Hematologic Diseases (1)

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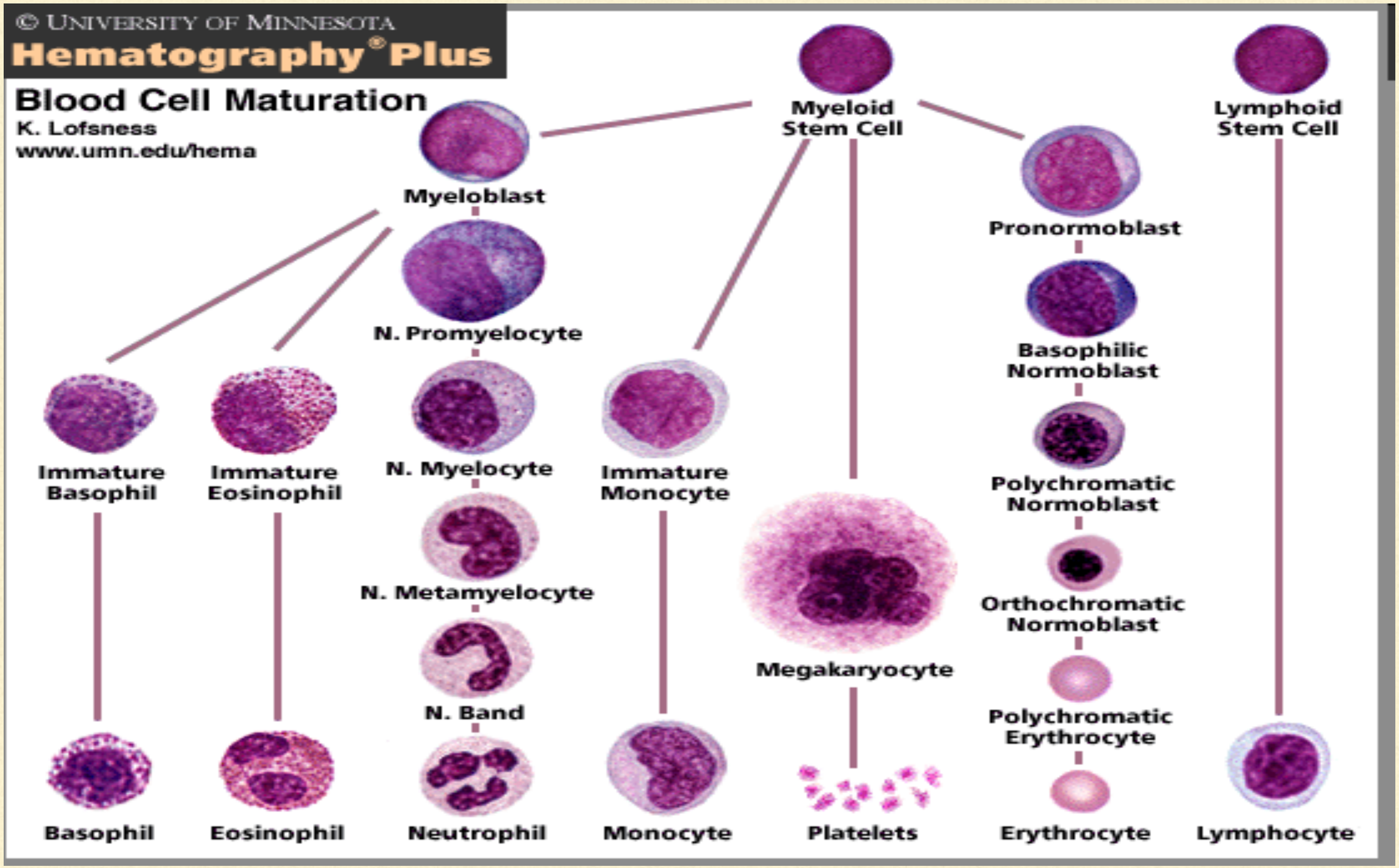
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Hematography® Plus
Blood Cell Maturation
K. Lofsness
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Myeloid Stem Cell
Lymphoid Stem Cell
Myeloblast
Pronormoblast
N. Promyelocyte
Basophilic Normoblast
Immature Basophil
Immature Eosinophil
N. Myelocyte
Immature Monocyte
Polychromatic Normoblast
N. Metamyelocyte
Orthochromatic Normoblast
Megakaryocyte
N. Band
Polychromatic Erythrocyte
Basophil
Eosinophil
Neutrophil
Monocyte
Platelets
Erythrocyte
Lymphocyte

- White blood cells (**WBCs**) are involved in inflammatory reactions, and they are responsible for cellular defense against **microorganisms** as well as for proinflammatory cytokine release.

- Red blood cells (**RBCs**) are responsible for gas exchange and **nutrient supply** to the periodontal tissues.

- **Platelets** are necessary for normal **hemostasis** as well as for the recruitment of cells during inflammation and wound healing.

Hematologic Diseases

- APLASTIC ANEMIA
- RED BLOOD CELL DISORDERS.
- WHITE BLOOD CELL DISORDERS

- **Aplastic anemia (AA).**

Aplastic anemia (AA).

- Aplastic anemia (AA) is a rare heterogenous and potentially fatal blood dyscrasia characterized by pancytopenia (deficiency of all three types of blood cell, Red blood cell, White blood cell and Platelets) and hypo cellular bone marrow.
- AA is classified as **non severe** (NSAA), **severe** (SAA), or **very severe** (VSAA) based on the extent of peripheral blood cytopenia.
- Etiologically, AA is classified as either inherited or acquired.

- **Inherited conditions** predisposing to AA includ. Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenital, congenital amegakaryocytic thrombocytopenia, and Diamond-Blackfan anemia.
- The genetic defects associated with these disorders result in altered DNA damage repair mechanisms, telomerase dysfunction, and altered ribosomal function.
- **Acquired AA** may occasionally be attributed to a known **trigger** such as drugs (e.g., chloramphenicol, quinine), benzene, pregnancy, or seronegative hepatitis; however, most cases of acquired AA are ultimately classified as idiopathic that lead to contraction of the stem cell compartment.

Clinical and Oral Manifestations.

- Patients with NSAA may have mild symptoms and need no therapy, whereas patients with severe disease may present with life-threatening pancytopenia.
- An abnormal hematologic profile may be the first and only clue to the presence of mild AA. The oral manifestations of AA reflect the underlying hematologic aberrations of the disease.
- Potential signs and symptoms of AA are nonspecific and include **fatigue, dyspnea on exertion, headache, fever, easy bruising, epistaxis, gingival hemorrhage, and heavy menses.**
- The most commonly observed findings attributed to AA were **petechiae, spontaneous gingival bleeding, herpetic infection.** Gingival hyperplasia was attributed to prior cyclosporine use.
- The hemorrhagic events were associated with platelet counts $<25 \times 10^9/\mu L$.

Diagnosis.

- A hypocellular BM along with evidence of depression of at least blood cell lineages is required to establish the diagnosis.
- Classification of severity (NSAA, SAA, VSAA) is determined by the peripheral blood values.
- SAA is diagnosed when two of three blood lineages are depressed: **absolute neutrophil count <500/μL, absolute reticulocyte count <60,000/μL, and platelet count <20,000/μL.**
- Very severe AA is established when the absolute neutrophil count <200/ μL.
- Further cytogenetic testing is useful to distinguish inherited from acquired forms of AA.

Treatment.

- Patients with NSAA should be monitored for progression to SAA.
- Supportive therapy with **blood transfusions** to correct anemia and thrombocytopenia in severe disease can be lifesaving. Transfusions from family members should be avoided to prevent sensitization to potential bone marrow donors.
- **Immunosuppressive therapy** (IST) with cyclosporine is effective for restoring blood cell production.
- For children and young adults with AA, **hematopoietic stem cell transplantation (HSCT**) is potentially curative and the treatment of choice.

Oral Health Considerations.

