by chemotherapy – survival rates are the same with both approaches.

⑦ — Non-Wilms renal tumors include *rhabdoid* (2% of renal tumors, probably neurogenic in origin, often presents with metastatic disease in the lung, liver or brain, and has a very poor prognosis), *clear cell sarcoma of the kidney* (4% of renal tumors, 40–60% have bone metastases, poor prognosis), *renal cell carcinoma* (very rare in children and behaves like adult cases) and *congenital mesoblastic nephroma* (two subtypes, one benign and one malignant, treated like Wilms tumor).

⑧ — CSF and/or bone marrow involvement in B-cell lymphoma permits diagnosis without an abdominal biopsy as may paracentesis of malignant ascites. Tumor lysis syndrome can be present at diagnosis in these rapidly dividing tumors. See *'Recognition and management of tumor lysis syndrome'*, p 94.

⑨ — See *'Assessment of a pelvic mass'* (p 80) for more information on B cell lymphomas. When Hodgkin disease arises in the abdomen, there may be no signs or symptoms until there is spread to clinically palpable nodes. Eosinophilia occurs in approximately 15% of patients (see *'Assessment of a mediastinal mass'* (p 76).

⑩ — The urinary catecholamines (VMA and HVA) are measured. Elevation of urinary catecholamines HVA and/or VMA occurs in 95% of neuroblastomas; diagnosis by these catecholamines alone does not assess prognostic markers such as histologic classification or MYCN gene amplification. Involved bone marrow can confirm the diagnosis and MYCN status.

⑪ — Incidentalomas are adrenal masses coincidentally identified by ultrasound, CT or MRI done for other reasons. They occur on about 3% of all abdominal CTs. They are small (usually <3 cm), may have calcifications and are probably residual from old adrenal trauma. 10% of these secrete catecholamines and need further intervention – the rest are 'incidental', benign and may be left alone.

⑫ — Embryonal neural tumors from the sympathetic nervous system range from malignant (neuroblastoma) to completely benign (ganglioneuroma). Prognosis is dependent on age (less than one improves prognosis), stage, tumor histology and resectability. Molecular biologic markers like MYCN gene amplification confer a worse prognosis. Cortical bony metastases confer a worse prognosis. Children less than 1 year of age with metastatic disease not involving cortical bone, and a small primary mass have stage IVs which can spontaneously regress without treatment.

⑬ — Pheochromocytomas are very rare in childhood and less than 10% are malignant. Adrenal carcinomas and benign adenomas are very rare in childhood. 80% are hormone-secreting tumors and in 60% there are symptoms of hormone excess with weight loss and malaise.

⑭ — CT/MRI of brain is necessary to identify pituitary tumors that can cause precocious puberty.

⑮ — Adrenal tumors can cause Cushing syndrome or either feminization or virilization. Extragonadal abdominal germ cell tumors are generally retroperitoneal, usually in children under the age of 2 years, and can cause precocious puberty. They present with pain and/or obstructive symptoms of bowel or urinary tract. Hepatic teratomas are seen soon after birth and are associated with very elevated AFP levels.

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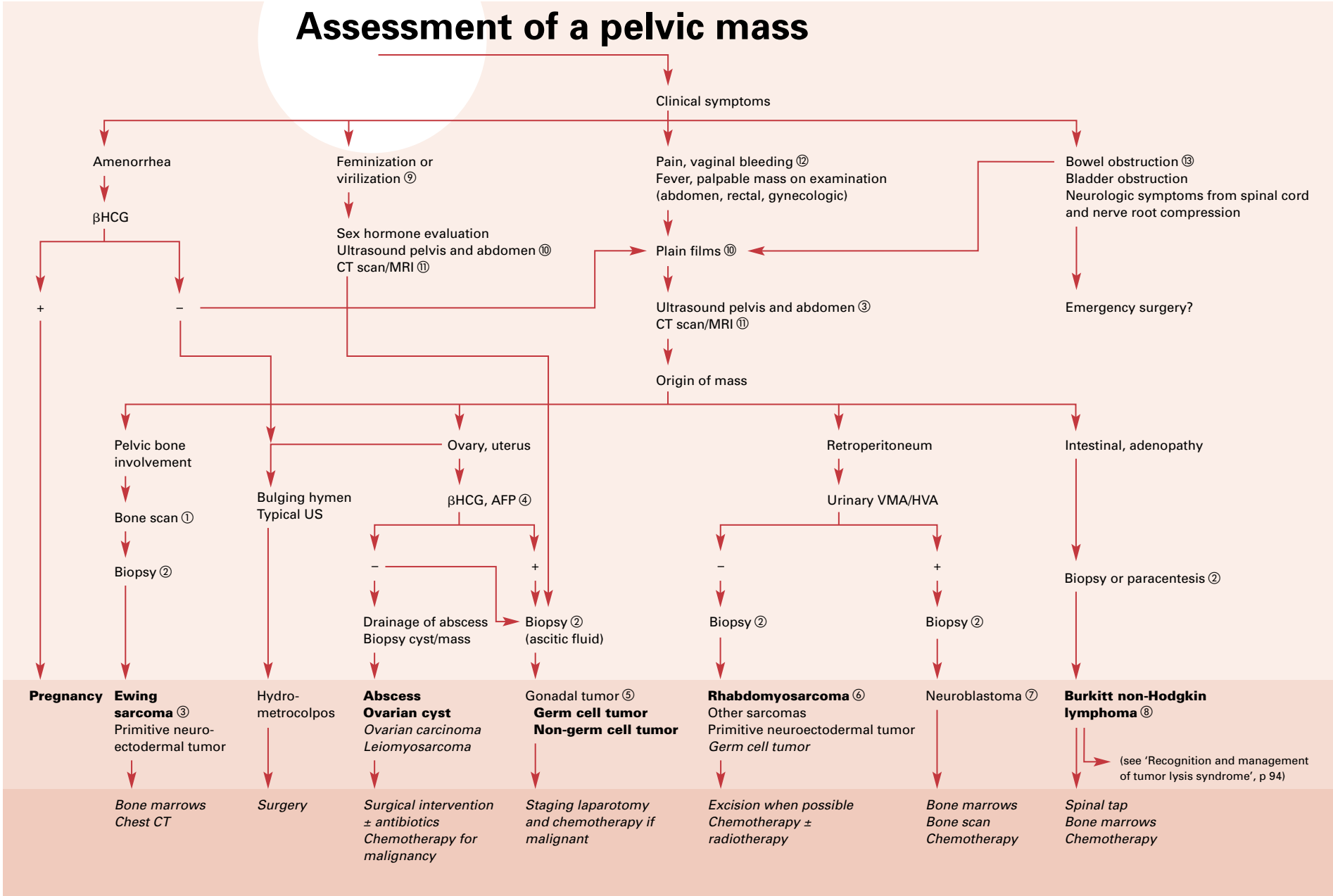
Assessment of a pelvic mass



① — A bone scan can determine the extent of tumor in the pelvic bones and other distant sites of osseous involvement.

② — There are several options for obtaining tissue for histologic diagnosis. US-guided biopsy (fine-needle aspirate or needle-core biopsy), biopsy through rectoscopy or cystoscopy, laparoscopy or open biopsy through laparotomy. If the tumor has associated ascites, a paracentesis may yield diagnostic fluids (especially in GCT and lymphomas). The approach is determined by the skill and experience of the surgeon as well as the information needed (such as whether there are peritoneal studs in a GCT which may require direct visualization by laparotomy). Fine-needle aspirate may be performed in very sick children but in most cases does not provide enough material to obtain all of the histologic and molecular genetic information required.

③ — Ewing sarcoma and primitive peripheral neuroectodermal tumor (PNET) belong to the same family of neural-derived tumors. PNET tends to be more differentiated and has a higher incidence of positive pathology markers such as neuron-specific enolase (NSE) and S100 which are indicators of more mature neural differentiation within the tumor.

④ — α-Fetoprotein (AFP) levels are normally very high in neonates and this may mask tumor-induced elevation of AFP. The majority of germ cell tumors (GCT) in neonates are benign, requiring surgical excision only. Sacrococcygeal tumors are more frequent in children under the age of three. Fifty percent of these are in neonates, primarily in girls.

⑤ — Gonadal tumors are ovarian and testicular. The majority of gonadal tumors are germ cell in origin and one-third of these GCT arise in the ovary; peak incidence is at 10 years of age, and 70% are mature teratomas which require surgical excision only. Ovarian tumors may not present until they are very large and may present with torsion or rupture. The pattern of spread of malignant GCT is ascites and peritoneal implants followed by metastases to lung, lymph nodes and liver. GCT occurring in extragonadal sites are most frequently benign mature teratomas, but they may contain some malignant components requiring therapy; therefore, careful pathologic study of the entire tumor is essential. The majority of malignant GCT involve extraembryonal differentiation and secrete either AFP and/or βHCG (AFP in yolk sac tumor and βHCG in choriocarcinoma). Elevation of these markers in the serum is of great value both in diagnosis and management. GCT can arise outside the gonad, most commonly as sacrococcygeal teratoma identified as an external protuberance. GCT occasionally originate in the retroperitoneum. Non-GCT gonadal tumors include sex cord-stromal tumors (granulosa and Sertoli Leydig cell) or epithelial tumors. Ovarian carcinomas are extremely rare in childhood.

⑥ — Rhabdomyosarcoma (RMS) arises from mesenchymal cells committed to developing into striate muscle. The histologic subtypes are correlated with the prognosis. Botryoid and spindle-cell RMS are the rarest subtypes and have the best prognosis. Alveolar RMS (high incidence of a t2;13 chromosomal translocation) is generally seen in the extremities in adolescents, and has the worst prognosis. Two-thirds of all RMS are embryonal which are more often seen in the trunk of younger children and have an intermediate prognosis. About 25% of all RMS occur in the GU/retroperitoneal area and they can be very large masses before causing physical symptoms such as bladder obstruction. Botryoid RMS typically presents as a grape-like cluster protruding from the cervix or vagina in very young girls. RMS are sensitive to both chemotherapy and radiation with most successful treatment regimens incorporating both if the resection is not complete (for sarcomas other than rhabdomyosarcoma, see *'Assessment of a soft tissue mass'*, p 82).

⑦ — Neuroblastoma rarely originates in the pelvis but when it does it can extend into the neural foramina and compress the nerve roots (see *'Assessment of an abdominal mass'*, p 78).

⑧ — The pelvis/abdomen is the most frequent primary site (90%) of Burkitt (B cell) lymphoma. The most common presentation is a rapidly growing mass, often producing ascites. This leads to pain, abdominal swelling and intestinal obstruction, and can serve as a lead point for an intussusception. Tumor lysis is very common and often life threatening. Diagnosis can be made from tumor biopsy, ascitic fluid or involved bone marrow. The cells are clonal B cells with surface immunoglobulin and there are characteristic translocations seen that are pathognomonic (t8;14, t8;22 or t2;8). Chemotherapy is very effective.

⑨ — Precocious puberty or virilization can result from ovarian non-germ cell (stromal) tumors, less often from germ cell tumors, and rarely from extragonadal pelvic germ cell tumors. Keep in mind that adrenal adenomas and carcinomas will cause similar symptoms. Pediatric endocrine assessment is indicated.

⑩ — Plain X-rays and ultrasound can demonstrate calcifications in the case of benign gonadal tumors or neuroblastoma. US is very useful in assessing ureteral obstruction which could require emergency urinary diversion to preserve renal function. Ovarian masses can be determined to be cystic or solid and hydrometrocolpos can be identified.

⑪ — Contrast-enhanced CT gives information on the primary tumor and intra-abdominal metastases. Spiral CT and MRI have the advantage of imaging the tumor in the coronal and sagittal planes. MRI better defines spinal cord invasion.

⑫ — Vaginal bleeding can be due to a botryoid rhabdomyosarcoma which presents as a grape-like cluster of clear tissue protruding from the vagina or cervix, which should be excised or biopsied. Vaginal bleeding is also caused by feminization due to sex-hormone-secreting ovarian or adrenal tumors.

⑬ — The predominant symptoms of malignant pelvic tumors are pain, palpable swelling/masses, fever, and signs of obstruction of either GI or GU tract. Compression of nerve roots can lead to leg weakness and paresthesias. These symptoms may increase rapidly over a short period or remain constant for several months.

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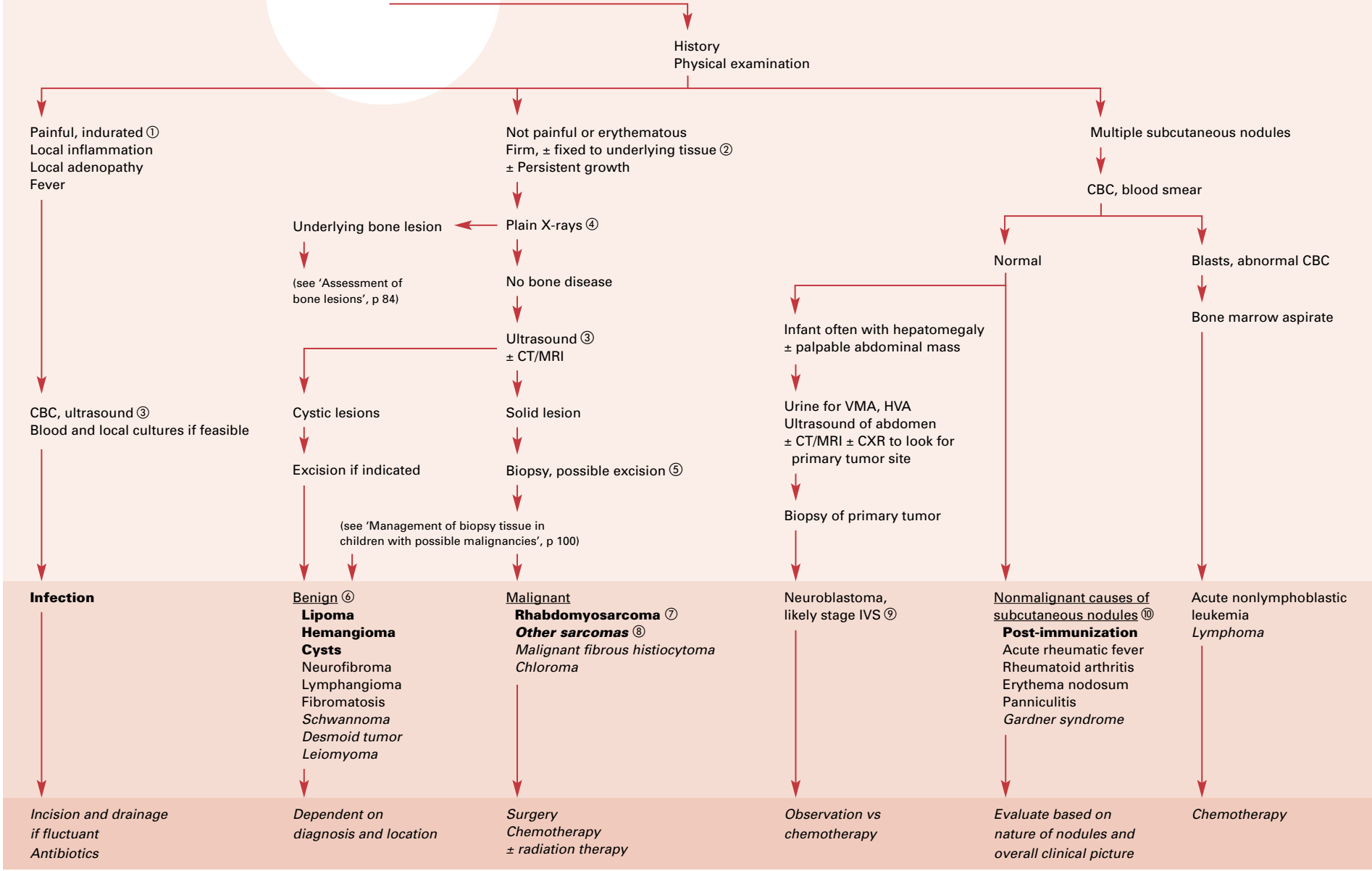
Assessment of a soft tissue mass



① — Pain, induration and inflammation are hallmarks of infection. Although superficial tumors can get irritated by trauma and demonstrate similar symptoms, infections are usually easily identified clinically. A trial of antibiotic therapy is reasonable before proceeding to an expensive evaluation. If there is fluid or fluctuance (which may be better defined by ultrasound), needle aspiration and culture or incision and drainage may take priority over other tests. Ultrasound can also help define the extent of a deep soft tissue infection.

