
بنام هستی آفرین

Anemia

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- Introduction
- Pysiologic anemia
- Functional anemia

Etiologic classification and major Diagnostic features of Anemia in children

Etiologic Classification	Diagnosis features
I. Impaired red cell formation	
A. Deficiency	
Decreased Dietary intake (e.g., excessive milk-iron-Deficiency anemia , vegan-vitamin B12 deficiency	
Increased demand , e.g,. Growth (iron) hemolysis (folic acid)	
Decreased absorption	
Specific: intrinsic factor lack (vitamin B12)	
Generalized: malabsorption syndrome (e.g,. Folic acid, iron)	
Increased loss	
Acute: hemorrhage (iron)	
Chronic: gut bleeding (iron)	

Etiologic classification and major Diagnostic features of Anemia in children…

Etiologic Classification	Diagnosis features
1. Iron deficiency	Hypochromic , microcytic red cells; low MCV , low MCH , low MCHC , high RDW , a low serum ferritin , high FEP , guaiac positivity
2. Folate deficiency	Macrocytic red cells , high MCV,high RDW,megaloblastic marrow . Low serum and red cell foliate
3. Vitamin B12 deficiency	Macrocytic red cell , high MCV,high RDW,megaloblastic marrow , low serum B12 gastric acidity; schilling test
4. Vitamin C deficiency	Clinical scurvy
5. Protein deficiency	kwashiorkor
6. Vitamin B6 deficiency	Hypochromic red cells , sideroblastic bone marrow , high serum ferritin
7. Thyroxine deficiency	Clinical cretinism , low T4 , high TSH

Etiologic classification and major Diagnostic features of Anemia in children…

Etiologic Classification	Diagnosis features
B. Bone marrow failure	
1. Failure of a single cell line	
a. megakaryocytes	
(1) Amegakaryocytes thrombocytopenic purpura	Iimb abnormalities , absent megakaryocytes
b. Red cell precursors	
(1) Congenital red cell aplasia (Diamond-Blackfan anemia)	Absent red cell precursors
(2) Acquired red cell aplasia (transient erythroblastopenia of childhood,TEC)	Absent red cell precursors

Etiologic classification and major Diagnostic features of Anemia in children…

Etiologic Classification	Diagnosis features
c. White cell precursors	
(1) Congential neutropenia	Neutropenia , recurrent infection
2. Failure of all cell lines (produces aplastic anemia characterized by pancytopenia and acellulare or hypocellular marrow)	
a. constitutional	
(1) Fanconis anemia	Multiple Congential anomalies , chromosomal breakage
(2) Familial without anomalies	Familial history , no Congential anomalies
(3) Dyskeratosis congentia	Marked mucosal and cutaneous abnormalities
b. acquired	
(1) idiopathic	No identifiable cause
(2)secondary	History of exposure to drugs , radiation , household toxins , infections;associated immunologic disease

Etiologic classification and major Diagnostic features of Anemia in children…

Etiologic Classification	Diagnosis features
3. infiltration	
a. De novo (e.g., leukemia)	Bone marrow:morphology cytochemistry , immunologic markers , cytogenestics
b. Secondary (e.g., neuroblastoma , lymphoma)	VMA , skeletal survery , bone marrow
c. Dyshematopoietic anemia (decreased erythropoiesis , decreased iron utilization)	
1. Infection	Evidence of systemic illness
2. Renal failure and hepatic disease	BUN and liver-function tests
3. Disseminated malignancy	Clinical evidence
4. Connective tissue diseases	Rheumatoid arthrities

Etiologic classification and major Diagnostic features of Anemia in children…

Etiologic Classification	Diagnosis features
II. Blood loss	Over or occult-guiac
III. Hemolytic anemia	
A. Corpuscular	
1. Membrane defects (spherocytosis , elliptocytosis)	Morphology osmotic fragility
2. Enzymatic defects (pyruvate kinase , **G6PD**)	Autohemolysis , enzyme assays
3. Hemoglobin defects	
a. Heme	
b. Globin	
(1) Qualitative (e.g., sickle cell)	Hb electrophoresis
(2) Qualitative (e.g., thalassemia)	HbF , A2 content