- The most serious fatal complication of AA is infection and patients with SAA are at increased risk for viral, fungal, and bacterial infections. There are no standard guidelines to manage these patients, but a proactive approach to prescribe **prophylactic antibiotics** (when deemed clinically appropriate), antivirals, and antifungals in this patient population is imperative.
- The **goal of dental therapy** is to establish and maintain good oral health, thus reducing the risk of an oral sourced infection.
- Patients with NSAA can generally tolerate routine care and the need for prophylactic antibiotic prophylaxis in this AA cohort remains unanswered.
- Patients with SAA or very severe AA are at a high risk for hemorrhagic and infectious (both oral sourced and nosocomial) events. They should be **managed in a hospital** setting to ensure appropriate perioperative and follow-up management. For patients who are severely neutropenic (neutrophil count <200/μL), prophylactic antibiotics and antifungals should be used and foods that may be contaminated with bacteria or fungal pathogens avoided.

Red Blood Cell Disorder.

1. Erythrocytosis.

- Erythrocytosis occurs when the red-cell mass exceeds 125% of the predicted value for body mass of the patient.
- It is typically characterized by an elevated hemoglobin (Hb) level (18.5 mg/dL for males, >16.5 mg/dL for females) or an elevated hematocrit (HCT) level (>52% males, >48% females).

- **Relative erythrocytosis** generally only occurs with significant dehydration, use of diuretics, diarrhea, or burns, such that the RBC mass is in the normal reference range but the plasma volume is below the reference range.
- **Absolute erythrocytosis** is diagnosed when an individual's measured RBC mass exceeds 125% of the predicted value. Once an absolute erythrocytosis has been confirmed, it is desirable to identify the underlying etiology, which may be classified as either primary or secondary.

- **Primary erythrocytosis** is a condition in which the erythropoietic compartment is expanding independently of extrinsic influences or by responding inadequately to them. The predominant form of primary erythrocytosis is polycythemia vera (PV).
- **Secondary erythrocytosis** are driven by factors extrinsic to the erythroid compartment. Common causes of hypoxia include **chronic lung disease, high altitude habitat, smoking, and renal artery stenosis, tumors** .
- **Idiopathic erythrocytosis (IE)** is reserved for cases in which all primary and secondary causes of increased red-cell mass have been ruled out. As a consequence of increased recognition of primary and secondary causes of erythrocytosis, patients classified as having IE are on the decline.

Polycythemia Vera.

- PV is a clonal disorder characterized by independent proliferation of a single erythroid cell line.
- PV shares several features with two other forms of myeloproliferative neoplasia: essential thrombocytosis and primary myelofibrosis. Collectively, these three conditions exhibit relatively normal cellular maturation, phenotypic and genotypic mimicry, *JAK2* gene mutations, and a tendency to evolve into each other or develop myelofibrosis

Clinical and Oral Manifestations

- PV is usually asymptomatic and often only discovered incidentally.
- PV should be suspected in patients with **elevated Hb or HCT levels, splenomegaly, or portal venous thrombosis.** When symptoms occur, they may include pruritis, vertigo, gastrointestinal pain, headache, paresthesias, fatigue, weakness, visual disturbances, tinnitus, plethora, and bleeding gums. It is postulated that the paradoxical increased bleeding risk results from an altered degradation and function of von Willebrand factor.
- Pruritis following a bath or shower is often the predominant complaint and has been attributed to mast cell degranulation.

Polycythemia Vera.

- **Major complications of PV** (e.g., stroke, venous thromboembolism) are attributable to blood hyperviscosity and the qualitative and quantitative platelet alterations observed in the disease.
- Factors associated with higher thrombotic risk include age >60 year, a prior history of thrombosis, and the presence of concurrent cardiovascular disease. Factors associated with shortened survival include history of thrombosis, leukocytosis, and advanced age (>60 years).The median survival rate for the patient with PV in the absence of advanced age and leukocytosis is about 23 years. In contrast, the median survival rate for the patient with PV with advanced age and/or leukocytosis is about 9 years.
- PV can manifest intraorally with erythema (red–purple color) of mucosa, glossitis, and erythematous, edematous gingiva. Spontaneous gingival bleeding can occur because the principal sites for hemorrhage, although rare, are reported to be the skin, mucous membranes, and gastrointestinal tract.

Polycythemia Vera.

- Diagnosis
- **Major criteria are:**

1. **Hb >18.5g/dL for males, >16.5 g/dL for females,** or other evidence of increased red-cell mass and
2. presence of *JAK2* V617F **mutation** or similar mutation such as *JAK2* exon 12 mutation.

- **Minor criteria are:**

3. BM showing hypercellularity with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation,
4. serum Epo level below the reference range for normal, and
5. endogenous erythroid colony formation in vitro.

- The presence of both major criteria plus one minor criterion or the first major criterion plus two minor criteria are required for the diagnosis.

Treatment

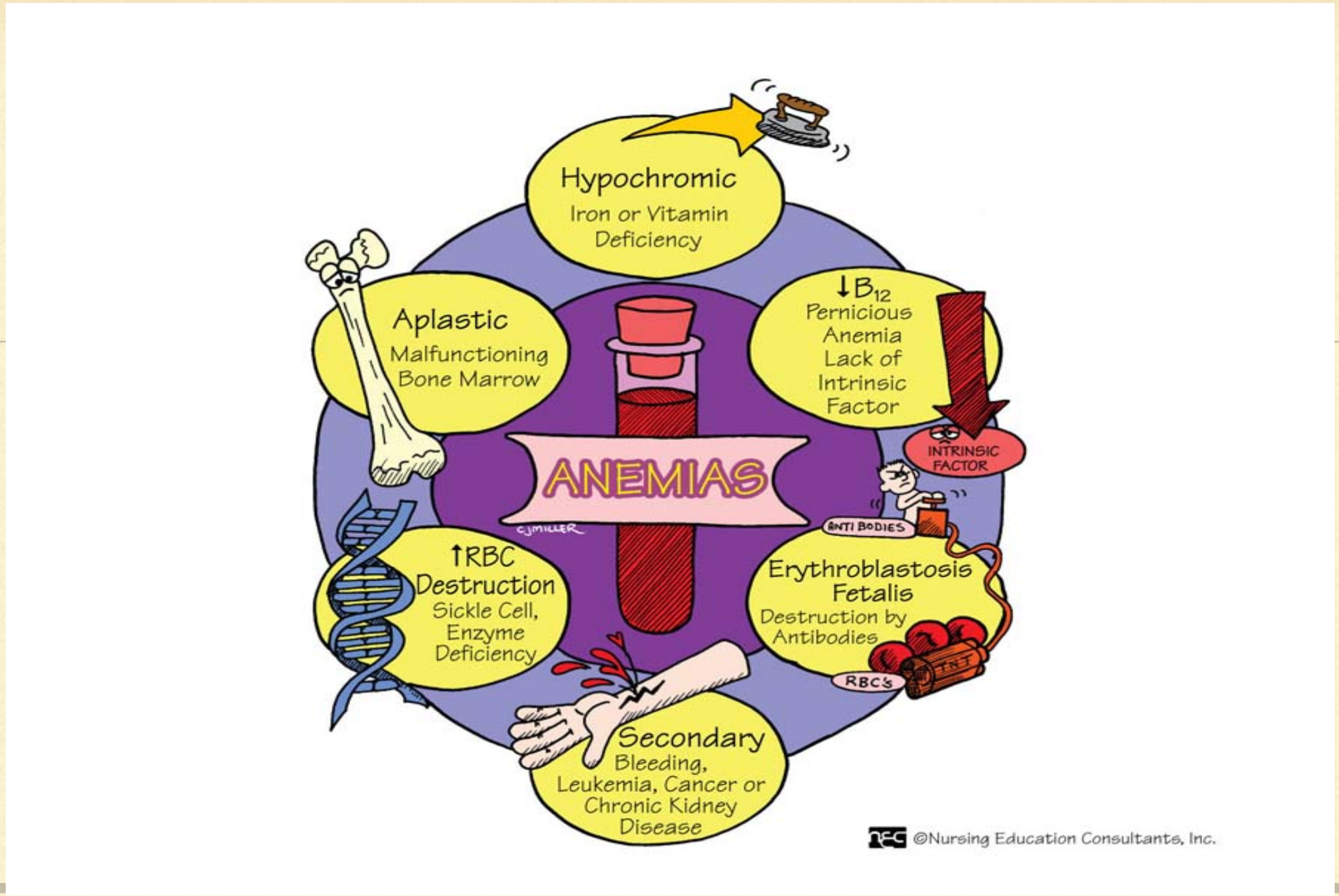
- Contemporary PV therapy is focused on reducing vascular risks and tailored to the thrombotic risk stratification of the patient.
- Patients with low or intermediate risk PV with a high HCT level are treated with **phlebotomies** to reduce the HCT (target: <0.45% for males and <42% for females) **plus low-dose aspirin**, if no contraindications are present.
- Poorly compliant patients or those who manifest progressive myeloproliferation warrant **myelosuppressive therapy. Hydroxyurea** is the primary drug of choice, with anagrelide or peg-interferon-α as alternatives. All of these agents have potential side effects even when used properly. Hydroxyurea is a ribonuceotide reductase inhibitor and is an effective agent in managing PV, but is associated with leukemogenic potential. Radioactive phosphorus (^{32}P) has been used in the past, with a success rate of 80 to 90%; however, its association with an increased incidence of acute leukemic transformation severely restricts its usefulness to patients >75 years of age. The discovery of the *JAK2* gene mutations as the underlying cause of PV has prompted research to develop potential targeted inhibitors; however, to date no new agents or proto- cols have been approved.