② — Most tumors, whether benign or malignant, are painless and firm. Malignant lesions can be fixed to underlying tissue as they infiltrate tissue planes but even some benign lesions can be very infiltrative, aggressive and locally destructive.

③ — Ultrasound can be helpful if the soft tissue mass has no underlying bone pathology. It can distinguish cystic from solid lesions and is very helpful in identifying hemangiomas. In defining soft tissue masses, MRI appears to be superior to CT scan. The former can often identify vascular involvement without contrast enhancement.

④ — Plain X-rays may identify bone fractures, hematomas, calcifications, cystic components or a primary bone lesion with a soft tissue extension/reaction. In Langerhans cell histiocytosis, there may be soft tissue swelling over bony osteolytic lesions.

⑤ — Fine-needle aspirates and needle core biopsies can establish malignancy but often do not provide adequate material to identify subtypes of sarcoma or to do necessary cytogenetic and molecular studies. Excisional biopsy may be done especially if likely benign or if significant damage can be avoided to normal tissue. Soft tissue cysts are almost always benign and are simply excised if clinically indicated.

⑥ — Benign tumors can be locally invasive and destructive but do not metastasize. Lipomas are common and occur most in subcutaneous fat. Hemangiomas most commonly occur in the skin with 60% in the head and neck region. Large hemangiomas can produce serious complications such as airway obstruction or thrombocytopenia from platelet consumption. Most start in the neonatal period and often enlarge for the first few months following birth, followed by spontaneous involution. If they are causing symptomatology they will often regress in response to high dose corticosteroids and/or interferon-α. Neurofibromas and schwannomas primarily occur along peripheral nerves but can also occur in the central trunk. They are seen primarily in individuals with neurofibromatosis and can be very large and locally destructive. Surgical resection is the only effective treatment modality. Rarely, they can become malignant. Desmoid tumors are derived from fibroblasts and are locally very aggressive. They do respond to low-dose chemotherapy which can make resection easier. Fibromatosis arises from neoplastic myoblastic-fibroblastic tissue and is most common in early childhood. Infantile myofibromatosis arises as a solitary mass in the very young. Lymphangiomas are lymphatic malformations that can be localized or generalized, and commonly occur in the cervicofacial region, thorax or axilla. Leiomyoma is a very rare smooth muscle tumor and must be differentiated from leiomyosarcoma.

⑦ — Rhabdomyosarcoma (RMS) is the most common soft tissue tumor (STS) in childhood (see *'Assessment of a pelvic mass'*, p 80, for more details on RMS in general).

⑧ — Non-rhabdomyosarcoma soft tissue tumors (NRSTS) are a heterogeneous group of tumors which range from well-differentiated and nonaggressive to aggressive and metastasizing. They are rare in children but increase in frequency with age. The most common sites are extremities, trunk wall and peritoneum. Involvement of regional nodes is less frequent than in rhabdomyosarcoma. In general, larger tumors have a worse prognosis. Because of their rarity, our therapeutic experience is limited. Complete surgical resection is critical. Most do respond to chemotherapy. Preresection chemotherapy may shrink an inoperable mass and make its complete resection possible. In metastatic disease chemotherapy is the prime treatment. Radiation therapy may be beneficial when the surgical margins are not free of tumor. Some NRSTS include: peripheral primitive neuroectodermal tumor is neural-derived and presents most commonly around the chest. Synovial sarcoma (40% of NRSTS) often has fibrous and glandular components with epithelial differentiation, usually around the knee or thigh. The translocation tX;18 is seen in this tumor. Fibrosarcoma (13% NRSTS) is the most common NRSTS in children less than one year of age. It arises from fibrous tissue and in children under age five it is usually low grade. In older children fibrosarcomas are much more aggressive with a high local recurrence rate and lung metastases. Malignant fibrous histiocytoma can be very aggressive locally and also has the ability to metastasize. The cell of origin is not known in this tumor. Neurofibrosarcoma (10% NRSTS) and schwannomas arise from peripheral nerves, with almost 50% occurring in patients with neurofibromatosis (NF1). They have a very poor long-term prognosis. Alveolar soft part sarcoma is a slow-growing tumor arising in the head, neck and extremities. However, over 10–20 years it is almost universally fatal so aggressive surgical management is warranted at diagnosis. Hemangiopericytoma, angiosarcoma and hemangioendothelioma arise from vascular tissue with lymphangiosarcoma originating from vascular or lymphatic endothelium. Angiosarcomas most commonly present in the liver. Hemangiopericytomas have an infantile form that has an excellent prognosis. Leiomyosarcomas occur primarily in the uterus or the GI tract. Those in the GI tract are more likely to have metastases and a poorer prognosis. There is an increased incidence of this type of sarcoma in chronically immunosuppressed patients. Chloromas are soft tissue masses due to acute nonlymphoblastic leukemia, which may precede CBC changes.

⑨ — Children with neuroblastoma can have subcutaneous nodules of tumor that can appear and regress without treatment. This is most common in stage IVS which by definition is children under the age of one with a small primary and no bone metastases. Urinary VMA/HVA are elevated in 95% of neuroblastomas (see *'Assessment of an abdominal mass', 78*).

⑩ — Many benign disorders cause subcutaneous nodules, a number of which are included in the algorithm.

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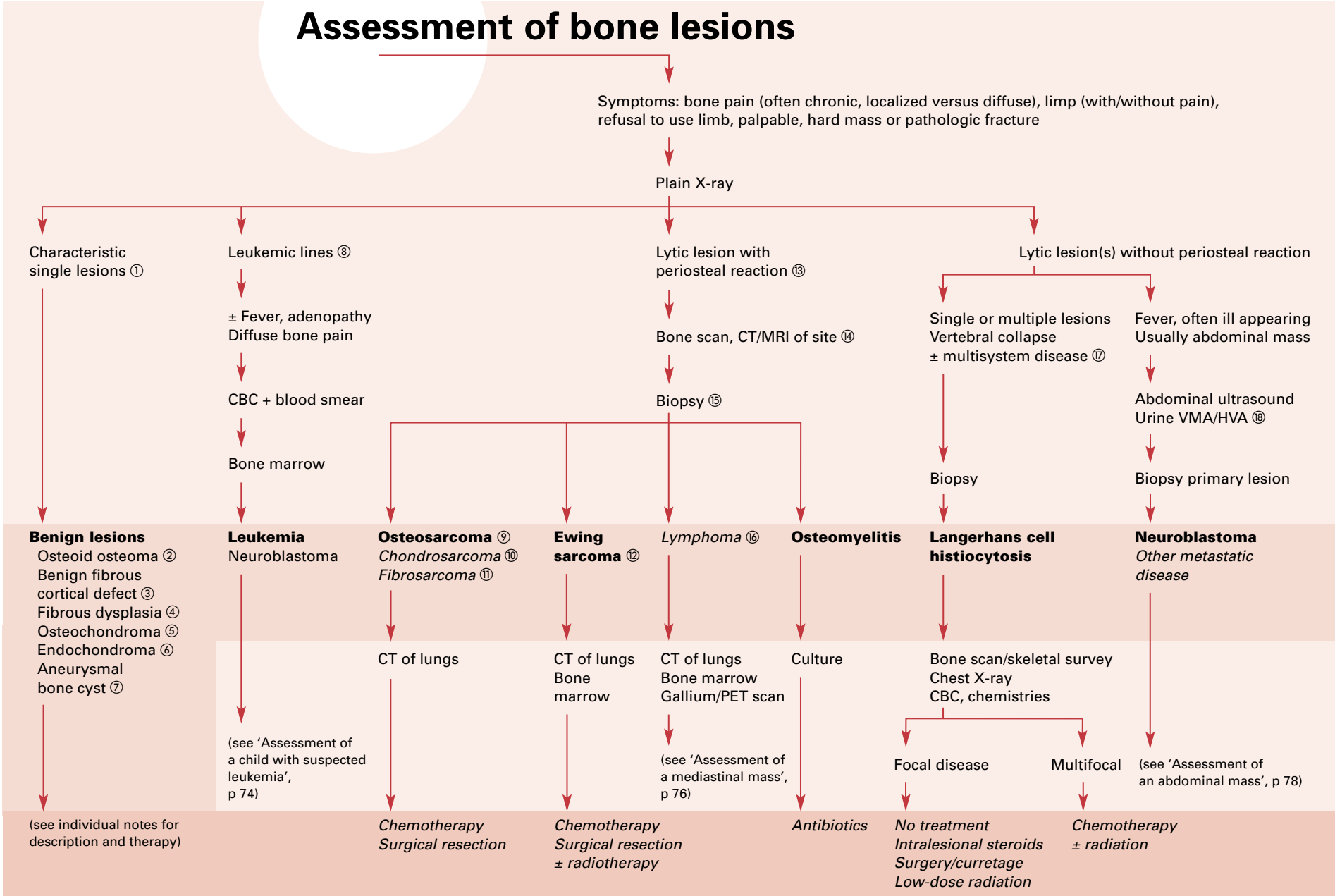
Assessment of bone lesions



① — The radiologic appearance of most benign bone tumors establishes the diagnosis without CT, MRI or biopsy.

② — Occurs primarily in second decade, usually in lower extremities. Severe pain at rest is common. The characteristic X-ray pattern is a radiolucent nidus of osteoid tissue surrounded by sclerotic bone.

③ — Peak occurrence is at 4–10 years of age with 90% located in the distal femur. 50% of cases are bilateral. X-ray shows a loculated lesion with a sclerotic medullary border. They usually regress spontaneously.

④ — The most common developmental osseous anomaly. It occurs primarily in adolescence, is more common in males, and can present with a pathologic fracture. Generally, resection is delayed until growth is complete.

⑤ — The most common benign tumor of bone in adolescence generally occurs near the knee. If it causes pain it can be removed surgically. Classically, it is sessile and pediculated, arising from the cortex of a long tubular bone, adjacent to the epiphyses.

⑥ — Single or multiple lesions of mature hyaline cartilage that can be locally aggressive and painful, and can undergo malignant degeneration. 30% arise in either metacarpals or metatarsals. Plain films show areas of rarefied bone and stippled calcifications.

⑦ — These cysts affect any bone and appear as a lytic expansile lesion that is well demarcated. Treatment is surgical.

⑧ — 25% of children with ALL present with symptoms of bone pain that can be multifocal. X-rays can be normal or show leukemic lines (faint lines that look like growth arrest).

⑨ — Osteosarcoma is the most common malignant bone tumor with a peak incidence during adolescence and early adult life. It arises from mesenchyme and produces abnormal osteoid tissue. It can arise in any bone but mostly in the long bones with distal femur being the most common (followed by proximal humerus and proximal tibia). 15% are metastatic at diagnosis with the lungs most commonly involved. Osteosarcoma is relatively radiation resistant so therapy is based on chemotherapy and definitive resection at the time of limb salvage after several cycles of chemotherapy, when surgically possible. Tumors with >95% necrosis at the time of limb salvage have a better prognosis.

⑩ — Chondrosarcoma: most common in older adults and primarily in the pelvis.

⑪ — Fibrosarcoma: primarily in distal extremities, behaves similarly to osteosarcoma but does not produce osteoid.

⑫ — Ewing sarcoma originates in neural tissue of the intramedullary cavity but often invades cortex into surrounding soft tissue. Pathologically, it is a small round blue cell tumor similar to lymphoma and neuroblastoma. However, neural markers can be present and there is a characteristic chromosomal translocation t11:22 which forms a chimer between the EWS gene and a known oncogene, Fli1. Some tumors have a t21:22 translocation instead. Half of Ewing sarcomas occur in the axial skeleton and half in the extremities. 25–30% of the tumors are metastatic at diagnosis. It is both chemotherapy and radiation sensitive. Radiation is reserved for tumors that are unresectable after initial chemotherapy, or after partial excision. As with osteosarcoma, limb salvage procedures are used when possible and the degree of necrosis at the time of limb salvage is prognostically significant.

⑬ — Destructive bony lesions can have soft tissue extension (most common in Ewing sarcoma). In osteogenic sarcoma there may be calcifications from aberrant new bone formation. Any destructive lesion can show periosteal reactions – slower-growing lesions typically show onion-skinning (thin arches of concentric periosteum over the area of destroyed bone) while rapid growth causes Codmans triangle (rapidly elevated periosteum appears angulated) or a sunburst pattern. Only biopsy can definitively distinguish these lesions.

⑭ — CT and MRI can delineate the extent of the lesion, for both soft tissue and intraosseous extension. It is helpful to do these scans before the biopsy to help the surgeon analyze the best approach. Bone scans are necessary to look for evidence of distant bony metastases.

⑮ — When a malignant bone tumor is anticipated, the biopsy is best done by an oncologic orthopedist experienced with limb salvage procedures. After biopsy and chemotherapy, the mass is removed while avoiding amputation when surgically possible. For local tumor control, the biopsy site must be excised so it is best that one surgeon does both procedures. Needle biopsies may provide enough tissue for a diagnosis, but not enough for important biologic studies, and the procedure may allow tumor spread into soft tissue sites.

⑯ — Primary bone lymphoma is rare in children, occurring mainly in adolescents. Radiographically, it most resembles Ewing sarcoma. It is generally a large B cell lymphoma histologically. A bone lymphoma is considered disseminated at diagnosis and treated with aggressive chemotherapy with radiation reserved for resistant lesions.