Etiologic classification and major Diagnostic features of Anemia in children…

Etiologic Classification	Diagnosis features
B. extracorpuscular	
1. Immune	Coombs test
a. Isoimmiune	
b. Autoimmune	
(1) Idiopathic	Coombs test , antibody identification
(2) Secondary	Decreased C3 , C4 , CH50;
Immunologic disorder (e.g., lupus)	Positive ANA
One cell line (e.g., red cell)	Anemia: coombs positive
Multiple cell line (e.g., white blood cells , platelets)	Neutropenia immunotropenia , thrombocytopenia-ITP
2. Nonimmune (idiopathic , secondary)	

تالاسمی

- تعریف:hereditary chronic.h.Anemia

- انواع هموگلوبینوپاتی ها:

- Thalassemia
- Sickle – cell
- Sickle – thalassemi

انواع تالاسمی

- α- thalassemia
- β – thalassemia:

  silent carrier-mino-intermedia-major
- αβ – thalassemia
- Delta - β thalassemia
- Gama delta β thalassemia
- ...

علایم کلینیکی بتاتالاسمی ماژور

- رنگ پریدگی
- اختلال رشد
- هپاتواسپلنومگالی
- تغییرات استخوانی بخصوص در چهره
- کاردیومگالی و ...

تشخیص بتاتالاسمی

- آنمی هیپوکروم میکروسیتیک
- الکتروفورز هموگلوبین:
- در silent carrier طبیعی
- در مینور هموگلوبین A2 از 3.5 گرم در دسی لیتر بیشتر است.
- در اینترمدیا هموگلوبین F افزایش قابل توجهی دارد.
- در نوع ماژور بیش از 90% هموگلوبین F وجود دارد.

تشخیص سیکل تالاسمی

- آنمی هیپوکروم میکروسیتیک(MCV,MCH کاهش یافته)

- هموگلوبین F افزایش قابل توجهی دارد ولی هموگلوبین S اکثریت هموگلوبین تشکیل می دهد.

درمان بیماران تالاسمی

- تزریق مناسب خون
- پیشگیری از عفونت هایی که از طریق خون منتقل می شوند.
- مصرف مناسب دفع کننده های آهن(دسفرال،L1،Exjade)
- مانیتورینگ قلب و کبد،چشم و گوش و غدد و...
- هیدروکسی اوره
- درمان قطعی با پیوند مغز استخوان

Bone Marrow transplantation

- در سال ۱۹۸۲ اولین پیوند مغز استخوان در درمان تالاسمی با موفقیت انجام شد.
- بیش از ۸۰۰ بیمار تالاسمی در بخش پیوند پیسارو در ایتالیا توسط پروفسور لوکارلی و همکارانش بهبود یافتند.
- بر اساس پروتکل لوکارلی بیماران از نظر فاکتورهای ریسک با وجود هپاتومگالی و فیبروز کبدی و چگونگی مصرف دفع کننده های آهن به سه دسته تقسیم می شوند:

Class I,Class II , Class III

Bone Marrow transplantation…

- در کلاس یک بدون فاکتور ریسک Overall Survival= 95% و

  Event Free Survival= 90% است.

- در کلاس دو با یک یا دو فاکتور ریسک ,OS=85% و EFS=81%

- در کلاس سه با هر سه فاکتور ریسک OS=78% و EFS=54%

برنامه های پیشگیری

- کنترل ناقلین هموگلوبینوپاتی های مختلف با شناسایی ژن و سنتز زنجیره گلوبین
- PND (تشخیص قبل از تولد جنین) و تشخیص جنین با انجام CVS و یا نمونه برداری از خون بند ناف در هفته ۱۰ تا ۱۴ سن حاملگی

و اما مشکلات تشخیصی؟!

- افرادی که MCV و MCH نرمال دارند ولی ممکن است Silent carrier باشند که موارد بسیار نادر است.
- افرادی که MCV و MCH پایین تر از نرمال دارند ولی الکتروفورز هموگلوبین نرمال دارند.
- افرادی که MCV و MCH نرمال دارند ولی carrier سیکل سل هستند.
- ناقلین آلفا یا بتا تالاسمی که ژن های آن ها قابل شناسایی نیست.