Polycythemia Vera.

Oral Health Considerations

- There are no established guidelines addressing the delivery of dental care for the patient with PV. The delivery of routine dental care for the well-controlled patient with PV likely incurs minimal risk. Low-dose aspirin is rarely associated with hemorrhagic complications from dental extractions. **Poorly controlled patients are at an increased risk for both thrombotic and hemorrhagic due to blood hyperviscosity and concurrent qualitative and quantitative platelet alterations.**
- Thus, a medical consultation to determine the current patient status should be obtained and referral is warranted for patients who are poorly controlled or who exhibit signs and symptoms of poor control.

2. Anemia.


Hypochromic
Iron or Vitamin Deficiency
Aplastic
Malfunctioning Bone Marrow
↓B12
Pernicious Anemia
Lack of Intrinsic Factor
INTRINSIC FACTOR
ANEMIAS
C.J.MILLER
ANTI BODIES
↑RBC Destruction
Sickle Cell, Enzyme Deficiency
Erythroblastosis Fetalis
Destruction by Antibodies
RBC's
Secondary
Bleeding, Leukemia, Cancer or Chronic Kidney Disease
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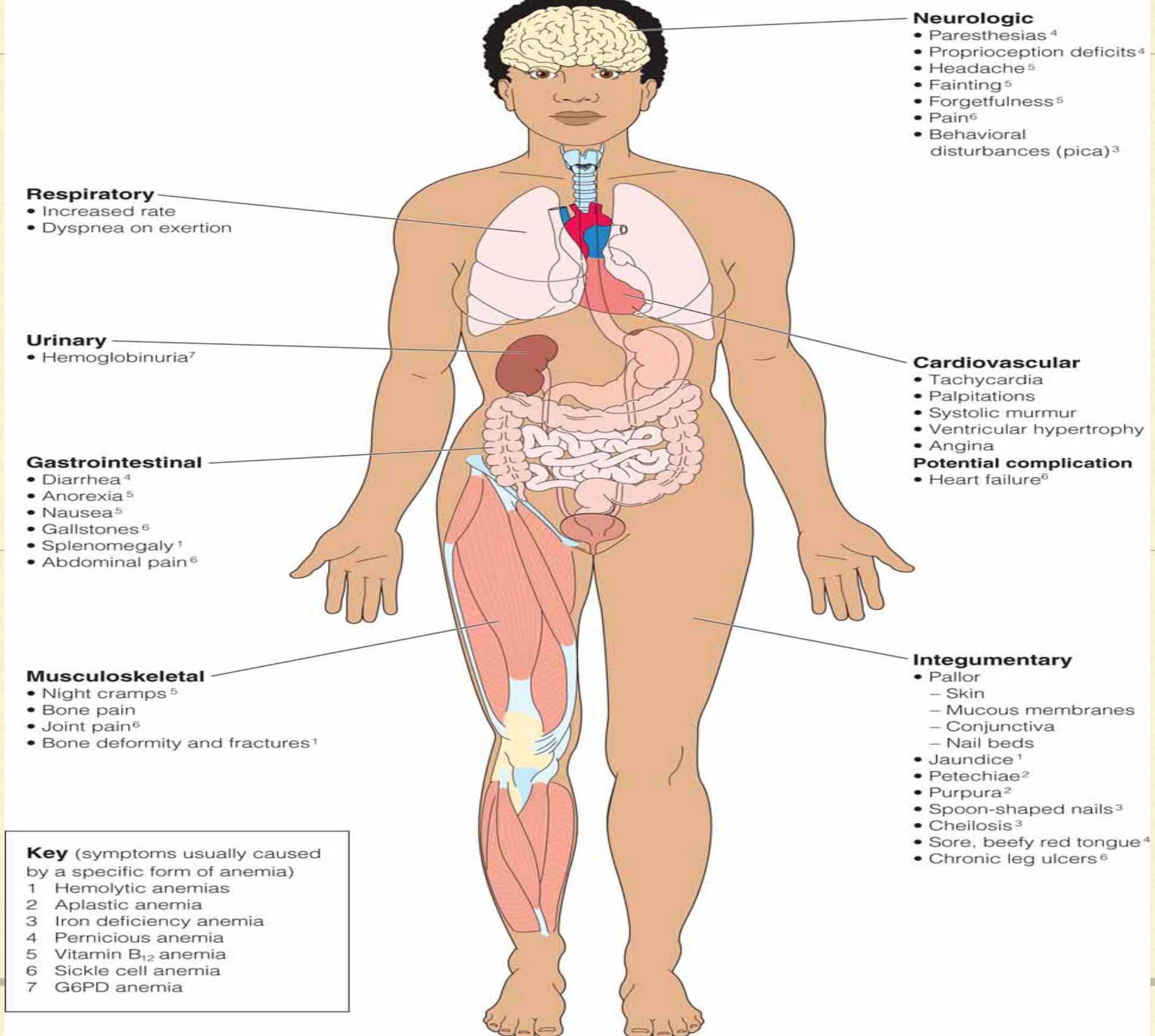
2. Anemia.

- Anemia is a syndrome finding defined as a lower than normal Hb concentration (<13 g/dL for males and <12 g/dL for females).
- The signs and symptoms of anemia occur as a consequence of the **hypoxia** and compensatory physiologic responses produced. Typical symptoms include **fatigue and dizziness. The classic sign of anemia is pallor, which may be observed in the conjunctivae, face, nail beds, tongue, and palmar creases.**
- In the elderly, anemia is associated with decreased physical performance of daily activities, cognitive impairment, depression, diminished quality of life, increased hospital admissions, and impaired survival.
- The initial laboratory tests used to assess suspected anemia are the CBC and the blood smear. The blood smear is used to morphologically characterize the red cells (e.g., macrocytic, normocytic, microcytic, hypocytic).

A. Iron Deficiency Anemia (IDA) and Anemia of Chronic Inflammation (ACI)

- Iron deficiency anemia (IDA) is defined as a reduction in total body iron to an extent that iron stores are fully exhausted and some degree of tissue iron deficiency is present.
- It may occur as a consequence of **low dietary intake, impaired absorption, or excessive iron loss.**
- ACI, also known as anemia of chronic disease, mimics several clinical and laboratory features of IDA and is the second most frequent form of anemia observed in practice.
- Conditions in which ACI is frequently observed include autoimmune diseases, acute and chronic infection, malignancies, and chronic kidney disease. Not surprisingly, ACI is more likely to be encountered in the elderly and inpatients.