⑰ — A well-circumscribed osteolytic lesion is typical of Langerhans cell histiocytosis. Isolated lesions often present as a lump, with or without pain. Any bone can be affected, but skull is the most common. Diagnosis is confirmed by biopsy. This nonmalignant disorder can be localized to one or more osseous sites or it can have multiorgan involvement (including pituitary with diabetes insipidus, skin rashes resembling seborrheic dermatitis, liver, lung and bone marrow). Treatment modalities include simple curettage or intralesional corticosteroids for isolated bony lesions, chemotherapy (depending on location and extent of the disease) and, occasionally, low-dose radiation. Smaller lesions in less critical, non-weight-bearing bones often resolve spontaneously without therapy.

⑱ — Bone metastases present as a lump or as a persistent area of pain. Most often due to neuroblastoma with positive urinary VMA and HVA, but rarely due to other malignancies.

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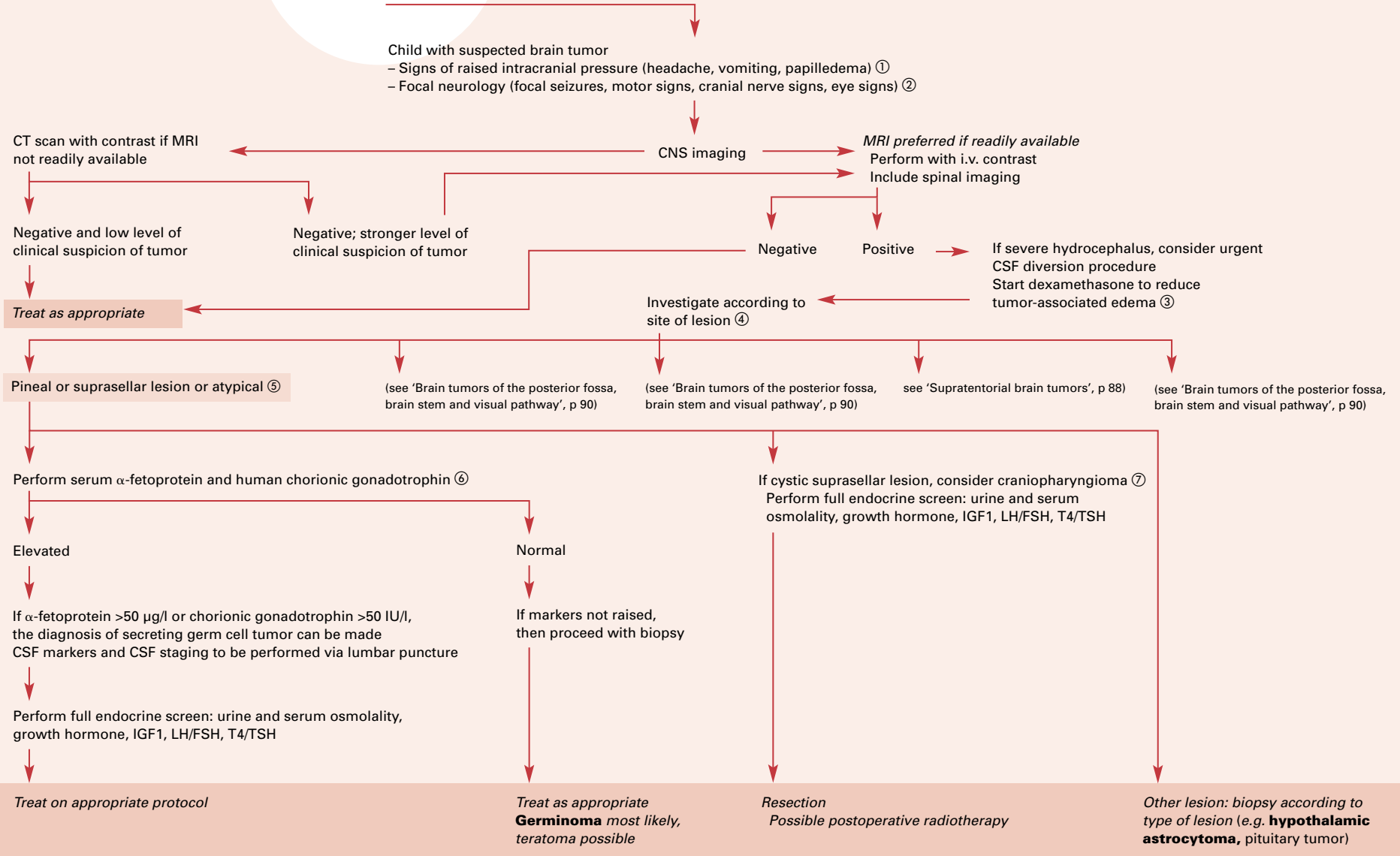
Initial management of a child with a newly diagnosed brain tumor



① — Raised intracranial pressure headaches are typically present on waking. However, this is not universally so. Vomiting may occur in isolation and an index of suspicion must be maintained. The headaches typically get worse over time and last for longer each day. Papilledema is a relatively late sign. In extremis the child will show signs of coning and become obtunded. A sixth nerve palsy may be present.

② — All unexplained focal seizures in children require CNS imaging as do unexplained neurological signs.

③ — MRI with i.v. contrast is the preferred imaging study and should be done if available readily. CT imaging is more widely and often more rapidly available and if so should be done first. CT scanning should always be done with contrast when looking for brain tumors and is best read by a radiologist experienced in neuroradiology. CT scanning can occasionally miss a brain tumor so MRI should be performed if the clinical level of suspicion is strong. If the CT scan is positive, MRI scanning of head and spine is mandatory before definitive treatment is given. Postoperative imaging is very difficult to interpret especially when looking for spinal disease since a lot of post-surgical debris may be present.

④ — If a biopsy is performed it must be noted that pathology of brain tumors can be very difficult. The results should be seen initially or reviewed by a neuropathologist with significant experience of pediatric brain tumors prior to the institution of therapy beyond the initial surgery.

⑤ — Given the close proximity or involvement of the hypothalamus/pituitary axis in suprasellar lesions, a basic pre-operative endocrine workup is essential to detect any gross endocrine disturbances. This should involve measures of both anterior and posterior pituitary function including growth hormone, IGF1, LH/FSH, T4/TSH. Diabetes insipidus must be considered; it is commonly the presenting feature in germinomas. It is advisable to involve a pediatric endocrinologist prior to surgery, as they may suggest more detailed investigations prior to surgery in certain cases but will certainly be needed for long term follow-up.

⑥ — Germ cell tumors are typically found in the pineal or suprasellar region but may be found elsewhere. A high index of suspicion of these tumors must be maintained especially if the lesion is not typical for any other type of tumor. Secreting germ cell tumors will have raised serum markers (α-fetoprotein and/or human chorionic gonadotrophin, HCG) in both the serum and/or the CSF. A diagnosis can be made on raised markers and biopsy is not needed. These tumors respond well to a combination of chemotherapy and radiotherapy. Germinomas may have marginally raised markers but do not reach the 50 µg/l level. These tumors respond very well to radiotherapy.

⑦ — Craniopharyngiomas present at a median of 8 years of age. The majority of these tumors are cystic. These children may present with raised ICP, visual changes, disorders in pituitary function and sometimes mental abnormalities. Most centers use postoperative radiotherapy.

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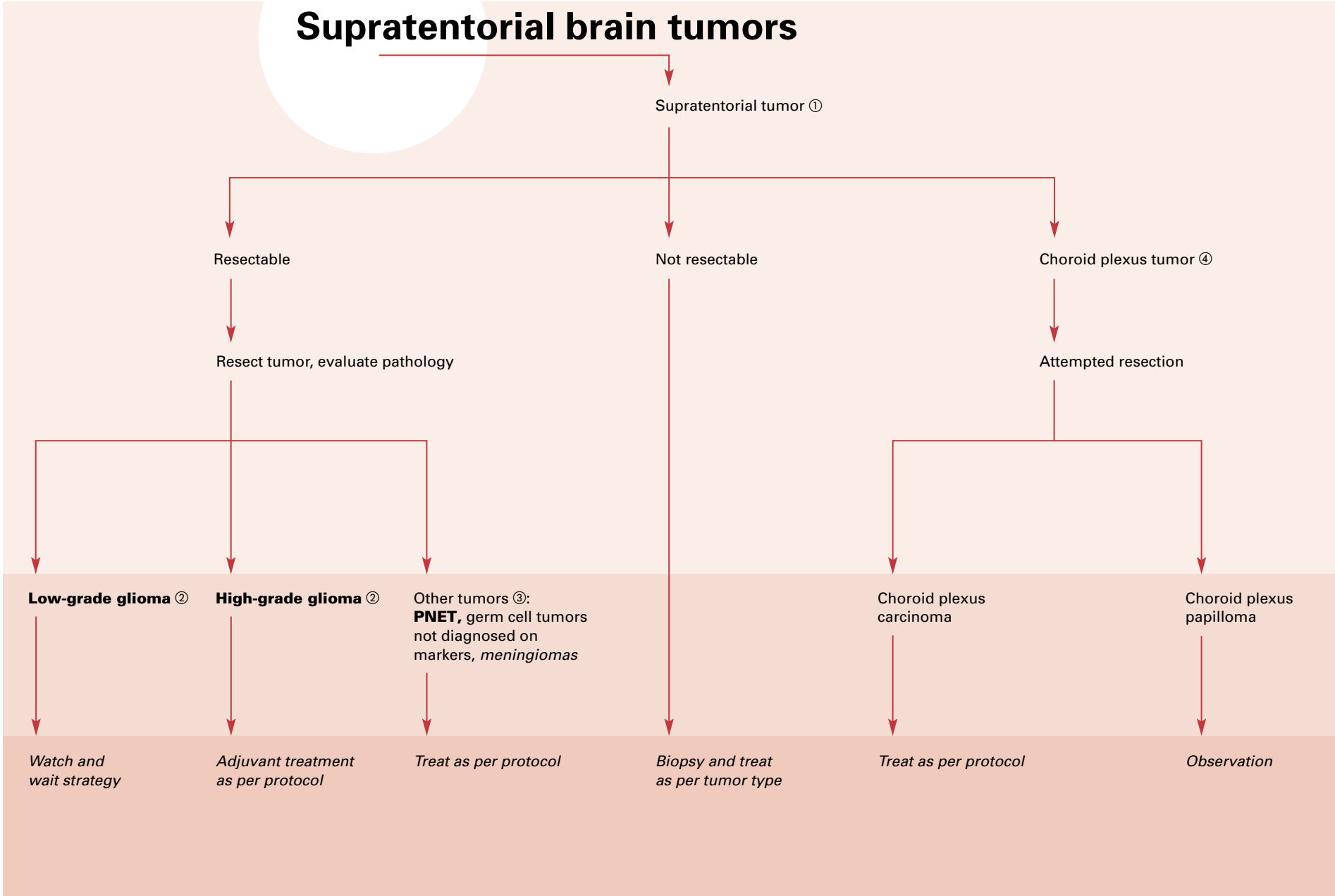
Supratentorial brain tumors



① — Supratentorial tumors may present in a variety of ways; focal seizures, headaches and neurological deficits are the most common. If a supratentorial tumor is not typical of any tumor type, then germ cell markers (α-fetoprotein, human chorionic gonadotrophin) need to be done prior to biopsy/resection; positive germ cell markers allow the diagnosis of a secreting germ cell tumor to be established without biopsy. Chemotherapy and radiotherapy, the best initial therapy for secreting germ cell tumors, can then be started.

② — Low-grade gliomas can be observed with serial MRI scanning unless resection has not been possible. If unresectable, either chemotherapy or radiotherapy are very good treatment options. High-grade gliomas (anaplastic astrocytomas and glioblastoma multiforme) need adjuvant treatment with radiotherapy ± chemotherapy. Survival rates for these tumors are only in the region of 20%.

③ — Other tumors such as PNET, germ cell tumors and meningeal tumors are treated according to the current treatment recommendations for those tumors.

④ — Choroid plexus tumors are usually easily recognizable on MRI scan. They are treated initially with surgery and if papillomatous then no further treatment is usually needed in the case of complete resection. Choroid plexus carcinomas, however, need adjuvant treatment usually with chemo- and radiotherapy.

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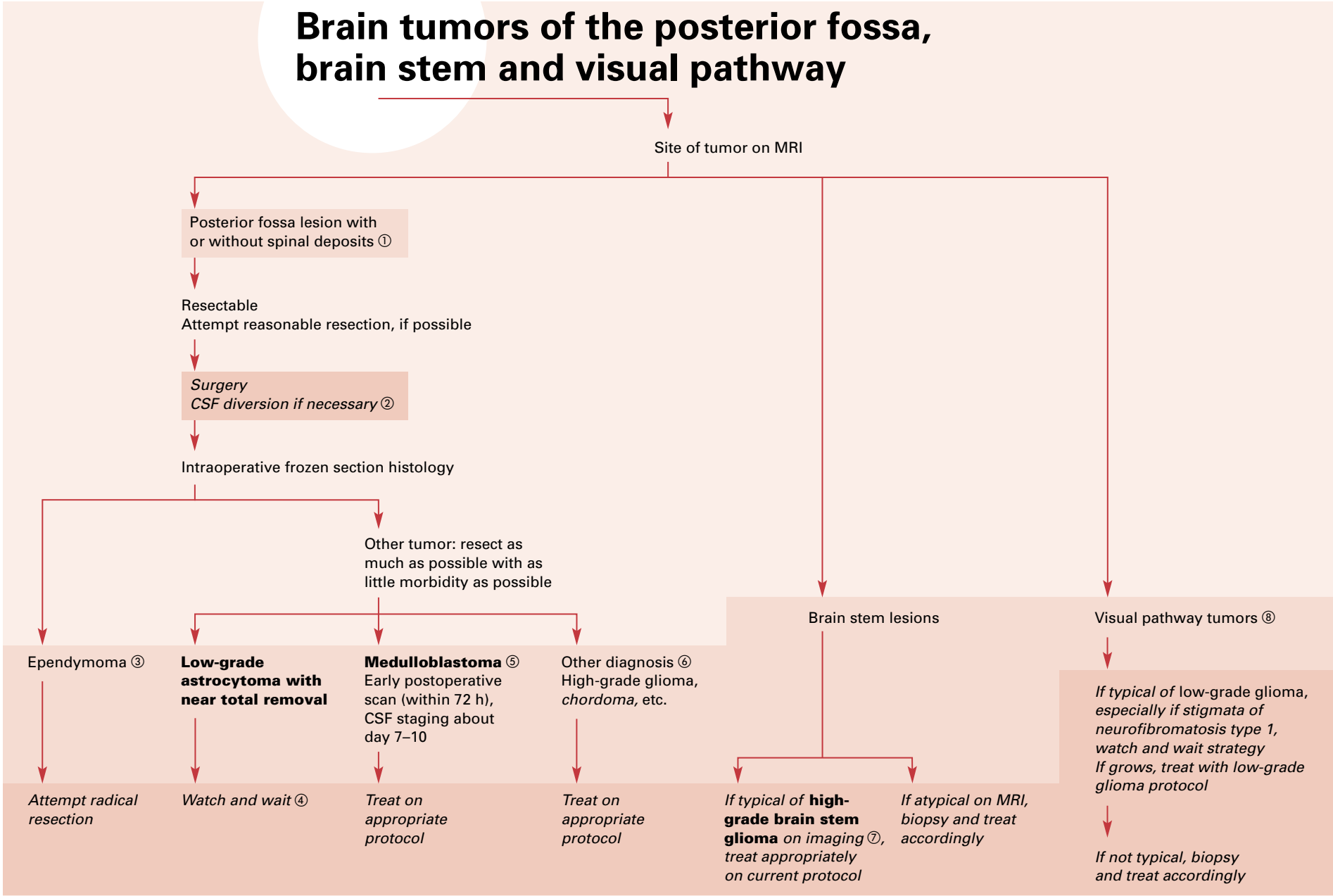
Brain tumors of the posterior fossa, brain stem and visual pathway



① — If a MRI scan shows a posterior fossa lesion it is critical to closely study the spinal imaging especially if a medulloblastoma or ependymoma is suspected. The presence of metastases alters the prognosis and may have a bearing on treatment decisions. Contrast must always be given for these scans.