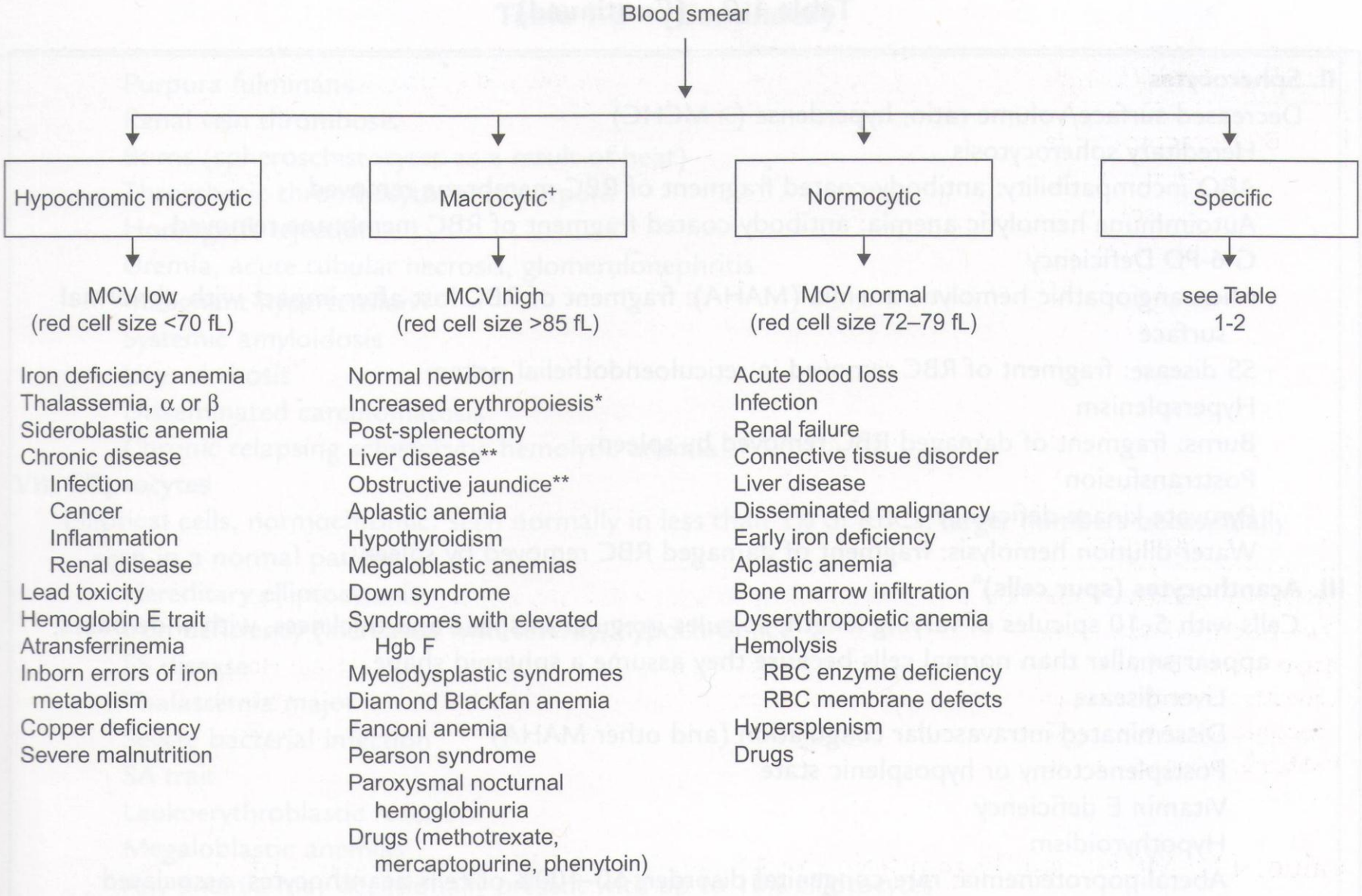
Blood smear
Hypochromic microcytic
Macrocytic+
Normocytic
Specific
MCV low
(red cell size <70 fL)
MCV high
(red cell size >85 fL)
MCV normal
(red cell size 72–79 fL)
see Table
1-2
Iron deficiency anemia
Thalassemia, α or β
Sideroblastic anemia
Chronic disease
Infection
Cancer
Inflammation
Renal disease
Lead toxicity
Hemoglobin E trait
Atransferrinemia
Inborn errors of iron metabolism
Copper deficiency
Severe malnutrition
Normal newborn
Increased erythropoiesis*
Post-splenectomy
Liver disease**
Obstructive jaundice**
Aplastic anemia
Hypothyroidism
Megaloblastic anemias
Down syndrome
Syndromes with elevated Hgb F
Myelodysplastic syndromes
Diamond Blackfan anemia
Fanconi anemia
Pearson syndrome
Paroxysmal nocturnal hemoglobinuria
Drugs (methotrexate, mercaptopurine, phenytoin)
Acute blood loss
Infection
Renal failure
Connective tissue disorder
Liver disease
Disseminated malignancy
Early iron deficiency
Aplastic anemia
Bone marrow infiltration
Dyserythropoietic anemia
Hemolysis
RBC enzyme deficiency
RBC membrane defects
Hypersplenism
Drugs