- **Clinical and Oral Manifestations**
- The most important clinical symptom of anemia is chronic fatigue. Outward signs may be subtle and include **pallor** of the conjunctivae, lips, and oral mucosa; **brittle nails** with spooning, cracking, and splitting of nail beds; and palmar creases that have traditionally been used by physicians in the diagnosis of anemia.
- Other findings may include palpitations, shortness of breath, numbness and tingling in fingers and toes, and bone pain.


Neurologic
• Paresthesias [4]
• Proprioception deficits [4]
• Headache [5]
• Fainting [5]
• Forgetfulness [5]
• Pain [6]
• Behavioral disturbances (pica) [3]
Respiratory
• Increased rate
• Dyspnea on exertion
Urinary
• Hemoglobinuria [7]
Cardiovascular
• Tachycardia
• Palpitations
• Systolic murmur
• Ventricular hypertrophy
• Angina
Potential complication
• Heart failure [6]
Gastrointestinal
• Diarrhea [4]
• Anorexia [5]
• Nausea [5]
• Gallstones [6]
• Splenomegaly [1]
• Abdominal pain [6]
Musculoskeletal
• Night cramps [5]
• Bone pain
• Joint pain [6]
• Bone deformity and fractures [1]
Integumentary
• Pallor
– Skin
– Mucous membranes
– Conjunctiva
– Nail beds
• Jaundice [1]
• Petechiae [2]
• Purpura [2]
• Spoon-shaped nails [3]
• Cheilosis [3]
• Sore, beefy red tongue [4]
• Chronic leg ulcers [6]
Key (symptoms usually caused by a specific form of anemia)
1 Hemolytic anemias
2 Aplastic anemia
3 Iron deficiency anemia
4 Pernicious anemia
5 Vitamin B_{12} anemia
6 Sickle cell anemia
7 G6PD anemia

- Glossitis and stomatitis are recognized oral manifestations of anemia.
- IDA or ACI should be suspected in every case of glossitis, glossodynia, angular cheilitis, erythematous mucositis, oral candidiasis, recurrent oral ulcers, and burning mouth when no other obvious causes are identified.These findings are believed to be caused by the impaired cellular immunity, deficient bactericidal activity of polymorphonuclear leukocytes, inadequate antibody response, and epithelial abnormalities attributed to iron lack.
- Clinically evident atrophic changes of the tongue, defined by a smooth red tongue appearance, in patients with iron deficiency anemia have been associated with a significant reduction in the mean epithelial thickness of the buccal mucosa as determined histologically.

- Diagnosis
- The finding of a reduced Hb and HCT on the **CBC** is typically the first clue to IDA, which is classically characterized as a **microcytic hypochromic anemia**.
- **Serum ferritin levels <25 mcg/L** are highly suggestive of IDA, while levels >100mcg/L are reflective of good iron stores. For intermediate results, attainment of the serum iron level, total iron-binding, and transferrin saturation is recommended to further refine the diagnosis. When the diagnosis remains ambiguous, further testing to include **BM** may be necessary.
- Discrimination of ACI from IDA is frequently challenging. Serum ferritin levels are increased with chronic inflammatory conditions such as inflammatory bowel disease (IBD), infections, liver disease, malignancies, and chronic liver failure. Indeed a patient with an inflammatory condition such as IBD may manifest both IDA and ACI. However, patients with ACI have normal transferrin receptor levels and high hepcidin levels, while patients with IDA have high transferrin receptor levels and normal or low hepcidin levels.

- **Treatment**
- In addition to treating the underlying cause of the anemia, **iron supplementation** should be provided.
- Oral iron supplementation is safe, cost-effective and convenient. The goal is to raise serum Hb by 1–2 g/dL every 2 weeks, and ultimately restore iron stores in about 3–4 months.
- Ferrous sulfate and ferrous gluconate have good bioavailability and contain 20% and 12% of elemental iron for absorption, respectively. The recommended dose for both is 325mg three times per day. **To maximize absorption, they should be taken with orange juice, since iron is better absorbed in an acidic environment.**
- Foods and medications that inhibit iron absorption include tea, coffee, phosphate-containing carbonated beverages, antacids, proton-pump inhibitors, and H_2-blockers.
- Adverse effects of oral iron therapy are dose related, can adversely affect effect compliance and include nausea, epigastric discomfort, and constipation. For such cases a lower dosage regimen should be attempted.

- When oral iron supplementation is ineffective due to poor patient compliance or intolerance, **intravenous iron therapy** is indicated. Other possible indications for intravenous iron therapy are: high iron requirements due to chronic uncorrectable bleeding or chronic hemodialysis; iron malabsorption secondary to a GI condition; IBD with ineffective erythropoiesis, poor iron absorption, and intolerance to oral iron supplementation; and the need for rapid restitution of iron stores (e.g., preoperative).Intravenous iron products are made up of nanoparticles of iron oxyhydroxide gel in colloidal suspension held within a stabilizing carbohydrate shell.
- Serious and potentially life-threatening hypersensitivity reactions may occur, with the highest risk associated with high molecular weight preparations.

B. Plummer-Vinson Syndrome.

- Plummer-Vinson syndrome, also called **Paterson-Kelly syndrome**, is a rare syndrome characterized by the **classic triad of dysphagia, iron deficiency anemia, and upper esophageal webs or strictures.** It usually affects middle-aged white women in the fourth to seventh decade of life but has also been described in children and adolescents.

- The **dysphagia** may be intermittent or progressive over years, is usually painless and limited to solids, and may be associated with weight loss. Symptoms resulting from anemia (weakness, pallor, fatigue, tachycardia) predominate the clinical picture.Other potential findings include glossitis, glossopyrosis, glossodynia, angular cheilitis, koilonychia, fragility, thinning of nails, and brittle hair.

- Radiologic examination of the pharynx shows the presence of webs. The etiopathogenesis is unknown, but it is postulated that iron deficiency adversely affects iron dependent enzymes in the epithelium of the upper GI tract increasing free radical stress, DNA damage, and malignant transformation.

- Plummer-Vinson syndrome can often be treated effectively with **iron supplementation.** In cases of significant obstruction of the esophageal lumen by esophageal webs/ strictures with persistent dysphagia despite iron supplementation, rupture and **mechanical dilation of the web** may be required.
- Since Plummer-Vinson syndrome is associated with an increased risk of squamous cell carcinoma of the pharynx and the esophagus, the patients should be monitored closely.

Oral Health Considerations

- For dental patients with extremely low Hb levels, physician consultation prior to surgical treatment is recommended.
- **Routine care should be deferred in those patients whose Hb is <11 g/dL or those who manifest signs and symptoms such as shortness of breath, abnormal heart rate, or oxygen saturation less than 91% (as determined by pulse oximetry) until their health status improves.**
- Narcotic use should be limited for those with severe anemia, and dentists should be aware that **anemia places a patient at increased risk for ischemic heart disease.**

C. Macrocytosis.

- The term macrocytosis refers to a blood condition in which **RBCs are larger than normal and is reported in terms of mean corpuscular volume (MCV).**
- MCV, the average volume of RBCs, is calculated as HCT × 1,000 divided by RBC (millions/μL). Normal MCV values range from 80 to 100 femtoliters depending on gender, age, and reference laboratory.
- Macrocytosis is identified by reviewing peripheral blood smears and/or by automated RBC indices and is diagnosed when the MCV is >100 fL. It is a relatively common finding with a reported incidence ranging from 1.7% to 3.6%.·
- There are numerous causes, and approximately 60% of cases are not associated with anemia. Potential causes include **alcoholism, B_{12} and folate deficiency, hemolysis or hemorrhage, hypothyroidism, liver dysfunction, and myelodysplasia.**
- **Medications** that interfere with nucleic acid metabolism such as hydroxyurea, trimethoprim/ sulfameth- oxazole, methotrexate, metformin, zidovudine, stavudine, lamivudine, valproic acid, and phenytoin may result in macrocytosis. Measures to address the underlying cause often results in normalization of the MCV.