② — If there is associated hydrocephalus (as is usually the case) CSF diversion may be necessary. Often removal of the tumor is sufficient to allow drainage although an external ventricular drain is usually left in for a few days. If further CSF diversion is needed a third ventriculostomy offers many advantages although a ventricular peritoneal shunt is often used. If an experienced pediatric neurosurgeon is not available then a temporary external ventricular drain (EVD) with resection a few days later may be the best option.

③ — Intraoperative frozen section is mandatory in cases where an ependymoma is suspected. Ependymomas require radical excision for cure and a more aggressive surgical approach is needed even at the cost of increased morbidity. It is not as critical to remove the entire tumor from a patient with medulloblastoma, as a small amount of residual tumor does not alter the prognosis.

④ — Low-grade astrocytomas often have a typical MRI appearance with a small enhancing nodule and a large cystic component. Treatment is usually surgical resection alone even if there is a small residual mass.

⑤ — Medulloblastomas are usually treated with a combination of chemotherapy, and craniospinal radiotherapy with a boost in dose to the posterior fossa. CSF staging alters the prognosis but not necessarily the treatment. Medulloblastoma cells should be looked for in the CSF 7–10 days postsurgery as the presence of these may affect the prognosis. Early postoperative scan provides a better measure of residual tumor mass as well as a baseline for follow-up. Early postoperative scanning is indicated in most tumors except for low-grade astrocytomas in which it is best to wait 3 months unless there is a clinical indication for an earlier scan.

⑥ — Other posterior fossa tumors are rare but include the high-grade gliomas and their variants which are treated as per high-grade gliomas elsewhere (see note 7 below). Chordomas are base of skull tumors that are very slow growing and cured by surgery alone. Chordomas are usually resistant to chemotherapy and radiotherapy.

⑦ — If brain stem lesions look typical of an infiltrating high-grade glioma on MRI scan most centers do not biopsy these lesions but treat on their current protocol in which radiotherapy ± chemotherapy is the mainstay of treatment. These children do not have a good outlook with a survival rate of around 10%. They usually present with cranial nerve palsies and pyramidal signs. Atypical lesions require a tissue diagnosis.

⑧ — Biopsy is not usually performed in a child with a lesion typical of a visual pathway astrocytoma. Visual pathway tumors are common in children with neurofibromatosis type 1 but do occur in others as well. Visual pathway tumors, especially in those with NF1, often remain static with no further treatment although regular imaging as well as ophthalmologic assessment is mandatory. In those children needing treatment a combination of vincristine and carboplatin is often successful. If the lesions are not typical of low-grade glioma then biopsy may need to be performed.

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Initial management of a child with a tumor involving or near the spinal cord

Suspicion of spinal cord pathology
Focal neurology including motor signs, bladder and bowel dysfunction and altered sensation
Back pain, especially in the presence of cancer elsewhere ①

Urgent MRI of spine, especially if acute spinal cord compression ②

If no tumor seen, consult pediatric neurologist

Tumor in or near spine ③
Start dexamethasone 0.5–2.0 mg/kg

Tumor which appears to be rising from outside the CNS, but invading the CNS

Dumbbell shaped tumor, especially in younger child
Check for other signs of **neuroblastoma** ④
Send urine catecholamines
Biopsy

If acute cord compression, relieve compression ⑥

Surgical laminectomy

Radiotherapy

Chemotherapy

Treatment as for neuroblastoma

Other tumor ⑤
Osteosarcoma, Ewings, *lymphoma,* and others including metastases
Biopsy and decompression if necessary
Treatment as for primary tumor

Intrinsic spinal tumor

MRI of head

Tumor in dura or invading spinal cord from outside cord ⑦
Consider **drop metastases** from cranial lesion

If lesion elsewhere, biopsy most accessible lesion ⑥
Medulloblastoma, ependymoma, germ cell tumor (normal markers), *meningiomas, others*

Treat according to tumor type

Intrinsic spinal cord tumor

Biopsy and treat accordingly ⑧
Myxopapillary ependymoma
Astrocytomas

① — Spinal cord tumors constitute 4% of childhood tumors. A high index of suspicion must be maintained, as the onset of symptoms is often insidious. Back pain in children (especially younger children) is not a common complaint and should always be treated seriously. A careful neurological examination must always be performed.

② — CT scanning is not sufficient for imaging suspected spinal pathology and MRI scan is mandatory. MRI scan must be performed even if there is only a suspicion of pathology as early detection may make treatment options easier. The films need to be reviewed by an experienced neuroradiologist, as subtle abnormalities are easy to miss. Approximately 50% of children with acute spinal cord compression will regain neurological function after treatment. However, urgent treatment is required as the longer the signs are present the less likely the child is to recover.

③ — Dexamethasone must be used with caution if a lymphoma is suspected. The administration of dexamethasone in such patients may result in tumor lysis and adequate hydration plus allopurinol/urate oxidase must first be commenced if a lymphoma is suspected. (See *'Recognition and management of tumor lysis syndrome'*, p 94).

④ — Tumors arising from outside the CNS are likely to be neuroblastomas in younger children. Lesions compressing the spinal cord are classically dumbbell in shape. Treatment of cord compression can be either surgical or medical in the first instance. A laminectomy and biopsy has the advantage of providing tissue for histology and biology of the tumor although radical surgery is not recommended. Radiotherapy and chemotherapy are also very effective especially if there is not a total loss of function. Treatment for the neuroblastoma should follow the national guidelines for treatment. For diagnosis, urine catecholamines (VMA, HVA) should be measured on a spot urine catecholamine/creatinine ratio; 24-hour urine collections are not necessary and only serve to prolong the time needed to make a diagnosis.

⑤ — In older children and teenagers the most likely tumors to arise from outside the CNS are the bone tumors and in those cases laminectomy and biopsy is probably the best initial treatment. Metastatic disease needs to be evaluated but surgery is usually best for symptomatic control.

⑥ — The decision whether to use laminectomy, chemotherapy or radiotherapy is complex and requires discussion with an oncologist, neurosurgeon and radiotherapist. The view generally held is that chemotherapy is the most appropriate treatment for neuroblastoma causing spinal cord compression (unless there is complete paralysis). Once the compression is managed, a chemotherapy treatment protocol is then followed.

⑦ — Intrinsic spinal tumors are usually metastases from intracranial lesions ('drop metastases') and in children medulloblastoma is the most likely cause. The treatment is usually in the form of a combination of radio- and chemotherapy. Ependymomas and germ cell tumors are the other CNS tumors of childhood that are most likely to have drop metastases. If a germ cell tumor is suspected then serum markers are mandatory before biopsy; if elevated then biopsy is not necessary.

⑧ — Tumors that are isolated in the spinal cord are most likely to be myxopapillary ependymomas which are relatively indolent tumors unlike their supratentorial counterparts or astrocytomas (high or low grade). These tumors are treated as per the current national protocols.

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Recognition and management of tumor lysis syndrome

Tumor lysis syndrome

Anticipate problem (recognize tumor with a high risk of lysis) ①
- High count or bulky disease leukemia
- Non-Hodgkin lymphoma, especially Burkitt lymphoma
- Increased serum urate (uric acid) prior to starting treatment

If high chance of severe tumor lysis, consider insertion of central venous line capable of being used for hemodialysis/ hemofiltration

If metabolic instability is present, then attempt emergency stabilization before commencing treatment ②

Start hydration and xanthine oxidase inhibitor such as allopurinol (100 mg/m² 3×/day – oral or i.v.) or urate oxidase (uricozyme or rasburicase) (100 U/kg 1×/day i.v.)
Hydration according to protocol (usually ≥3 liters/m²/day) ③
Fluid should contain only dextrose and NaCl but not potassium ④

Monitor patient closely and allow a minimum of 12 h prior to starting treatment unless there are special circumstances ⑤
Four-hourly urea, electrolytes, phosphate and urate in high-risk patients, less frequently if lower risk
Careful fluid balance (urine output should exceed 2 ml/kg/h) ⑥
Monitor weight and blood pressure closely

Rising potassium (level >6 mmol/l)
Kayexelate (1–2 g/kg/day p.o. 6 h or retention enema in 20% sorbitol)
If ECG changes: salbutamol (albuterol), insulin/glucose, Ca gluconate
If no response possible hemodialysis/ hemofiltration ⑦

Rising phosphate
If level >3 mmol/l (9.3 mg/dl) contact renal physician for hemodialysis/ hemofiltration ⑧
There may be associated hypocalcemia

Signs of fluid overload (rising weight and BP) or decrease in urine output
Frusemide (furosemide) or mannitol ⑨
If continues to be problem consider hemodialysis/hemofiltration

Rising uric acid; level >0.5 mmol/l (8.5 mg/dl) may need treatment
Rising urea or creatinine associated with decrease in urine output
Frusemide (furosemide) or mannitol ⑨
Consider hemodialysis/hemofiltration

① — Tumor lysis syndrome (TLS) is a life-threatening emergency that may result in death if not appropriately managed. It consists of the triad of hyperkalemia, hyperuricemia and hyperphosphatemia. TLS most commonly complicates Burkitt lymphoma, acute lymphoblastic leukemia (particularly with high WBC and/or bulky disease such as hepatosplenomegaly or mediastinal mass), and occurs less commonly in non-lymphoblastic leukemias and very rarely in other solid tumors.

② — Although tumor lysis usually occurs after instituting antineoplastic therapy, it may be evident prior to treatment. This usually occurs in Burkitt lymphoma and ALL with high WBC or bulky disease. Elevated K, P, or uric acid levels in these children require immediate treatment to stabilize the child prior to commencing therapy.

③ — Tumor lysis occurs most commonly within 24 h of starting treatment although it can occur up to 5 days later. The likelihood of developing tumor lysis can be determined by a number of factors including tumor type, serum uric acid level prior to the starting of xanthine oxidase inhibitors or urate oxidase, very high lactate dehydrogenase levels (indicating tumor bulk) and abnormal electrolytes prior to starting treatment. Xanthine oxidase inhibitors block the conversion of hypoxanthine to xanthine and xanthine to uric acid. Urate oxidase converts uric acid to the more soluble allantoin and is thought to be more effective than xanthine oxidase inhibitors (but may not be universally available). If there is thought to be a high chance of tumor lysis, a central line capable of supporting hemofiltration should be inserted prior to starting treatment.

④ — Dialysis usually is only needed in the short term as kidney function usually returns to normal within a matter of days. Bicarbonate is not routinely used in hydration regimes for newly diagnosed hematological malignancies as it may increase the chance of calcium phosphate deposition in the kidneys. However, it is practice in some units to use sodium bicarbonate until the pH of the urine is 7.5 before chemotherapy (enhancing urate excretion), and then to discontinue it. Calcium phosphate crystals are more likely to occur if the phosphate × calcium product exceeds 4.6 mmol/l.

⑤ — A number of special circumstances may warrant earlier commencement of treatment. A mediastinal mass compromising airway patency should be treated promptly. Children with a leukostasis syndrome should also have early commencement of chemotherapy. The leukostasis syndrome is due to aggregation of leukemic blasts in various organs, usually the lungs or the brain and is more likely when the leukocyte count is greater than 100×10^9/l. Children may present with progressive neurological or respiratory signs. Leukostasis syndrome is more common in patients with AML than in patients with ALL.

⑥ — Six-hourly fluid balances and weights at least 12-hourly are necessary to adequately assess fluid status of patient. The urine output should be maintained at a minimum of 2 ml/kg/h and if necessary diuretics (frusemide or mannitol) should be used. Four-hourly electrolytes should be measured for the first 24 h if the child is at high risk of tumor lysis but less frequently in those at lower risk.

⑦ — If electrocardiographic changes of hyperkalemia occur then bicarbonate (0.5 mEq/kg as a bolus), calcium gluconate (0.5 ml/kg of 10% solution over 10 min) and glucose and insulin (0.5 g/kg of 10% glucose i.v. with 0.3 units of insulin per gram of glucose) should be given to stabilize the cardiac membrane.

⑧ — Hyperphosphatemia often occurs in association with hypocalcemia. Unless necessary calcium should not be given as it increases the chance of calcium phosphate deposition in the kidneys. If it is necessary, give calcium gluconate (0.5 ml/kg of 10% solution over 10 min). Aluminum hydroxide (50–150 mg/kg/day) may be used to treat hyperphosphatemia if necessary. The calcium × phosphate ratio should not exceed 4.6 mmol/l. A renal physician should be contacted if the value rises above this level.

⑨ — Rising uric acids rarely occur in isolation to the degree that warrants treatment. If xanthine oxidase inhibitors are not sufficient then urate oxidase should be used instead.