Table 1-2 Specific Red Cell Morphologic Abnormalities

I. Target cells

Increased surface/volume ratio (generally does not effect red cell survival)

- Thalassemic syndromes
- Hemoglobinopathies
  - Hb AC or CC
  - Hb SS, SC, S-Thal
  - HbE (heterozygote and homozygote)
  - HbD
- Obstructive liver disease
- Postsplenectomy or hyposplenic states
- Severe iron deficiency
- LCAT deficiency: congenital disorder of lecithin/cholesterol acyltransferase deficiency (corneal opacifications, proteinuria, target cells, moderately severe anemia)
- Abetalipoproteinemia

Table 1-2 (Continued)

II. Spherocytes

Decreased surface/volume ratio, hyperdense (>MCHC)

- Hereditary spherocytosis
- ABO incompatibility: antibody-coated fragment of RBC membrane removed
- Autoimmune hemolytic anemia: antibody-coated fragment of RBC membrane removed
- G-6-PD Deficiency
- Microangiopathic hemolytic anemia (MAHA): fragment of RBC lost after impact with abnormal surface
- SS disease: fragment of RBC removed in reticuloendothelial system
- Hypersplenism
- Burns: fragment of damaged RBC removed by spleen
- Posttransfusion
- Pyruvate kinase deficiency
- Water-dilution hemolysis: fragment of damaged RBC removed by spleen

III. Acanthocytes (spur cells)[a]

Cells with 5–10 spicules of varying length; spicules irregular in space and thickness, with wide bases; appear smaller than normal cells because they assume a spheroid shape

- Liver disease
- Disseminated intravascular coagulation (and other MAHA)
- Postsplenectomy or hyposplenic state
- Vitamin E deficiency
- Hypothyroidism
- Abetalipoproteinemia: rare congenital disorder; 50–100% of cells acanthocytes; associated abnormalities (fat malabsorption, retinitis pigmentosa, neurologic abnormalities)
- Malabsorptive states

IV. Echinocytes (burr cells)[a]

10–30 spicules equal in size and evenly distributed over RBC surface; caused by alteration in extracellular or intracellular environment

- Artifact
- Uremia
- Dehydration
- Liver disease
- Pyruvate kinase deficiency
- Peptic ulcer disease or gastric carcinoma
- Immediately after red cell transfusion
- Rare congenital anemias due to decreased intracellular potassium

V. Pyknocytes[a]

Distorted, hyperchromic, contracted RBC; can be similar to echinocytes and acanthocytes

VI. Schistocytes

Helmet, triangular shapes, or small fragments. Caused by fragmentation upon impact with abnormal vascular surface (e.g., fibrin strand, vasculitis, artificial surface in circulation)