D. B_{12} and Folate Deficiency Anemia

- Vitamin B are common causes of **macrocytic anemia.**
- Both vitamins participate in critical enzyme reactions **necessary for proper DNA synthesis.** From hematological perspective, lack of either vitamin results in an essentially identical megaloblastic anemia. These vitamins are also essential for proper neurological development.
- The underlying cause of either anemia may entail conditions of **decreased intake, impaired absorption, and/or increased requirements.** The predominant causes of folate deficiency involve scenarios of inadequate intake, such as may occur in malnutrition and alcoholism. The increased physiologic folate requirement associated with pregnancy, lactation, and conditions of chronic hemolysis or hemorrhage may lead to an anemic state.

D. B_{12} and Folate Deficiency Anemia

- Vitamin B deficiency occurs frequently (>20%) among the elderly, but it is often unrecognized because the clinical manifestations are subtle and many patients will not progress to severe deficiency.
- Most of these cases are believed to be caused by conditions that impair, but do not totally eliminate B_{12} absorption for the diet and include atrophic gastritis, gluten-induced enteropathy, and the use of proton-pump inhibitors.
- **Pernicious anemia is an autoimmune disease defined by autoantibodies directed against intrinsic factor (a substance needed to absorb vitamin B_{12} from the gastrointestinal tract) and gastric parietal cells.**
- Severe B_{12} deficiency develops when physiologic absorption is totally negated, such as may occur with pernicious anemia, total gastrectomy, or ileal resection.

Clinical and Oral Manifestations

- The typical nonspecific symptoms of IDA or ACI such as **fatigue, decreased mental concentration, and weakness** are characteristic of folate or B12 deficiency. B12 deficiency may present as neurological symptoms such as clumsiness, unsteady gait, and **paresthesia**. Prolonged severe B12 deficiency, as may be seen in pernicious anemia, may lead to demyelination of the dorsal columns of the spinal cord, resulting in more advanced signs and symptoms such as peripheral neuropathy and ataxia. Unfortunately, these advanced signs and symptoms are often not reversed with replacement therapy.
- Oral signs of folate and B12 deficiency are similar to those observed with IDA or ACI and include a **beefy red tongue with smooth or patchy areas of erythema.** Symptom complaints include soreness or a **burning sensation** affecting the tongue, lips, buccal mucosa, and other mucosal sites. **Paresthesia and taste alterations** have been reported.

Diagnosis

The diagnostic process begins by establishing the presence of vitamin B_{12} or folate deficiency and then determining the cause of deficiency. The primary laboratory investigations include a **CBC**, peripheral blood smear, **serum vitamin B_{12} assay**, and RBC and **serum folate assays**.

A single serum measurement of folate levels is insufficient to discriminate between a transient drop and true deficiency.

The measurement of RBC folate levels provides a good indication of folate levels over time, but the test is complex and not widely available. Two surrogate tests to assess folate and B_{12} levels are the homocysteine and methylmalonic acid levels. Both folate and B_{12} are necessary for the normal metabolic disposal of homocysteine, while only B_{12} is necessary for the metabolic disposal of methylmalonic acid. As such, folate deficiency is unlikely if the homocysteine levels are normal.

The diagnosis of vitamin B_{12} deficiency is complex. Serum levels of B_{12} <100 pg/mL likely indicate true deficiency. B_{12} levels of 100–400 pg/mL are considered equivocal and should be followed by measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B_{12} deficiency. The diagnosis of pernicious anemia requires demonstration of atrophic body gastritis and intrinsic factor deficiency.

Use of the Schilling test (which measures cyanocobalamin absorption by increasing urine radioactivity after an oral dose of radioactive cyanocobalamin) for detection of pernicious anemia has been supplanted for most part by serologic testing for parietal cell and intrinsic factor antibodies.

Treatment

Treatment strategies for folate or B 12 is dictated by the **underlying cause**. Fortunately the routine fortification of foods with folate has greatly reduced the occurrence of deficiency in most populations. However, prescribed folate supplementation may still be necessary in scenarios of alcoholism and malnutrition. Previously ingrained protocols entailing intramuscular B_{12} injections to manage deficiency have been largely supplanted by more convenient oral supplementation regimens. A recent evidence-based review of two studies suggests the oral administration of between 1000 μg–2000 μg of B_{12} initially daily and then weekly effectively raised serum B_{12} levels. Even when intrinsic factor is not present to aid in the absorption of vitamin B_{12}, as in pernicious anemia or in other diseases that affect the usual absorption sites in the terminal ileum, oral therapy was still effective.

E. Hemolysis

- The normal RBC life span is 110 to 120 days in the circulation.
- Hemolytic diseases result in anemia if the bone marrow is not able to replenish adequately the prematurely destroyed RBCs.
- The hemolytic anemias are classified as either inherited or acquired.
- **Inherited** forms include sickle cell anemia, thalassemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- **Acquired** forms are immune hemolytic anemia, mechanical hemolytic anemia, paroxysmal nocturnal hemoglobinuria, and exposure to certain infections, toxins, or snake venom.

- With acute hemolytic disease, the signs and symptoms depend on the mechanism that leads to red cell destruction.
- **The release of free Hb occurring in intravascular hemolysis may present as acute flank pain, free Hb in the plasma and urine, and renal failure.**
- In patients with chronic or progressive anemia, symptoms depend on the patients' age and adequacy of blood supply to critical organs. With moderate anemia, symptoms may include fatigue, loss of stamina, breathlessness, tachycardia, and, less commonly, jaundice and hemoglobinuria. Physical findings include jaundice of skin and mucosae, splenomegaly, and other findings associated with specific hemolytic anemia.

- A careful history and physical examination provide important clues to the diagnosis of hemolytic anemia. Once a patient presents with clinical signs and symptoms of anemia, laboratory testing should be supported by a complete drug and toxin exposure history and the family history.
- Laboratory tests in the patient with anemia may be ordered initially to demonstrate the presence of hemolysis and define its cause. **An elevated reticulocyte count is the most useful indicator of hemolysis**, reflecting erythroid **hyperplasia of the bone marrow**. Assessment of RBC morphology, findings on the peripheral blood smear, and, rarely, BM may provide additional clues to support the specific diagnosis.
- Oral signs indicating possible hemolytic anemia may include pallor or jaundice of oral mucosa, paresthesia of mucosa, and, for those with chronic conditions, hyperplastic marrow spaces in the mandible, maxilla, and facial bones.

I. Paroxysmal Nocturnal Hemoglobinuria.

- PNH is a rare acquired condition characterized by bone marrow failure, hemolytic anemia, thrombosis, and smooth muscle dystonia.
- Intravascular hemolysis leads to **release of free Hb**, a potent scavenger of **nitric oxide**. The subsequent lack of tissue nitric oxide is believed to underlie many of the clinical manifestations of PNH, including fatigue, pain, esophageal spasm, erectile dysfunction, and, possibly platelet activation.
- Patients with classic PNH are at an increased risk for thrombosis and other complications of intravascular hemolysis. Without therapy the median survival rate is 10 to 20 years.
- Allogeneic bone marrow transplantation is the only curative therapy available for PNH,

II. Glucose-6-Phosphate Dehydrogenase Deficiency.

- G6PD deficiency is inherited as an X-linked hemolytic anemia caused by mutations in the *G6PD* gene.
- G6PD deficiency is the most common enzyme deficiency affect mainly men.
- The *G6PD* enzyme acts via the hexose monophosphate shunt to catalyze the oxidation of glucose-6-phosphate to 6-phosphogluconate while concomitantly reducing the oxidized form of nicotinamide adenine dinucleotide phosphate (NADP+) to nicotinamide adenine dinucleotide phosphate (NADPH). NADPH, **a required cofactor in many biosynthetic** reactions, maintains glutathione in its reduced form. Reduced glutathione acts as a scavenger for dangerous oxidative metabolites in the cell. While other cells may produce NADPH via alternate pathways, the **RBC relies exclusively on G6PD activity.**
- Hemolysis typically occurs when the RBCs undergo excessive oxidative stress, usually due to an external trigger such as **drug exposure**, **fava bean** **ingestion, or infection.** Other potential triggering factors include diabetes, myocardial infarction, and strenuous exercise