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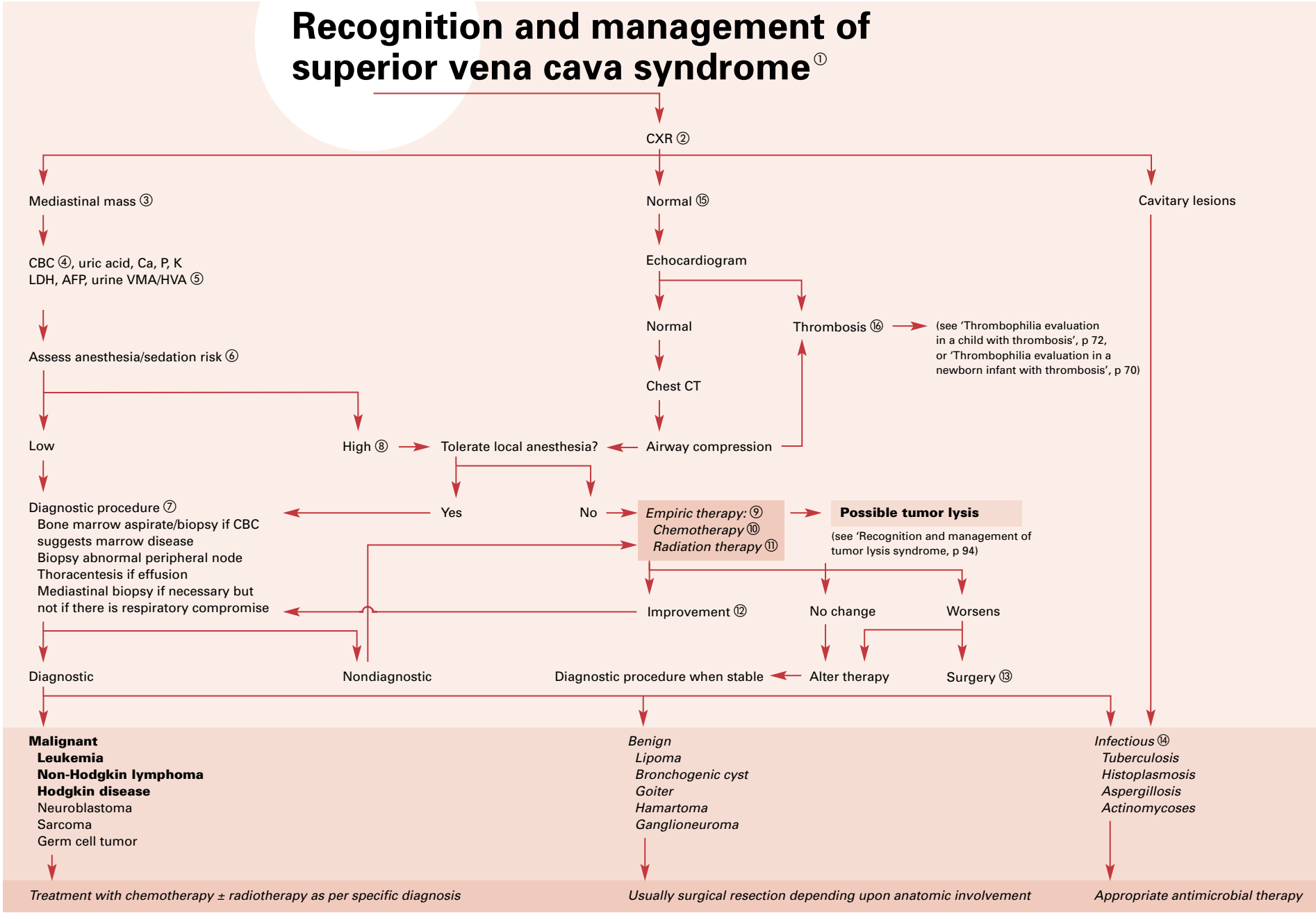
Recognition and management of superior vena cava syndrome ①



① — Superior vena cava (SVC) syndrome refers to signs and symptoms resulting from compression, obstruction, or thrombosis of the SVC. The classic signs and symptoms include plethora, facial edema, jugular venous distension, and respiratory symptoms such as dyspnea, orthopnea, cough, stridor, or wheezing. Anxiety, confusion, lethargy, headache, vision changes, and syncope indicate CO_2 retention and central venous stasis. Dysphagia can occur due to esophageal compression. The term superior mediastinal syndrome (often used synonymously with SVC syndrome in children) includes compression of the trachea.

② — The CXR often reveals a widened mediastinum or an anterior mediastinal mass, usually with a laterally deviated or compressed trachea. Pleural and pericardial effusions may need to be tapped both for symptomatic relief and diagnostic workup. Patients with mediastinal masses that are >45% of the transthoracic diameter on CXR are more likely to be symptomatic than those with ratios <30%.

③ — Any child with a mediastinal mass should be closely examined for signs or symptoms of respiratory compromise. If there are any respiratory symptoms the patient should follow the high-risk pathway outlined even if there is no evidence of SVC syndrome.

④ — A CBC may reveal cytopenias or peripheral blasts. A tentative diagnosis may be made from peripheral blasts using morphology and immunocytochemistry. If left shifted, the WBC may be indicative of an infectious etiology.

⑤ — Uric acid, LDH and ESR should be elevated in lymphomas. An AFP and βHCG may be elevated in germ cell tumors. Urine VMA/HVA will be elevated in neuroblastoma.

⑥ — A patient in respiratory distress at presentation is high risk. In a mildly symptomatic or an asymptomatic child, a thorough airway evaluation is necessary before using sedatives or general anesthesia. This includes pulmonary function tests including a volume flow loop to assess pulmonary reserve and resilience and an echocardiogram to assess cardiac function. When possible, a CT scan should be obtained. In a child with SVC syndrome, diagnosis should be attempted by the least invasive means possible. Circulatory collapse or respiratory failure may occur in patients receiving sedation or general anesthesia.

⑦ — If the CBC is abnormal a bone marrow aspirate or biopsy may reveal leukemic blasts, lymphoma, or metastatic neuroblastoma. If the patient has an enlarged, suspicious, peripheral lymph node, biopsy can be performed using local anesthesia in an attempt to make the diagnosis. If an effusion is present, thoracentesis or pericardiocentesis can offer immediate relief from respiratory compromise or cardiac tamponade, as well as provide diagnostic material. Send all tissue for morphologic exam, immunocytohistochemistry, and cytogenetics. Mediastinal biopsy should be reserved only for those patients who have no evidence of respiratory compromise and less invasive means of diagnosis are unrevealing.

⑧ — Proceed with a diagnostic procedure if it can be performed using only local anesthesia in a position that does not compromise the child's airway.

⑨ — If establishing a diagnosis is too risky it is usually in the patients best interest to start empiric pre-biopsy therapy. In such instances, the clinical, laboratory and radiologic data should support the likely diagnosis of a malignancy. Empiric therapy usually includes i.v. methylprednisolone at 2 mg/kg every 6 h concomitant with chemotherapy or radiation therapy. (see *'Recognition and management of tumor lysis syndrome'*, p 94).

⑩ — Although there are no established standards, there has been an increasing trend to using emergent chemotherapy in lieu of radiation therapy for chemosensitive malignancies such as leukemia and lymphomas. Cyclophosphamide alone or in combination with vincristine and an anthracycline are effective cytotoxic agents for leukemia, non-Hodgkin lymphoma or Hodgkin disease. Emergent chemotherapy should not be used for neuroblastoma, sarcomas, or germ cell tumors due to their slower response.

⑪ — Radiation oncologists often use focused radiation portals to treat the tumor enveloping the trachea while attempting to leave viable tissue laterally that can be biopsied when the patient is stable. The dose of radiation is generally 100–200 cGy twice daily. Children must be monitored for postradiation respiratory worsening due to tracheal edema.

⑫ — When the patient is stable, attempt to make the diagnosis. With emergent therapy lymph nodes may become palpable, and thus biopsied in 24–48 h. The patient may tolerate a mediastinal biopsy under general anesthesia. In a small percentage of cases no tissue or bone marrow will be obtainable for diagnosis and the patient should be treated empirically for the most likely diagnosis based upon exam, laboratory and radiologic data, and response to therapy.

⑬ — Surgical resection is the only treatment for benign tumors, such as lipomas, goiter, bronchogenic cysts, and hamartomas. Surgery may be inevitable for a malignant tumor that does not respond to radiation or chemotherapy. In this setting a pediatric anesthesiologist, cardiopulmonary bypass, and rigid bronchoscopy must be available.

⑭ — Infection is the second most common primary etiology of SVC syndrome. Mediastinal granulomas or fibrosis from tuberculosis, and fungi such as aspergillosis, histoplasmosis and actinomycoses cause compression of the SVC. Treatment consists of antibiotic or antifungal therapy in association with surgical debridement.

⑮ — In a child with no mediastinal mass or granulomas on CXR, an echocardiogram should be obtained emergently to look for a thrombosis of the SVC.

⑯ — Patients are at increased risk for thrombosis if they have a history of cardiac anomalies or cardiac surgery or if they have a central line in place. If there are no contraindications the central line should be left in place initially for infusion of antithrombolytic therapy.

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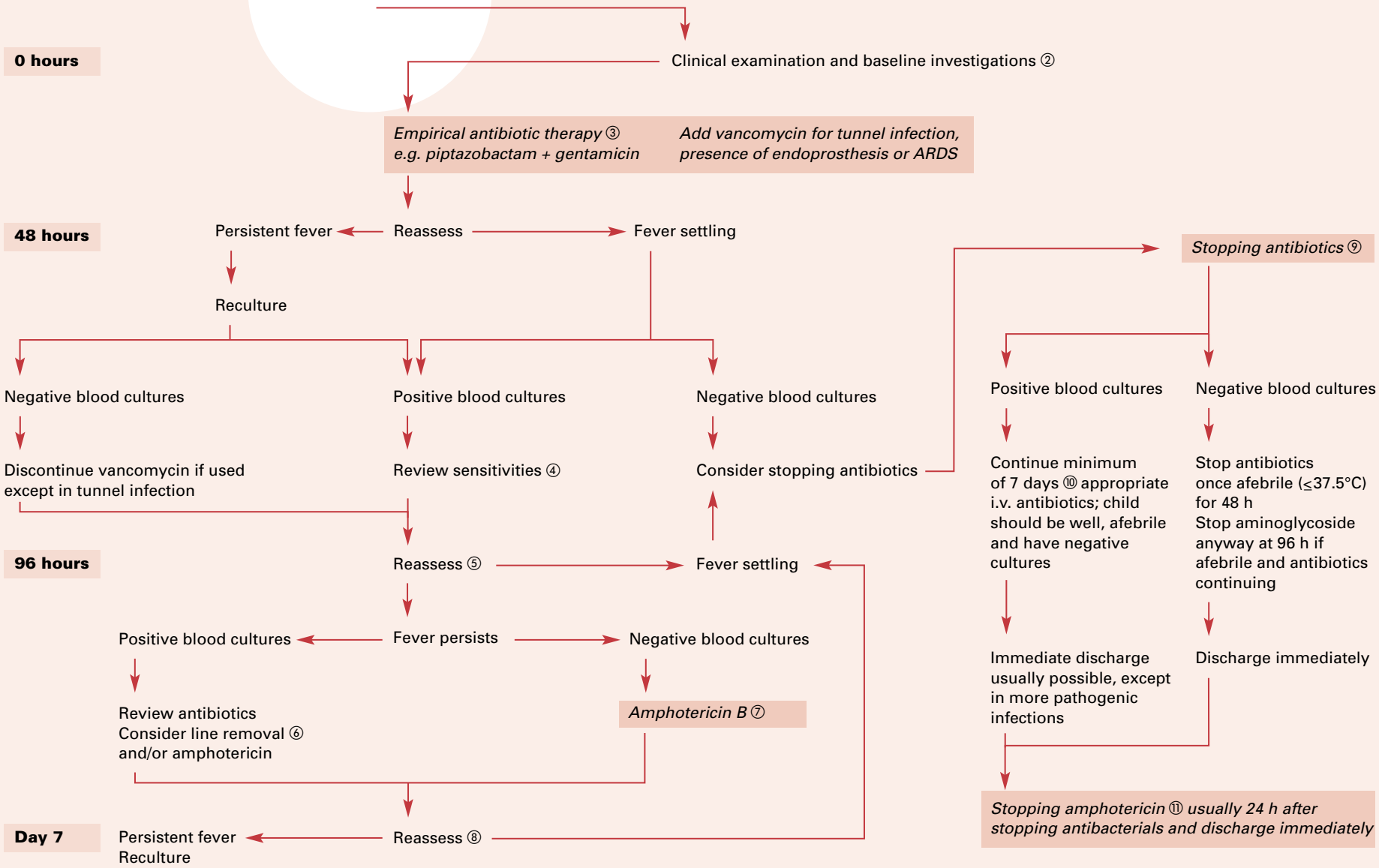
Febrile neutropenia ①



Important note: The above algorithm is based on a protocol agreed across all the London (UK) Paediatric Haematology centres. All large institutions should have a similar locally agreed protocol taking account of local patterns of infection and resistance. The above algorithm and notes are thus designed to show the principles of the management of febrile neutropenia, rather than recommend specific antibiotics.

① — Febrile neutropenia is defined as:
Neutropenia ($<1\times10^9$/l or 1,000/μl)
and fever >38°C for more than 4 h or on 2 occasions at least 4 h apart
or fever >38.5°C on one occasion
or clinical suspicion of sepsis in the absence of fever.
Fever should be unrelated to the transfusion of blood products. Febrile neutropenia requires urgent investigation and empirical antibiotic therapy.

② — A thorough examination for sites of sepsis including any central venous access device. Blood cultures *before* the start of antibiotic therapy are imperative. Each lumen of a central line should be sampled and/or peripheral venous cultures taken. Urine should be sent for microscopy and culture and swabs taken from sites of overt infection. CXR if deemed clinically appropriate.

③ — Most institutions still recommend an anti-pseudomonal penicillin and aminoglycoside as first-line therapy. The combination provides synergy against aerobic gram-negative bacteria. Oto- and nephrotoxicity are minimized by monitoring of drug levels and stopping the aminoglycoside at 96 h if blood cultures are negative. Single drug therapy with an anti-pseudomonal penicillin or third generation cephalosporin is not as effective, whereas monotherapy with a carbapenem (imipenem, meropenem) may be as effective, but is usually reserved for second-line or specific therapy. Viridans streptococci bacteremia in the neutropenic patient can lead to ARDS and there is evidence that the outcome is improved by the additional of vancomycin at the outset. In other situations, no benefit has been demonstrated for the initial inclusion of vancomycin. Many centers are now substituting teicoplanin for vancomycin because of decreased nephrotoxicity.

④ — Positive isolates should be discussed with the microbiology department and therapy optimized whilst maintaining broad-spectrum cover. High quality echocardiography should be arranged to look for signs of infective endocarditis if *Staphylococcus aureus* is isolated and the length of therapy discussed with microbiology, traditionally 4–6 weeks of high-dose intravenous therapy has been the standard.

⑤ — Arrange CXR (for aspergillus and interstitial pneumonitis) and consider echocardiography for vegetations, abdominal ultrasound for hepatosplenic candidiasis and high-resolution chest CT (aspergillus). Fungal infection is notoriously difficult to diagnose – it is thus now routine to initiate empirical amphotericin therapy at this stage.

⑥ — Although microbiologists recommend immediate line removal when *S. aureus, Stenotrophomonas* spp. or *Pseudomonas* spp. are isolated, this is not always clinically feasible and as long as the patient shows clinical recovery, many units will try to salvage the line. Clearly, persistently positive cultures in the face of appropriate antibiotic therapy necessitates line removal.