- Disseminated intravascular coagulation (DIC)
- Severe hemolytic anemia (e.g., G6PD deficiency)
- Microangiopathic hemolytic anemia
- Hemolytic uremic syndrome
- Prosthetic cardiac valve, abnormal cardiac valve, cardiac patch, coarctation of the aorta
- Connective tissue disorder (e.g., SLE)
- Kasabach–Merritt syndrome

Table 1-2 (Continued)

- Purpura fulminans
- Renal vein thrombosis
- Burns (spheroschistocytes as a result of heat)
- Thrombotic thrombocytopenia purpura
- Homograft rejection
- Uremia, acute tubular necrosis, glomerulonephritis
- Malignant hypertension
- Systemic amyloidosis
- Liver cirrhosis
- Disseminated carcinomatosis
- Chronic relapsing schistocytic hemolytic anemia

VII. Elliptocytes

Elliptical cells, normochromic; seen normally in less than 1% of RBCs; larger numbers occasionally seen in a normal patient

- Hereditary elliptocytosis
- Iron deficiency (increased with severity, hypochromic)
- SS disease
- Thalassemia major
- Severe bacterial infection
- SA trait
- Leukoerythroblastic reaction
- Megaloblastic anemias
- Any anemia may occasionally present with up to 10% elliptocytes
- Malaria

VIII. Teardrop cells

Shape of drop, usually microcytic, often also hypochromic

- Newborn
- Thalassemia major
- Leukoerythroblastic reaction
- Myeloproliferative syndromes

IX. Stomatocytes

Has a slit-like area of central pallor

- Normal (in small numbers)
- Hereditary stomatocytosis
- Artifact
- Thalassemia
- Acute alcoholism
- Rh null disease (absence of Rh complex)
- Liver disease
- Malignancies

X. Nucleated red blood cells

Not normal in the peripheral blood beyond the first week of life

- Newborn (first 3–4 days)
- Intense bone marrow stimulation
  - Hypoxia (especially postcardiac arrest)
  - Acute bleeding
  - Severe hemolytic anemia (e.g., thalassemia, SS hemoglobinopathy)
- Congenital infections (e.g., sepsis, congenital syphilis, CMV, rubella)

Table 1-3 Classification of Nature of the Anemia Based on MCV and RDW

	MCV Low	MCV Normal	MCV High
RDW Normal	***Microcytic Homogeneous***	***Normocytic Homogeneous***	***Macrocytic Homogeneous***
	Heterozygous thalassemia Chronic disease	Normal Chronic disease Chronic liver disease Nonanemic hemoglobinopathy (e.g., AS, AC) Chemotherapy Chronic myelocytic leukemia Hemorrhage Hereditary spherocytosis	Inherited bone marrow failure syndromes Preleukemia
RDW High	***Microcytic Heterogeneous***	***Normocytic Heterogeneous***	***Macrocytic Heterogeneous***
	Iron deficiency S β-thalassemia Hemoglobin H Red cell Fragmentation disorders	Early iron or folate deficiency Mixed deficiencies Hemoglobinopathy (e.g., SS) Myelofibrosis Sideroblastic anemia	Folate deficiency Vitamin B_{12} deficiency Immune hemolytic anemia Cold agglutinins