Clinical Manifestations

- The vast majority of individuals with G6PD deficiency remain clinically asymptomatic throughout their lives. If hemolysis occurs in an affected patient, characteristic signs and symptoms of fatigue, flank pain, anemia, and jaundice are evident.
- About one-third of male newborns who manifest **neonatal jaundice** within the first 1–4 days of age are G6PD deficient. The icterus of neonatal jaundice is not due to hemolysis, but the inability of the liver to adequately conjugate bilirubin.
- **Infection** is likely the most common trigger of hemolysis in at-risk patients. Common infectious triggers include Salmonella, *Escherichia coli*, β-hemolytic streptococci, rickettsia infections, hepatitis A and B, pneumonia, cytomegalovirus, and typhoid fever. While the mechanism triggering hemolysis is unknown, it is postulated that leukocytes release oxidative stressors during phagocytosis.
- **Ingestion of fava beans** is a recognized trigger. Toxic components of the bean are postulated to activate the hexose monophosphate shunt and promote hemolysis. Fava bean-related hemolysis occurs within the first 24 hours of ingestion, is usually severe, and often leads to acute renal failure.
- **Drug**-induced hemolysis typically occurs within 24 to 72 hours of exposure and dark urine due to hemoglobinuria is characteristic. The anemia progresses for about a week, followed by recovery over the next 8 to 10 days.

- **Treatment**
- Most cases of acute hemolysis are usually short-lived and resolve without complication. Severe cases of hemolysis may require **transfusion** and possibly hemodialysis due to acute renal failure.
- Neonatal jaundice is usually treated with **phototherapy** and, when severe, with exchange blood transfusion. Once the diagnosis of G6PD deficiency is established, measures to reduce exposure to oxidative stressors are warranted.
- Infections should be promptly treated and immunizations kept up-to-date. Patients susceptible to **fava bean**-induced hemolysis should **avoid ingestion.**
- Drug-induced hemolysis has been attributed to several medications. However, the validity of this association with many drugs has been questioned. It is likely that many drugs previously cited as causing hemolysis were in fact administered to patients suffering from an infection-induced hemolytic episode.
- Seven drugs clearly associated with drug-induce hemolysis: **dapsone, methylene blue, nitrofurantoin, phenazopyridine primaquine, and toluidine blue.**

III. Hemoglobinopathies.

- Hb is made up of **heme** (the iron-containing portion of Hb) and **globin** (amino acid chains that form a protein). Normal Hb types include adult **Hb A** (HbA; about 95%–98%), HbA contains two α chains and two β chains, **HbA2** (2%–3%) has two α and two δ chains, and fetal Hb (HbF; up to 2%) has two α and two γ chains. **HbF** is the primary Hb produced by the fetus during gestation. Its production usually falls to a low level shortly after birth.
- Hemoglobinopathies occur when point mutations in the globin genes cause changes in the amino acids that make up the globin protein, resulting in abnormal forms of Hb. **The structure of the Hb may be abnormal in its behaviour, production rate, and/or stability.** Several hundred Hb variants have been documented; however, only a few are common and clinically significant.
- The majority of these are b chain variants that are inherited in an autosomal recessive fashion. Because a person inherits one copy of each β-globin gene from each parent, if one normal β gene and one abnormal β gene are inherited, the person is said to be a carrier or heterozygous for the abnormal Hb. The abnormal gene can be passed on to any offspring but does not cause symptoms or disease in the carrier. If two abnormal β genes of the same type are inherited, the person is considered to have the disease and is homozygous for the abnormal Hb. A copy of the abnormal β gene will be passed on to any offspring. If two abnormal genes of different types are inherited, the person is doubly or compound heterozygous and one of the abnormal β genes will be passed on to each offspring.

VI. Sickle Cell Disease.

- Sickle cell disease (SCD), formerly known as sickle cell anemia.
- SCD occurs as a consequence of a Hb gene mutation, leading to a glutamic acid-to-valine substitution in the sixth position on the β-hemoglobin chain.
- Under normal physiologic conditions, the altered Hb (HbS) polymerizes resulting in the formation of distorted rigid sickle cells.
- **Sickle cells are prone to hemolysis and lose their ability to effectively transport oxygen to the microcirculation which in turn leads to end organ ischemia and necrosis.**
- While vasocclusive events clinically characterize SCD, the etiopathogenesis of SCD is far more complex and involves ongoing hemolysis; increased RBC dehydration and adherence to endothelium; vascular instability due to nitric oxide deficiency; proinflammatory events; and activation of the complement cascade.
- HbF acts to retard sickling and is considered to be a major modulator of SCD activity and patients with higher levels of HbF tend to experience milder disease.

SICKLE CELL ANEMIA CRISIS

(Inherited Red Blood Cell Disorder)

Vasoocclusive Crisis

- Pain
  - Acute Abdominal
  - Hand/Foot Syndrome
- Splenomegaly
  - Congested with Blood
  - Infarction
- Hemolytic Crisis
  - Anemia, Jaundice
- Stroke (Cerebral Infarction)
- Kidney - Ischemia

Obstruction of Vessels
by Clumped Sickled Cells

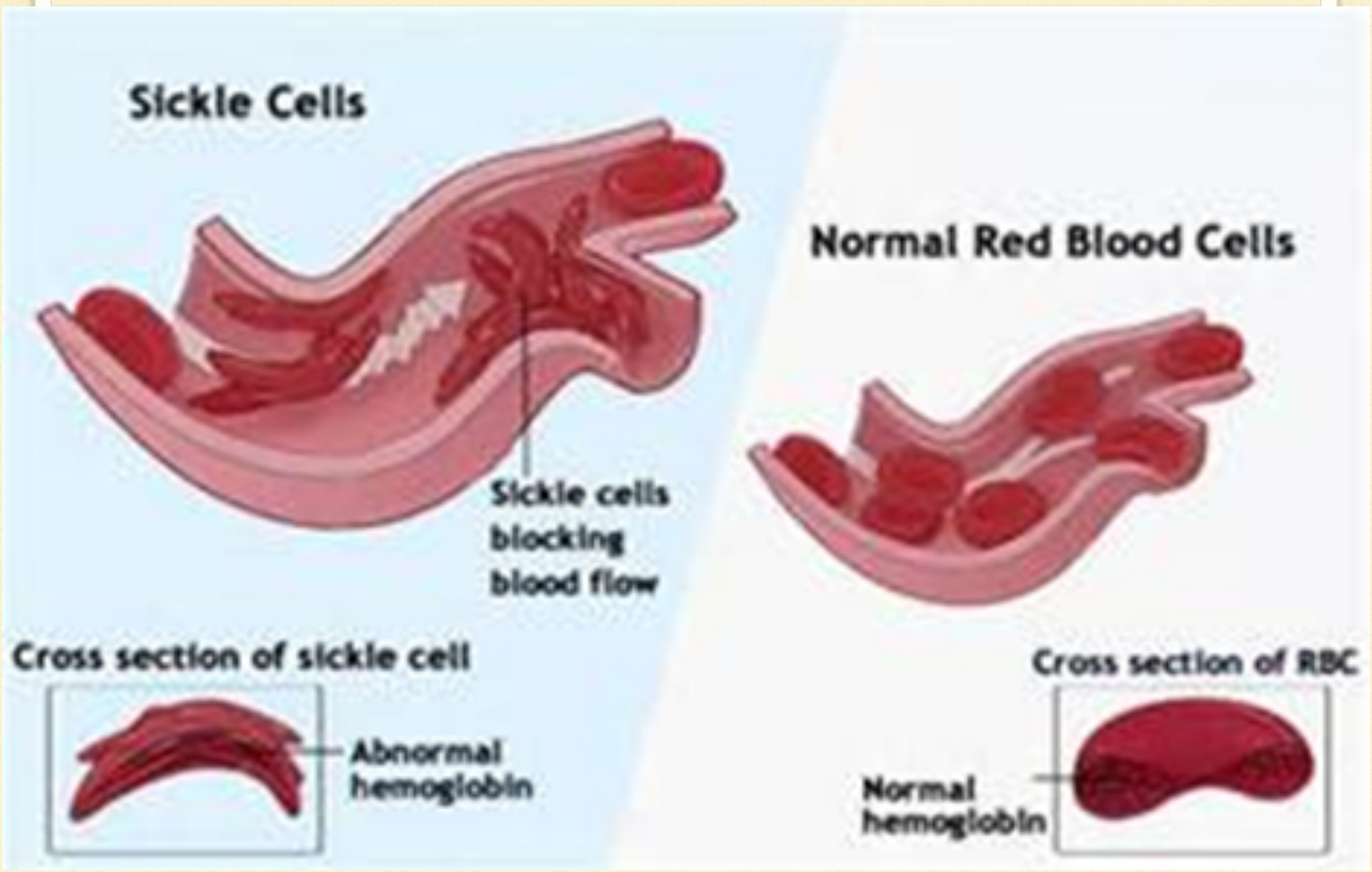
RBC Destruction
Acute Chest Pain
Fever
Cough
↑ Respiratory Rate
Hypoxia