⑦ — Conventional amphotericin B is an effective but nephrotoxic anti-fungal agent. Liposomal preparations are now available and are as efficacious, less nephrotoxic, but much more expensive. Most units begin with conventional amphotericin B and progress to the liposomal preparation when a predetermined rise in creatinine has occurred.

⑧ — Review antibiotics, consider second-line therapy. Ultrasound/echocardiogram if not already done. Repeat CXR. Consider drug fever – notoriously difficult to recognise. The addition of G-CSF may also be considered, but evidence to support its use in this situation is lacking. The evidence supporting the use of granulocyte transfusions is even less, although trials are now underway to try and identify particular situations where these may be of value.

⑨ — It is argued that antibiotics should be continued until neutropenia resolves, irrespective of the clinical condition of the patient or culture results. However, the algorithm above is suggested as a way of optimizing therapy whilst minimizing toxicity, development of antibiotic resistance and potential development of fungal infection.

⑩ — *Pseudomonas* spp. and *S. aureus* need a minimum of 14 days therapy. A decision to stop antibiotics after a positive culture should be taken in conjunction with the microbiology department.

⑪ — Clearly, proven or suspicious fungal infections will require longer therapy and future prophylaxis. Oral itraconazole can be used for aspergillus infections and fluconazole for other fungal infections in the out-patient setting.

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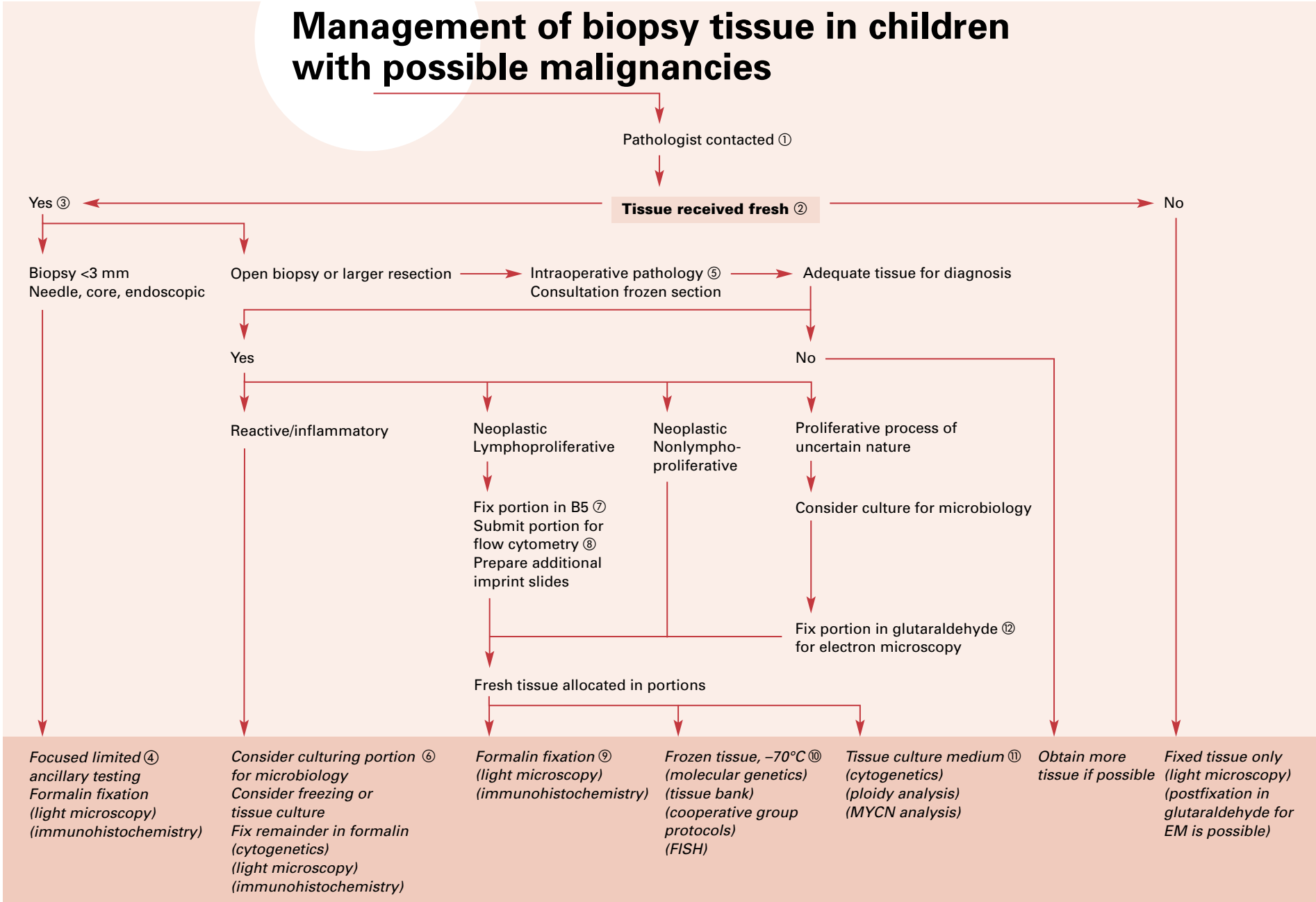
Management of biopsy tissue in children with possible malignancies



① — Prior consultation with the pathologist helps ensure that the contemplated procedure will be appropriate for making the diagnosis and that necessary ancillary studies are performed. As some studies require prompt processing of fresh tissue, these biopsies are best performed during normal working hours. If necessary to biopsy during off hours, arrangements to preserve tissue integrity are crucial.

② — With suspected malignancy, biopsy tissue should be sent fresh (without fixative) without delay. Small biopsies are placed on a moist, saline soaked sponge in a closed, properly labeled container, and not immersed in fluid. Larger specimens are also sent fresh. Once tissue is fixed, frozen section, culture, cytogenetic studies, and most molecular studies are not possible.

③ — Tumor may be sampled via fine-needle aspiration, percutaneous or fiberendoscopic needle (core) biopsy, wedge biopsy, excisional biopsy, or larger resection. Fine-needle aspiration samples are essentially limited to cytologic evaluation, and will not be discussed further. Needle biopsies are minimally invasive, but that is counterbalanced by the limited tissue available for potentially critical ancillary studies. Wedge and excisional open biopsies, with intraoperative pathologic assessment of sampling adequacy, usually provide sufficient tissue for both LM and ancillary studies. Major resection without an established histologic diagnosis is discouraged and amputation or limb resection never performed on the basis of frozen section. In certain situations such as suspected Wilms tumor, it is desirable to remove the organ primarily, as prior biopsy would increase tumor stage.

④ — The differential diagnosis determines how much of a limited tissue sample is used for ancillary studies, given that LM examination of properly fixed tissue is usually the most rewarding procedure.

⑤ — The major indication for intraoperative pathology is immediate therapeutic need for diagnosis. This usually involves frozen section. Other indications for frozen section include assessment of tissue adequacy for diagnosis, and assessment of operative margins. As frozen section morphology is inferior to permanent sections and sampling is limited, intraoperative diagnoses are preliminary, subject to permanent section review, and may only be sufficient to describe a lesion's general nature (e.g. reactive, inflammatory, benign, malignant), without providing a specific diagnosis. Freezing can alter histology and is generally reserved for specimens >3 mm in size. Frozen section is discouraged in suspected lymphomas, as diagnostic features may be obscured. Touch imprints of the freshly cut lesional surface, stained with H&E and/or Wright-Giemsa are useful, and do not waste tissue. Although heavily calcified tissue cannot be cut frozen, many bone tumors have soft areas that can be cryosectioned. Frozen section can also determine which ancillary studies are most indicated. If additional tissue is available for permanent sections, keep the frozen tissue at –70°C, making it available for ancillary studies such as molecular genetics.

⑥ — Sterile microbial tissue cultures can be obtained in the operating room, or in pathology prior to specimen fixation. Most inflammatory lesions are sent for routine bacterial, mycobacterial and fungal culture. Viral cultures may be useful.

⑦ — Special fixatives provide superior nuclear detail to formalin and are useful in evaluating lymphomas. B5, containing mercuric chloride, is widely used.

⑧ — Immunophenotyping using flow cytometry is critical in evaluating non-Hodgkin lymphomas. Fresh tissue placed in tissue culture medium (e.g. RPMI) is processed without delay. During off hours, tissue in RPMI should be refrigerated. The amount of tissue necessary is dependent upon the lesion's cellularity and cellular discohesiveness. In most pediatric lymphomas, a 5-mm^3 piece is sufficient.

⑨ — The most important pathologic technique remains LM examination of well-fixed tissue. With more available ancillary tests, a tendency towards less invasive (and therefore smaller) biopsies, and cooperative group requirements for research, obtaining adequate tissue is critical. The fixative for LM is most often 10% neutral-buffered formalin, which is inexpensive, infiltrates tissue well, and is excellent for general histologic purposes. Fortunately, most commercial immunohistochemical reagents work in formalin-fixed, paraffin-embedded specimens. Immunohistochemistry is very useful in evaluating pediatric malignancies, with standardized antibodies available for many antigens found in many tumors. In-situ hybridization procedures such as the EBER stain for latent Epstein-Barr virus RNA also work well in paraffin. DNA can also be extracted from paraffin blocks and analyzed by PCR to determine lineage and clonality of lymphoid populations.

⑩ — Frozen tissue is valuable for research and diagnostics, especially for molecular assays for chromosomal translocations in pediatric sarcomas. Specific gene fusions occurring in alveolar RMS, Ewings/PNET, desmoplastic small round cell tumor, and synovial sarcoma are best assayed via RT-PCR in snap-frozen tissue. Any remaining sample from frozen section kept at –70°C can be used for RT-PCR, with assurance that lesional tissue is present. If possible, additional fresh tumor should be snap frozen in liquid nitrogen at –70°C. This tissue may be used for cooperative group protocols, other molecular studies, research, and for RT-PCR.

⑪ — Fresh tissue, in culture medium such as RPMI, is used for conventional tissue cytogenetics. Characteristic chromosomal abnormalities occur in the Ewings/PNET family of tumors, RMS, synovial sarcomas, lymphoma/leukemias, retinoblastoma, Wilms tumor, and many rarer neoplasms. Cytogenetics may also be useful in 'reactive' processes such as inflammatory myofibroblastic tumors. Tumor cytogenetics is technically demanding, and variables such as tumor cellularity, viability, and proliferative activity can affect tissue growth in culture and the accrual of metaphase spreads. Optimization requires communication with and prompt submission of tissue to the cytogenetics laboratory. Fresh tissue in RPMI can be used for flow cytometry, ploidy analysis, and is the preferred substrate for MYCN analysis in cases of suspected NBL.

⑫ — Electron microscopy can be useful in tumor diagnosis. Ultrastructural features can be diagnostic in many lesions (e.g. LCH, NBL, and RMS). Very little tissue is needed as several 1-mm^3 blocks are sufficient. The sample must be placed in chilled glutaraldehyde; since it does not penetrate tissue well, small tissue sections are used. Tissue previously fixed in formalin before glutaraldehyde can be used, but inferior ultrastructural preservation is expected.

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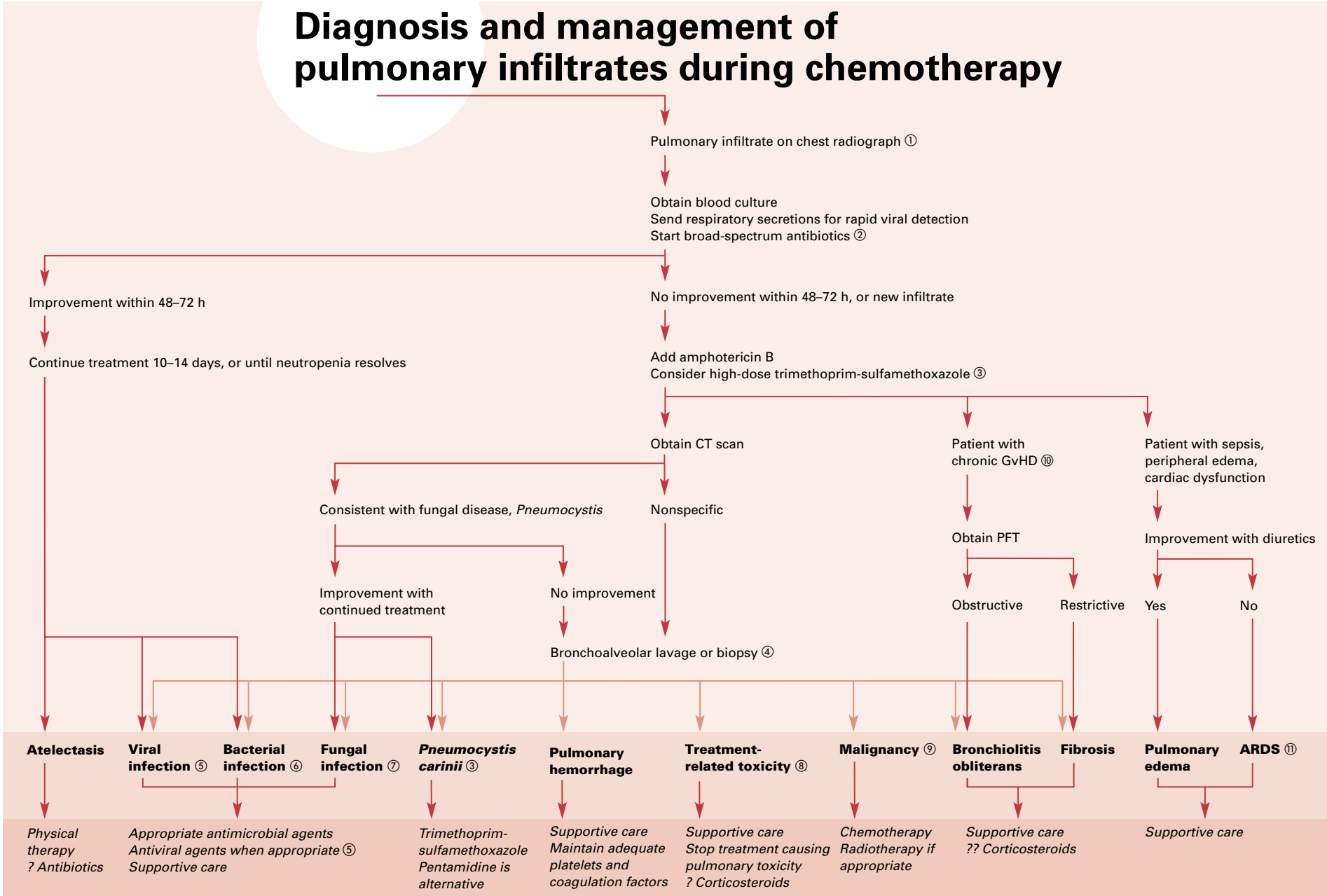
Diagnosis and management of pulmonary infiltrates during chemotherapy



① — Pulmonary infiltrates in patients who are receiving chemotherapy are most often due to infection, although other causes need to be considered. Patients with neutropenia (ANC <500, or <1,000 and falling) are at the highest risk of infection, in particular from bacteria or fungi. Some patients with a normal ANC, especially those with leukemia, lymphoma, or after BMT, may be immunocompromised for as long as several months after the completion of therapy. The pattern of infiltrate on the CXR may suggest a particular diagnosis, as a focal lesion is more likely to be bacterial, while nodular lesions are more likely either fungi or metastases. However, most patients with CXR findings will have diffuse infiltrates that are nonspecific. Moreover, many patients with fever and neutropenia will have a normal CXR even in the presence of pulmonary disease, and a CT scan may be necessary to identify lung lesions; in neutropenic patients, however, CT may underestimate the extent of disease. The initial empiric antibiotic treatment for patients with presumed pneumonia is the same as that for other patients with fever and neutropenia, but further evaluation of a pulmonary process is indicated if respiratory signs and symptoms, such as hypoxemia, tachypnea, cough, or dyspnea, persist despite initial antibiotic therapy.