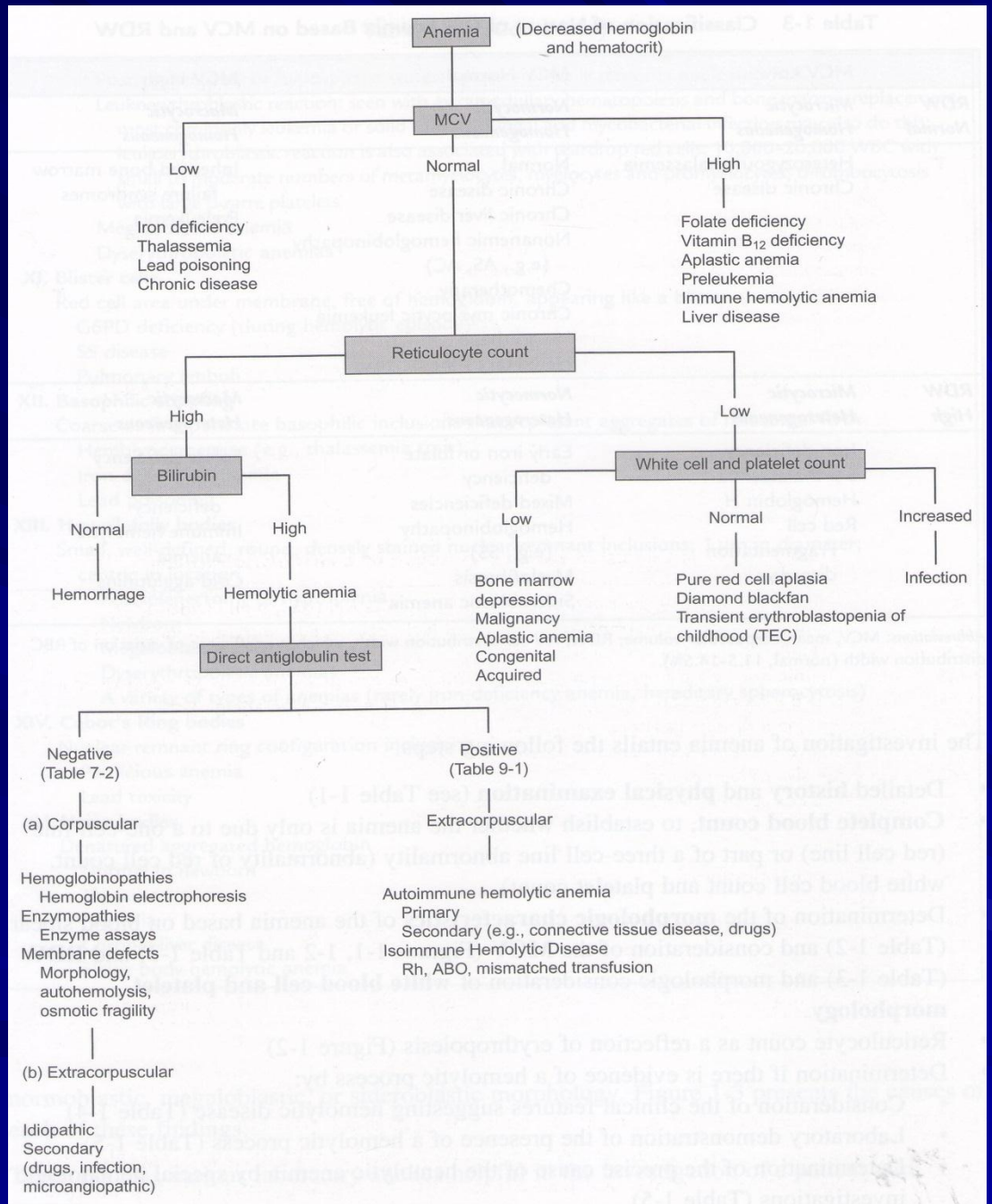

Figure 1-2 Approach to the Diagnosis of Anemia by MCV and Reticulocyte Count.