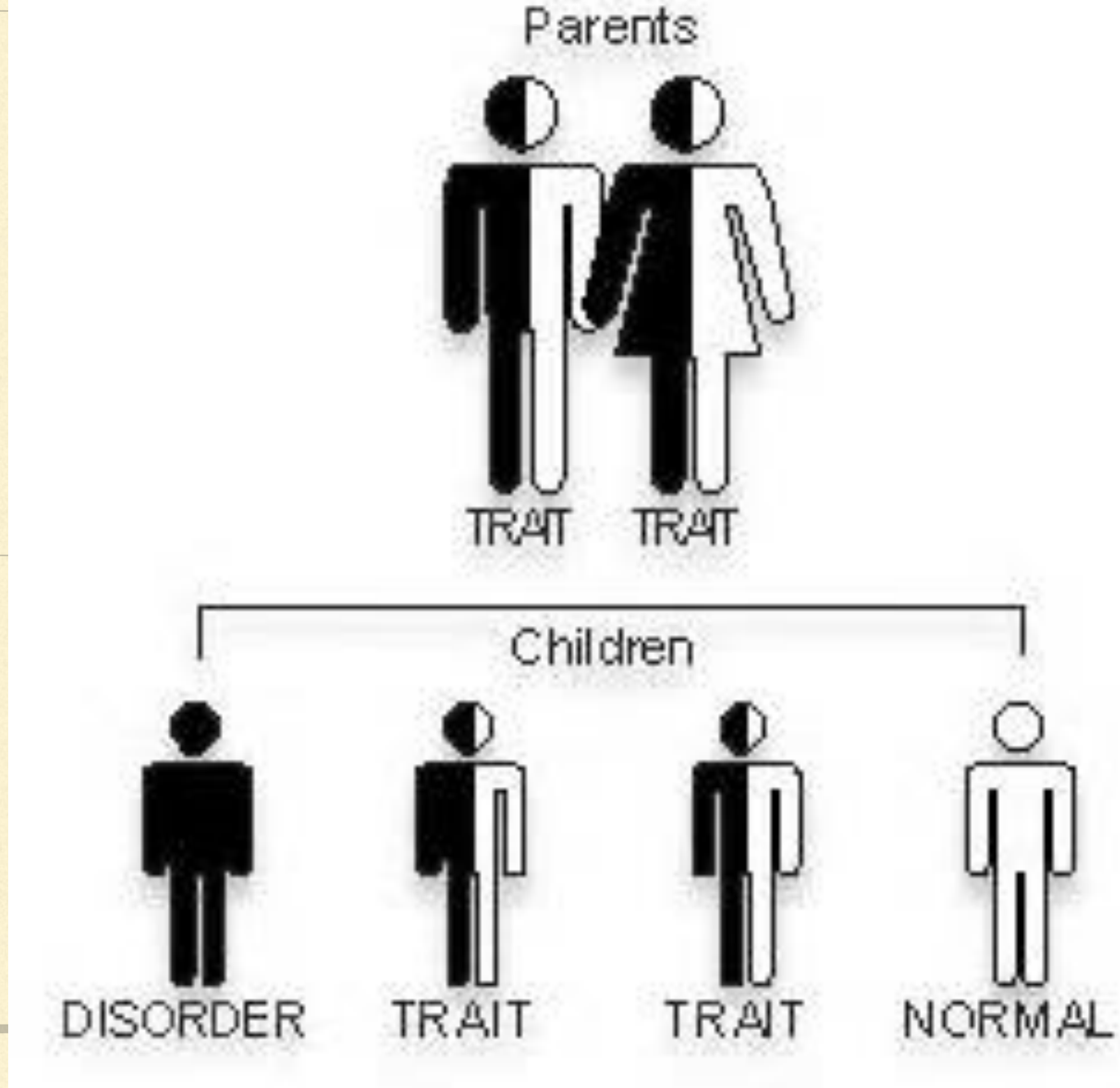
HOP -

Hydration and Electrolytes

Oxygen - Bed Rest to ↓ O_2 needs

Pain Relief


Sickle Cells
Sickle cells blocking blood flow
Normal Red Blood Cells
Cross section of sickle cell
Abnormal hemoglobin
Cross section of RBC
Normal hemoglobin


Parents
TRAIT
TRAIT
Children
DISORDER
TRAIT
TRAIT
NORMAL

D. Sickle Cell Disease.

- Endothelial activation, induced directly or indirectly by the proinflammatory behaviour of sickle erythrocytes, is the most likely initiating step toward vaso-occlusion.
- Stressors that can lead to vasoocclusion typically include viral and bacterial infection, hypoxia, dehydration, iron overload, and cell and fluid phase–related causes. Microvascular occlusion arises predominantly in localized areas of marrow, leading to necrosis. Inflammatory mediators activate nociceptive afferent nerve fibers, evoking the pain response. Commonly affected areas are the long bones, ribs, sternum, spine, and pelvis, often with multiple-site involvement.

Clinical and Oral Manifestations

- Target organ manifestations of SCD are wide-ranging and vary from acute to chronic, symptomatic to asymptomatic, and episodic to progressive. Acute complications of SCD include acute chest syndrome, aplastic crisis, fever/sepsis, osteomyelitis, pain, priapism, splenic sequestration, and stroke.
- Chronic conditions of SCD include asthma, avascular necrosis, gall bladder disease, hepatic dysfunction, leg ulcers, nephropathy, pulmonary hypertension, and silent infarcts.
- **Pain is characteristic of SCD and the most common reason for hospitalization.**
- Laboratory findings include elevated reticulocytes, lactate dehydrogenase, and C-reactive protein. The resolving phase occurs when the pain intensity is decreased, usually as a result of appropriate care.
- Acute chest syndrome is the leading cause of death in young adults with SCD. It can be defined as a *new* infiltrate in at least one segment of the lung, along with fever and respiratory symptoms.
- The impaired immune function associated with SCD places children at risk of developing life-Patients with SCD are at a greater risk of osteomyelitis than controls, and the most frequently implicated pathogenic agents are *Salmonella* and *Staphylococcal aureus*.

Clinical and Oral Manifestations

Numerous nonpathognomonic oral findings have been described in SCD and include mucosal pallor, delayed eruption, discolored and depapillated tongue,and increased periodontitis.

Vasoocclusive events affecting the oral cavity have been reported to cause pain, paresthesia, or swelling.