② — Multiple diagnoses may be present in an individual patient; in particular, patients treated with broad-spectrum antibiotics for a presumed bacterial pneumonia are at risk for a secondary fungal infection. Patients at risk for CMV infection should have the serum CMV antigen level measured. In many cases, patients will improve without a specific diagnosis or pathogen being identified. The initial empiric antibiotic regimen should treat both gram-positive and gram-negative bacteria, including *Pseudomonas*, and may be tailored to the predominant organisms at the treating institution and local patterns of antibiotic resistance. A macrolide antibiotic may be necessary for mycoplasma pneumonia.

③ — A new infiltrate or persistent fever while on broad-spectrum antibiotics is most commonly due to a fungal infection. Fluconazole may be adequate therapy for most *Candida* infections, but it is not effective against *Aspergillus* and some *Candida* species. Pneumonia due to *Pneumocystis carinii* is rare because of the regular use of trimethoprim-sulfamethoxazole as prophylaxis, but should be suspected in the patient with fulminant respiratory failure and alkalosis.

④ — The diagnosis of fungal or *Pneumocystis* pneumonia may be obtained from bronchoalveolar lavage (BAL), although this technique is not very sensitive for other pathogens. Samples from BAL or biopsy should be sent for histology, gram stain, culture (for bacterial, viral, and fungal causes), and silver stain or indirect immunofluorescent antibody testing for *Pneumocystis*. In patients who fail to improve with a combination of antibiotics and amphotericin B, a lung biopsy is more likely to provide a definitive diagnosis, especially if there are peripheral pulmonary lesions that are accessible by thoracoscopy. Thoracotomy carries a higher morbidity, but may be necessary in the patient whose lesions are less accessible. Sputum collection is usually impossible and rarely helpful in the neutropenic pediatric patient.

⑤ — The most common viral causes of pneumonia are CMV, respiratory syncytial virus, influenza, and parainfluenza. Herpes simplex, varicella zoster, human herpesvirus 6 and adenovirus are other potential pathogens. CMV is especially common after BMT. Specific antiviral therapy may be indicated for respiratory syncytial (ribavirin), CMV (ganciclovir), and varicella zoster viruses (acyclovir or famciclovir).

⑥ — The most common bacterial causes of pneumonia in the immunocompromised host are *Streptococcus pneumoniae, Staphylococcus aureus*, gram-negative bacillae (such as *Klebsiella, Pseudomonas, Escherichia coli, Serratia,* and *Enterobacter*), and *Mycoplasma. Streptococcus viridans* infections occur in some patients, particularly after high-dose cytarabine or stem cell transplantation, and are commonly associated with ARDS.

⑦ — The most common causes of fungal infections in the lung are *Aspergillus* and, less frequently, *Candida* species. *Aspergillus* is typically associated with a 'halo sign' on high-resolution CT scan. *Candida* pneumonia usually results from hematogenous spread, and therefore fungal lesions are often seen in other organs. GM-CSF may be a useful adjunct in the treatment of fungal infections.

⑧ — Pulmonary toxicity may result from a variety of chemotherapy agents, and may represent acute hypersensitivity reactions (all-trans retinoic acid, procarbazine, vinca alkaloids, cytarabine) or pathology that develops over weeks (bleomycin, methotrexate) to years after therapy (cyclophosphamide, BCNU, busulfan, methotrexate). Radiation pneumonitis may occur within 2–3 months after lung irradiation, and may respond to steroids, but late radiation fibrosis is less likely to be steroid-responsive.

⑨ — Tumors that commonly metastasize to the lungs include Wilms tumor, Ewing sarcoma, rhabdomyosarcoma, and osteogenic sarcoma. Lymphoma, Langerhans cell histiocytosis, and posttransplant lymphoproliferative disease may also present with pulmonary disease.

⑩ — Patients with chronic graft-versus-host disease (GvHD) are at risk for numerous pulmonary complications, both infectious and noninfectious. In the absence of infection, bronchiolitis obliterans due to GvHD and pulmonary fibrosis due to prior therapy are the most common causes of pulmonary dysfunction and may be differentiated by pulmonary function testing.

⑪ — Acute respiratory distress syndrome is often associated with bacterial or viral pneumonia, though a specific pathogen may not be identified.

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Monitoring for late effects in children with malignancies

Patient's gender, age at treatment, surgery, chemotherapy regimen (including doses of critical drugs such as anthracyclines and alkylating agents), radiotherapy (doses and fields), autologous or allogeneic marrow transplant, nephrotoxicity, transfusions, treatment complications (e.g. pulmonary), chronic infection (e.g. hepatitis B or C), secondary neoplasia, genetic/familial predisposition to malignancy ①

Patient underwent surgery ②

Determine specific procedure

Splenectomy ⇒ sepsis ③ ⇒ prophylactic antibiotics, aggressive antibiotic treatment of fever

Pelvic ⇒ orchiectomy/oophorectomy ⇒ monitor gonadal function ④
⇒ ? hormone replacement, counsel concerning reproductive options

Nephrectomy ⇒ monitor renal function (urine analysis, creatinine, BUN, blood pressure and hemoglobin), protect from trauma

Amputation ⇒ monitor limb function ⑤

Enucleation ⇒ protection of the normal eye ⑥

Patient received chemotherapy ⑦

Determine specific chemotherapy used

Corticosteroids (e.g. dexamethasone, prednisone) ⇒ avascular necrosis ⑧ ⇒ evaluate joint pain with X-ray/MRI

Anthracyclines (doxorubicin, daunomycin, idarubicin) ⇒ cardiotoxicity ⇒ monitor echocardiogram/ECG every 3 years ⑨

Bleomycin/nitrosureas (carmustine/lomustine) ⇒ pulmonary fibrosis ⇒ CXR + PFT every 3–5 years

Cisplatin/carboplatin ⇒ auditory loss ⇒ audiologic evaluation every 5 years ⇒ audiologic augmentation if necessary

Cisplatin/carboplatin/ifosfamide ⇒ renal tubular dysfunction ⇒ urinalysis, creatinine, and Mg yearly

Alkylating agents (mechlorethamine, melphalan, lomustine, carmustine, busulfan, cyclophosphamide, chlorambucil, procarbazine, cisplatin) ⇒ gonadal dysfunction ⑩ ⇒ monitor pubertal development, testicular and penile size, amenorrhea, menstrual irregularity, impotence, fertility ⇒ FSH

Alkylating agents (as above) also ⇒ secondary leukemia ⑪ ⇒ CBC annually

Topoisomerase inhibitors (etoposide [VP-16] and teniposide [VM-26]) ⇒ secondary leukemia ⑪ ⇒ CBC annually

Patient received radiation therapy ⑫

Determine areas radiated

Inhibition of bone growth if growth plate irradiated ⇒ monitor growth curves, sitting height – growth hormone is not effective

Second malignancies in fields ⇒ ↑ secondary bone and soft tissue sarcomas beginning 7 years after therapy ⇒ clinical follow-up ↑↑ risk breast Ca ⇒ self examination monthly, regular physical examinations, mammogram every 2 years >25 years of age ⑬

Head/neck ⑭
Cognition ⇒ learning disability ⇒ annual education assessment and intermittent neurocognitive testing
Eye ⇒ cataracts ⇒ annual eye examination
Thyroid ⇒ hypothyroidism ⇒ annual T4
Thyroid cancer ⇒ annual thyroid palpation
Dental ⇒ abnormal jaw and dental development + ⇒ ↑ caries ⇒ regular dental follow-up
Esophageal integrity ⇒ monitor symptoms
Pituitary
Growth ⇒ growth hormone deficiency ⇒ monitor growth
Puberty ⇒ precocious or delayed within 2 years

Thoracic ⑮
Cardiac ⇒ dysfunction and ⇒ ↑ risk of anthracycline toxicity ⇒ echocardiogram/ECG every 3 years
Pulmonary ⇒ fibrosis ⇒ PFT + CXR every 3 years if >15 Gy
Smoking cessation ⇒ must be encouraged
Scoliosis ⇒ screen annually (every 6 months prepuberty)

Abdominal/pelvic ⑯
Malabsorption ⇒ evaluate if symptoms
Gonadal function ⇒ see note on alkylating agents
Renal ⇒ nephritis ⇒ U/A, creatinine yearly

① — This summary focuses on therapy-associated late effects that might be prevented or ameliorated by early detection. Recommendations are general and may require alterations depending on the specific patient. Patients should learn about their previous treatment and be made aware of potential late effects so that they can inform caregivers throughout their lives.

② — Uncomplicated biopsies do not usually have long-term effects, but intestinal obstruction may occur following diagnostic laparotomy, permanent alopecia or a skull defect can follow craniotomy, and respiratory compromise may occur postpneumonectomy. The removal of organs or limbs poses risks for additional late effects.

③ — The risk of overwhelming sepsis from encapsulated organisms necessitates immunization against *Pneumococcus, Haemophilus influenzae,* and *Meningococcus.* Prophylactic antibiotics and instructions should be given to seek medical attention with any febrile illness.

④ — Pelvic surgery may involve orchiectomy and oophorectomy, hysterectomy, cystectomy, lymph node dissection, or pelvic exenteration. Bilateral orchiectomy or oophorectomy requires hormonal replacement. Monitoring of hormone levels is necessary following removal of a single organ and radiation to the remaining partner. Innovative options for parenting for both males and females should be explored.

⑤ — Amputation or limb salvage obligate examination of the surgical site and its function. Growing children require replacement prostheses so that an abnormal gait does not result in scoliosis.

⑥ — Enucleation of a single eye is usually not limiting except in certain specialized occupations. Clear discharge from the socket is not unusual during respiratory infections but a purulent discharge may require therapy. Growth necessitates revision or a new prosthesis.

⑦ — Chemotherapy is used to treat almost all pediatric neoplasms, but only some agents result in long-term problems. The total doses of anthracyclines, alkylating agents, and bleomycin should be calculated.

⑧ — Corticosteroids can cause diminished bone mineralization causing avascular necrosis. Pain is the major symptom, growing adolescents are at highest risk, and MRI is necessary for the diagnosis.

⑨ — The probability of myocardial damage and conduction abnormalities increases with doses of doxorubicin >200 mg/m^2 and begins about 10 years after treatment ends. Echocardiogram and ECGs are recommended with frequency dependent upon the total dose and any changes observed. Depending on dose received, counseling should include prohibition of unusually strenuous activity and cocaine use.

⑩ — Fertility can be impaired after treatment with alkylating agents; spermatogonia are especially vulnerable. Male infertility can be predicted after doses equivalent to 6 cycles of MOPP, but is less than complete when cyclophosphamide substitutes for mechlorethamine. Sperm count is the gold standard, but gonadotropins and testicular size are useful indicators. Females are considerably more resistant and can tolerate large doses of alkylators while still retaining normal menses. However, premature ovarian failure can occur after very large doses of alkylators, so postponement of childbearing may be unrealistic.

⑪ — Marrow stem cells are subject to mutations that lead to secondary myeloid leukemia following treatment with alkylators. The greatest risk occurs between 5 and 8 years from treatment, and is dose-related. Topoisomerase II inhibitors, such as etoposide, are also associated with secondary leukemia. Schedule and total dose may be related to level of risk. These leukemias usually occur between 2 and 4 years after treatment. There is no way to predict who will be affected or how to prevent these leukemias.

⑫ — Radiotherapy (RT) has profound effects on the growing bones, soft tissues, and viscera of children, with the late effects determined by the age of the child, the dose, and the organs or tissues in the field. RT to bone and soft tissues is associated primarily with growth reduction, especially if the growth plates are exposed/involved.

⑬ — The risk of secondary sarcomas of bone and soft tissue is greatest after doses >40 Gy. The risk of breast cancer is increased beginning 10 years after treatment in girls who have received doses >30 Gy, but lower doses with longer latent periods can also cause it. A baseline mammogram, followed by periodic physical examinations and mammograms is recommended for girls who have received chest RT beginning 10 years after treatment or by 25 years of age.

⑭ — RT to the head and neck may affect the thyroid gland, salivary glands, developing dentition, pituitary gland and brain; young children are at greatest risk, including the development of benign and malignant tumors even after relatively low doses. Hypothyroidism, and, rarely, hyperthyroidism, can result from doses >20 Gy. Learning disabilities are seen with doses >20 Gy and are more severe if methotrexate follows RT.

⑮ — Thoracic or spinal RT can potentiate the effects on the heart and lungs of anthracyclines, bleomycin, and the nitrosoureas. Young children and those who received doses >15 Gy are at higher risk for cardiac and pulmonary dysfunction. Regular cardiac and pulmonary function testing should be performed, with the frequency depending on the age at treatment (young children are more vulnerable), the RT dose, concomitant chemotherapy, and co-morbidities during therapy. Smoking and occupations involving exposure to respiratory toxins should be strongly discouraged.

⑯ — Abdominal and pelvic RT, in addition to the general risk of carcinogenesis, can cause adhesions and subsequent intestinal obstruction associated with abdominal surgery. Mucosal damage after abdominal doses in the range of 25 Gy can cause lactose intolerance and malabsorption. When both ovaries are exposed to 10 Gy or more, prepubertal girls may fail to achieve menarche and post-pubertal survivors are at risk of premature ovarian failure; both groups will require hormone replacement. Small-for-dates babies have been noted following abdominal RT. Although male germ cells are readily destroyed with as little as 1 Gy, doses >30 Gy are necessary to abolish male hormone production. In the absence of kidney shielding, radiation nephritis can occur with doses as low as 12 Gy.