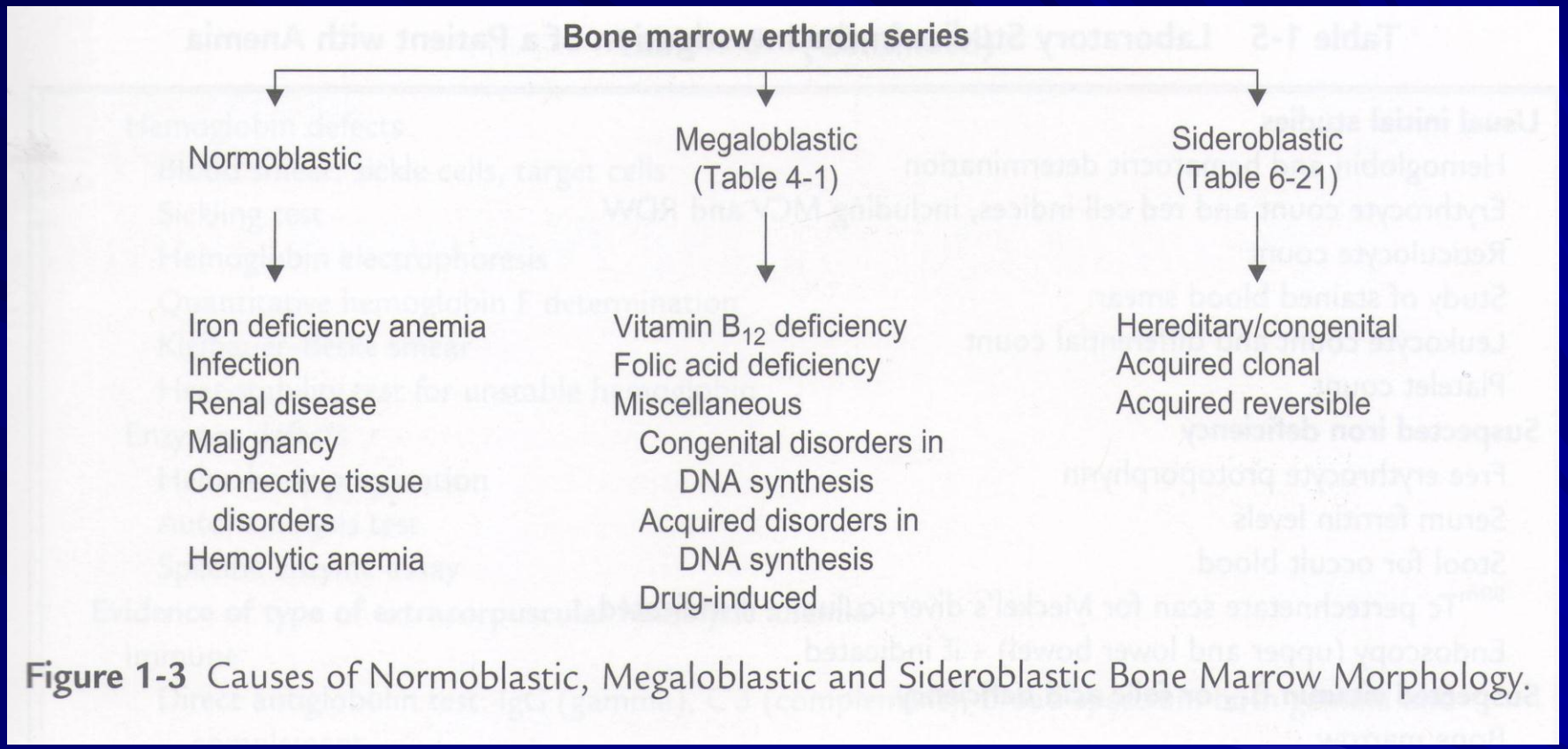

Figure 1-3 Causes of Normoblastic, Megaloblastic and Sideroblastic Bone Marrow Morphology.

Table 1-4 The Clinical Features Suggestive of a Hemolytic Process

- Ethnic factors – incidence of sickle gene carrier in the black population (8%), high incidence of thalassemia trait in people of Mediterranean ancestry and high incidence of glucose-6-phosphate dehydrogenase (G6PD) deficiency among Sephardic Jews
- Age factors – anemia and jaundice in an Rh-positive infant born to a mother who is Rh negative or a group A or group B infant born to a group O mother (setting for a hemolytic anemia)
- History of anemia, jaundice or gallstones in family
- Persistent or recurrent anemia associated with reticulocytosis
- Anemia unresponsive to hematinics
- Intermittent bouts or persistent indirect hyperbilirubinemia
- Splenomegaly
- Hemoglobinuria
- Presence of multiple gallstones
- Chronic leg ulcers
- Development of anemia or hemoglobinuria after exposure to certain drugs
- Cyanosis without cardiorespiratory distress
- Polycythemia (2,3-diphosphoglycerate mutase deficiency)
- Dark urine due to dipyrroluria (unstable hemoglobins, thalassemia and ineffective erythropoiesis)


Many thanks