Oral Health Considerations

- Measures to reduce oral disease burden and infection in patients with SCD are clearly indicated.
- Long-term penicillin prophylaxis in children with SCD under age 6 years inhibits acquisition of mutans streptococci, resulting in significantly lower caries rates in these children.
- Cases of periodontal infections and mandibular osteomyelitis precipitating a sickle cell crisis have been reported.
- Given the wide variability in disease severity, it is essential a comprehensive history and medical consultation be obtained to determine the patient's status.
- During noncrisis periods, there are no contraindications concerning the delivery of routine dental care under local anesthesia with inhalational sedation.
- The avoidance of using a local anesthetic agent **without a vasoconstrictor** is unwarranted.
- The need for providing **antibiotic prophylaxis** before rendering dental care is controversial and there exists no clear consensus or guidance.Amoxicillin was the most commonly chosen antibiotic, and the perceived risk of infectious complication was highest for extractions, followed by restorative treatment and tooth polishing.
- Pain management may be challenging and usually consists of anti-inflammatory agents, opioid/nonopioid analgesics, and proper hydration.
- For patients deemed at moderate or high risk, dental therapy should be rendered in a **hospital** setting where appropriate medical support is readily available.

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V. Thalassemias

- The thalassemias are a group of **inherited autosomal recessive disorders** of Hb synthesis characterized by a disturbance of either alpha (α) or beta (β) Hb chain production. Worldwide, an estimated 1.7% of the population has α- or β-thalassemia trait (they carry only one β gene affected or one to two α genes affected).
- Alpha Hb production is controlled by two genes on each chromosome. In α-thalassemia there is insufficient synthesis of α globin chains, resulting in excess β-like globin chains which form γ4 tetramers, termed Hb Bart's (in fetal blood) and β4 tetramers, termed HbH (in adult blood).
- Mutations affecting one or two genes result in a trait status. Mutations affecting three of the four genes result in significant production of HbH and mild to moderate anemia called HbH disease. Mutations affecting all four genes result in significant production of Hb Bart's in the fetus and the typically fatal hydrops fetalis syndrome.
- Beta hemoglobin production is controlled by one gene on each chromosome. In β-thalassemia insufficient β-globin synthesis, results in excess α Hb production. One gene defects result in β-thalassemia trait manifesting microcytosis and mild anemia. A variety of two gene defects may occur, resulting in either the β-thalassemia intermedia form or the more severe major form (aka Cooley's anemia). As β Hb synthesis is only activated after birth, the signs and symptoms of β-thalassemia usually do not develop until six months of age

Thalassemia

Definition:
a blood disorder passed down through families (inherited) in which the body makes an abnormal form of hemoglobin, the protein in red blood cells that carries oxygen

Formal Names:
Mediterranean anemia; Cooley's anemia; Beta thalassemia; Alpha thalassemia

This disease is inhereited

Starts from birth, you can get tested for it.

Affects the Bone Marrow

Treatment involves blood transfusions that must be given every 4 to 6 weeks to sustain life.

Can be acute or chronic, depends whether it's major or minor

Clinical and Oral Manifestations

Clinical signs and symptoms of thalassemia are dependent on the severity of the disease and range from none to life threatening. Apart from mild to moderate microcytic hypochromic anemia (detected on a routine blood count), patients with α-thalassemia trait are asymptomatic. Patients with HbH typically manifest anemia and splenomegaly, with possible jaundice, growth retardation in children, infections, leg ulcers, gall stones, folic acid deficiency, and drug-induced hemolysis. Infants with the Hb Bart's hydrops fetalis syndrome almost always either die in utero (23–38 weeks) or shortly after birth.

Patients with β-thalassemia trait are usually asymptomatic but may have mild anemia. Cooley's anemia patients develop signs and symptoms between 6 and 24 months to include failure to thrive, pallor, weakness, jaundice, protruding abdomen with enlarged spleen and liver, dark urine, abnormal facial bones, and growth retardation. Compensatory hypertrophy of erythroid marrow with extramedullary erythropoiesis may result in deformities of the long bones and typical craniofacial changes (see below). Patients with β-thalassemia intermedia manifest variable signs and symptoms of anemia that are milder than and occur later than those observed in Cooley's anemia. However, patients with β-thalassemia intermedia are prone to experience **thrombotic events,** especially if splenectomized. Such events include deep vein thrombosis, stroke, portal vein thrombosis,+ and pulmonary embolism.

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Clinical and Oral Manifestations

Significant oral manifestations related to thalassemia appear to occur more frequently in patients with β-thalassemia and are reflective of the underlying extramedullary erythropoiesis observed in the more severe phenotypes. Characteristic craniofacial deformities include a Class II skeletal base relationship with a short mandible, a reduced posterior facial height, increased anterior facial proportions, and *chipmunk facies*.Other reported potential findings include spiky-shaped and short roots, taurodontism, attenuated lamina dura, enlarged bone marrow spaces, small maxillary sinuses, absence of inferior alveolar canal, and thin cortex of the mandible.[103] Dental arch morphologic changes include a narrower maxilla and smaller incisor widths for the maxillary and mandibular arches. Consistent with general growth retardation, the dental development of 31 of 39 patients with Cooley's anemia was delayed by a mean of 1.11 years and 0.81 years for boys and girls, respectively.

Patients with thalassemia appear to experience similar rates of gingivitis and periodontitis as healthy controls. An increased caries risk has been reported, which may be attributable to such factors as disease-induced immunological dysfunction, decreased access to care, and insufficient patient oral hygiene.While the parotid salivary flow rates in patients with Cooley's anemia are similar to controls, quantitative changes consisting of reduced levels of phosphorus, IgA, and urea have been reported. Increased oral cavity levels of *Streptococcus mutans* and Candida have also been reported.

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Oral Health Considerations

There are no contraindications for providing routine dental care for thalassemia patients under proper medical management. Splenectomized patients are more susceptible to developing postsplenectomy sepsis from encapsulated bacteria (e.g., *Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis*).

Prevention of postsplenectomy sepsis includes immunization against the above mentioned bacteria, antibiotic prophylaxis, and early antibiotic treatment for fever and malaise. As such, consideration to provide antimicrobial prophylaxis (American Heart Association (AHA) regimen) for manipulative dental care is recom- mended by some authorities. Patients with β-thalassemia intermedia may be on an antithrombotic.

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TYPE OF ANEMIA	INTERDISCIPLINARY CARE
Iron-deficiency anemia	■ Increased dietary intake of iron-rich foods ■ Oral or parenteral iron supplements
Vitamin B_{12} deficiency anemia	■ Increase dietary intake of foods containing vitamin B_{12} (e.g., meats, eggs, and dairy products) ■ Oral or parenteral vitamin B_{12} supplements ■ Parenteral vitamin B_{12} for deficency due to malabsorption or lack of intrinsic factor
Folic acid deficiency anemia	■ Increased dietary intake of foods rich in folic acid (folate) ■ Oral folic acid supplements ■ Folic acid supplements recommended for women who are pregnant or may become pregnant to prevent neural tube defects

Sickle cell anemia	■ Treatment is primarily supportive
	■ Hydroxyurea 10–30 mg/kg per day
	■ Sickle cell crisis:
	  ■ Rest
	  ■ Oxygen therapy to maintain SAO_2
	  ■ Narcotic analgesia
	  ■ Vigorous hydration
	  ■ Treatment of precipitating factors
	■ Acute chest syndrome:
	  ■ Careful hydration; hemodynamic monitoring
	  ■ Oxygen therapy
	  ■ Transfusion
	■ Folic acid supplements
	■ Blood transfusions during surgery or pregnancy as necessary
	■ Genetic counseling recommended

Thalassemia	■ Regular blood transfusions ■ Folic acid supplements ■ Possible splenectomy ■ Genetic counseling
Aplastic anemia	■ Withdrawal of the causative agent, if known ■ Blood transfusions ■ Bone marrow transplant as indicated

Best wishes