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Useful normal laboratory values

Normal blood count values from birth to 18 years

Age	Hb g/dl	RBC $\times 10^{12}$/l	HCT	MCV fl	WBC $\times 10^{9}$/l	Neutrophils $\times 10^{9}$/l	Lymphocytes $\times 10^{9}$/l	Monocytes $\times 10^{9}$/l	Eosinophils $\times 10^{9}$/l	Basophils $\times 10^{9}$/l	Platelets $\times 10^{9}$/l
Birth (term infants)	14.9–23.7	3.7–6.5	0.47–0.75	100–125	10.0–26.0	2.7–14.4	2.0– 7.3	0.00–1.9	0.00–0.85	0.00–0.10	150–450
2 weeks	13.4–19.8	3.9–5.9	0.41–0.65	88–110	6.0–21.0	1.5– 5.4	2.8– 9.1	0.10–1.7	0.00–0.85	0.00–0.10	170–500
2 months	9.4–13.0	3.1–4.3	0.28–0.42	84– 98	5.0–15.0	0.7– 4.8	3.3–10.3	0.40–1.2	0.05–0.90	0.02–0.13	210–650
6 months	10.0–13.0	3.8–4.9	0.30–0.38	73– 84	6.0–17.0	1.0– 6.0	3.3–11.5	0.20–1.3	0.10–1.10	0.02–0.20	210–560
1 year	10.1–13.0	3.9–5.1	0.30–0.38	70– 82	6.0–16.0	1.0– 8.0	3.4–10.5	0.20–0.9	0.05–0.90	0.02–0.13	200–500
2–6 years	11.0–13.8	3.9–5.0	0.32–0.40	72– 87	6.0–17.0	1.5– 8.5	1.8– 8.4	0.15–1.3	0.05–1.10	0.02–0.12	210–490
6–12 years	11.1–14.7	3.9–5.2	0.32–0.43	76– 90	4.5–14.5	1.5– 8.0	1.5– 5.0	0.15–1.3	0.05–1.00	0.02–0.12	170–450
12–18 years											
Female	12.1–15.1	4.1–5.1	0.35–0.44	77– 94	4.5–13.0	1.5– 6.0	1.5– 4.5	0.15–1.3	0.05–0.80	0.02–0.12	180–430
Male	12.1–16.6	4.2–5.6	0.35–0.49	77– 92	4.5–13.0	1.5– 6.0	1.5– 4.5	0.15–1.3	0.05–0.80	0.02–0.12	180–430

Compiled from various sources. Red cell values at birth derived from skin puncture blood; most other data from venous blood.
Reproduced with permission from Elsevier Science, from *Hinchliffe RF:* Reference values; in *Lilleyman J, Hann I, Blanchette V (eds):* Pediatric Hematology, ed 2. London, Churchill Livingstone, 1999, p 2.

Reference values for coagulation tests and inhibitors of coagulation in the healthy full-term infant during the first 6 months of life and in adults

Tests	Day 1 (n)	Day 5 (n)	Day 30 (n)	Day 90 (n)	Day 180 (n)	Adult (n)
PT, s	13.0 ± 1.43 (61)[1]	12.4 ± 1.46 (77)[1, 2]	11.8 ± 1.25 (67)[1, 2]	11.9 ± 1.15 (62)[1]	12.3 ± 0.79 (47)[1]	12.4 ± 0.78 (29)
PTT, s	42.9 ± 5.80 (61)	42.6 ± 8.62 (76)	40.4 ± 7.42 (67)	37.1 ± 6.52 (62)[1]	35.5 ± 3.71 (47)[1]	33.5 ± 3.44 (29)
Fibrinogen, g/l	2.83 ± 0.58 (61)[1]	3.12 ± 0.75 (77)[1]	2.70 ± 0.54 (67)[1]	2.43 ± 0.68 (60)[1, 2]	2.51 ± 0.68 (47)[1, 2]	2.78 ± 0.61 (29)
FII, U/ml	0.48 ± 0.11 (61)	0.63 ± 0.15 (76)	0.68 ± 0.17 (67)	0.75 ± 0.15 (62)	0.88 ± 0.14 (47)	1.08 ± 0.19 (29)
FV, U/ml	0.72 ± 0.18 (61)	0.95 ± 0.25 (76)	0.98 ± 0.18 (67)	0.90 ± 0.21 (62)	0.91 ± 0.18 (47)	1.06 ± 0.22 (29)
FVII, U/ml	0.66 ± 0.19 (60)	0.89 ± 0.27 (75)	0.90 ± 0.24 (67)	0.91 ± 0.26 (62)	0.87 ± 0.20 (47)	1.05 ± 0.19 (29)
FVIII:C, U/ml	1.00 ± 0.39 (60)[1, 2]	0.88 ± 0.33 (75)[1, 2]	0.91 ± 0.33 (67)[1, 2]	0.79 ± 0.23 (62)[1, 2]	0.73 ± 0.18 (47)[2]	0.99 ± 0.25 (29)
VWF_{Ag}, U/ml	1.53 ± 0.67 (40)[2]	1.40 ± 0.57 (43)[†]	1.28 ± 0.59 (40)[2]	1.18 ± 0.44 (40)[2]	1.07 ± 0.45 (46)[2]	0.92 ± 0.33 (29)[2]
FIX, U/ml	0.53 ± 0.19 (59)	0.53 ± 0.19 (75)	0.51 ± 0.15 (67)	0.67 ± 0.23 (62)	0.86 ± 0.25 (47)	1.09 ± 0.27 (29)
FX, U/ml	0.40 ± 0.14 (60)	0.49 ± 0.15 (76)	0.59 ± 0.14 (67)	0.71 ± 0.18 (62)	0.78 ± 0.20 (47)	1.06 ± 0.23 (29)
FXI, U/ml	0.38 ± 0.14 (60)	0.55 ± 0.16 (74)	0.53 ± 0.13 (67)	0.69 ± 0.14 (62)	0.86 ± 0.24 (47)	0.97 ± 0.15 (29)
FXII, U/ml	0.53 ± 0.20 (60)	0.47 ± 0.18 (75)	0.49 ± 0.16 (67)	0.67 ± 0.21 (62)	0.77 ± 0.19 (47)	1.08 ± 0.28 (29)
FXIIIa, U/ml	0.79 ± 0.26 (44)	0.94 ± 0.25 (49)[1]	0.93 ± 0.27 (44)[1]	1.04 ± 0.34 (44)[1]	1.04 ± 0.29 (41)[1]	1.05 ± 0.25 (29)
FXIIIb, U/ml	0.76 ± 0.23 (44)	1.06 ± 0.37 (47)[1]	1.11 ± 0.36 (45)[1]	1.16 ± 0.34 (44)[1]	1.10 ± 0.30 (41)[1]	0.97 ± 0.20 (29)
Plasminogen CTA, U/ml	1.95 ± 0.35 (44)	2.17 ± 0.38 (60)	1.98 ± 0.36 (52)	2.48 ± 0.37 (44)	3.01 ± 0.40 (47)	3.36 ± 0.44 (29)
AT	0.63 ± 0.12 (58)	0.67 ± 0.13 (74)	0.78 ± 0.15 (66)	0.97 ± 0.12 (60)[1]	1.04 ± 0.10 (56)[1]	1.05 ± 0.13 (28)
HCII	0.43 ± 0.25 (56)	0.48 ± 0.24 (72)	0.47 ± 0.20 (58)	0.72 ± 0.37 (58)	1.20 ± 0.35 (55)	0.96 ± 0.15 (29)
Protein C	0.35 ± 0.09 (41)	0.42 ± 0.11 (44)	0.43 ± 0.11 (43)	0.54 ± 0.13 (44)	0.59 ± 0.11 (52)	0.96 ± 0.16 (28)
Protein S	0.36 ± 0.12 (40)	0.50 ± 0.14 (48)	0.63 ± 0.15 (41)	0.86 ± 0.16 (46)[1]	0.87 ± 0.16 (49)[1]	0.92 ± 0.16 (29)

NOTE: All factors except fibrinogen and plasminogen are expressed as units per milliliter where pooled plasma contains 1.0 U/ml. Plasminogen units are those recommended by the Committee on Thrombolytic Agents (CTA). All values are expressed as mean ± 1 SD.

[1] Values that do not differ statistically from the adult values.

[2] These measurements are skewed because of a disproportionate number of high values. The lower limit that excludes the lower 2.5th percentile of the population has been given in the respective figures. The lower limit for factor VIII was 0.50 U/ml at all time points for the infant.

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Index of Signs and Symptoms

Abbreviations

Ab	Antibody
ACD	Acid citrate dextrose
ACE	Angiotensin converting enzyme
ACL	Anticardiolipin antibody
ACS	Acute chest syndrome
AFP	Alpha fetoprotein
Ag	Antigen
AIHA	Autoimmune hemolytic anemia
ALL	Acute lymphoblastic leukemia
AML	Acute myeloblastic leukemia
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
APCR	Activated protein C resistance
APLA	Antiphospholipid antibody
ARDS	Adult respiratory distress syndrome
ASO	Anti-streptolysin O
ASSC	Acute splenic sequestration crisis
AT	Antithrombin
BCNU	Carmustine
BM	Bone marrow
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BMT	Bone marrow transplant
BP	Blood pressure
BT	Brain tumor
BU	Bethesda units
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Cluster of differentiation (in flow cytometry)
CGD	Chronic granulomatous disease
CHF	Congestive heart failure
CML	Chronic myelogenous leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CPDA-1	Citrate-phosphate-dextrose-adenine
CSF	Cerebrospinal fluid
CT	Computerized tomography
CVA	Cerebrovascular accident
CVL	Central venous line
CXR	Chest X-ray
DBA	Diamond Blackfan anemia
DCT	Direct Coombs test or direct antiglobulin test
DDAVP	1-deamino-8-D-arginine vasopressin
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
Dx	Diagnosis
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ELISA	Enzyme-linked immunoabsorbent assay
EM	Electron microscopy
Epo	Erythropoietin
ESR	Erythrocyte sedimentation rate
FFP	Fresh frozen plasma
FII	Factor II (prothrombin)
FISH	Fluorescence in situ hybridization
FIX	Factor IX
fl	Femtoliter
FSH	Follicle stimulating hormone
FSP	Fibrin split products
FV	Factor V
FVII	Factor VII
FVIII:C	Factor VIII coagulant activity
FX	Factor X
FXI	Factor XI
FXII	Factor XII
FXIII	Factor XIII
G-CSF	Granulocyte colony stimulating factor
G6PD	Glucose 6-phosphate dehydrogenase
GCT	Germ cell tumor
GI	gastrointestinal
GM-CSF	Granulocyte-macrophage colony stimulating factor
GPI	Glycosyl-phosphatidylinositol
GU	Genitourinary
GVHD	Graft-verses-host disease
H&E	Hematoxylin and eosin stain
Hb	Hemoglobin
HbA	Hemoglobin A – adult hemoglobin
HbA_2	Hemoglobin A_2
HbF	Hemoglobin F – fetal hemoglobin
HbH	Hemoglobin H
HBL	Hepatoblastoma
HbS	Hemoglobin S - sickle hemoglobin
$HbS\beta^+T$	Sickle β^+ thalassemia
$HbS\beta^0T$	Sickle β^0 thalassemia
HbSβT	Sickle β thalassemia
HbSC	Hemoglobin S-C disease
HbSS	Homozygous sickle cell anemia
HCG	Human chorionic gonadotrophin
HCT	Hematocrit
HE	Hereditary elliptocytosis
HELLP	Syndrome of hemolysis, elevated liver enzymes, low platelets
HLA	Human leucocyte antigen
HPFH	Hereditary persistence of fetal hemoglobin
HUS	Hemolytic uremic syndrome
HVA	Homovanillic acid
Hx	History
ICH	Intracerebral hemorrhage
IDA	Iron deficiency anemia
IGF-1	Insulin growth factor-1
IL	Interleukin
ITI	Immune tolerance induction
ITP	Immune thrombocytopenic purpura
IUGR	Intrauterine growth retardation
IVIg	Intravenous immunoglobulin
JRA	Juvenile rheumatoid arthritis
LAP	Leukocyte alkaline phosphatase
LCH	Langerhans cell histiocytosis
LDH	Lactate dehydrogenase
LFTs	Liver function tests
LH	Luteinizing hormone

LM	Light microscopy
LMWH	Low molecular weight heparin
LP	Lumbar puncture
MAHA	Microangiopathic hemolytic anemia
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MetHb	Methemoglobin
MOPP	Mechloramine, vincristine, prednisone, procarbazine
MPS	Myeloproliferative syndrome
MPV	Mean platelet volume
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NAIT	Neonatal alloimmune thrombocytopenia
NBL	Neuroblastoma
NBT	Nitroblue tetrazolium
NEC	Necrotizing enterocolitis
NF1	Neurofibromatosis type 1
NHL	Non-Hodgkin lymphoma
NI	Normal
NRBC	Nucleated erythrocytes
NRSTS	Non-rhabdomyosaroma soft tissue sarcoma
NSAID	Nonsteroidal antiinflammatory drugs
O+P	Stool sample for ova and parasites
PCC	Prothrombin complex concentrates
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PET	Positron emission tomography
PEx	Physical examination
PFT	Pulmonary function tests
PK	Pyruvate kinase
PMN	Polymorphonuclear neutrophil
PNET	Primitive neuroectodermal tumor
PNH	Paroxysmal nocturnal hemoglobinuria
PRBC	Packed red blood cells
PT	Prothrombin time
PTT	Partial thromboplastin time
R/O	Rule out
RBC	Red blood cell
RCM	Red cell mass
RDW	Red cell distribution width
RES	Reticuloendothelial system
RETIC	Reticulocyte count
rFVIIa	Recombinant activated factor VII
RIA	Radioimmunoassay
RMS	Rhabdomyosarcoma
RT	Radiotherapy
RT-PCR	Reverse transcriptase polymerase chain reaction
RUQ	Right upper quadrant
Rx	Treatment
SCD	Sickle cell disease
SI	Serum iron
SLE	Systemic lupus erythematosus
SMEAR	Blood smear
SVC	Superior vena cava
TAR	Thrombocytopenia-absent radii syndrome
TEC	Transient erythroblastopenia of childhood
TIBC	Total iron binding capacity
TNF	Tissue necrosis factor
TP	Thrombocytopenia
TPA	Tissue plasminogen activator
TS	Transferrin saturation
TSH	Thyroid stimulating hormone
TT	Thrombin time
TTP	Thrombotic thrombocytopenic purpura
U/A	Urine analysis
UA	Uric acid
UAC	Umbilical arterial catheter
US	Ultrasound
V/Q	Ventilation/perfusion
VMA	Vanillylmandelic acid
VWD	von Willebrand disease
VWF	von Willebrand factor
VWF:RCo	von Willebrand factor activity (ristocetin co-factor activity)
VWF_{Ag}	von Willebrand antigen activity
W/U	Workup
WAS	Wiskott-Aldrich syndrome
WBC	White blood cell
XR	X-ray
⇓	Decreased
⇑	Increased

Diagnoses in **bolded** text represent very common etiologies of that problem.

Diagnoses in *italicized* text represent rare etiologies of that problem.