Hemoglobinopathies

Hemoglobinopathies: Pathophysiology

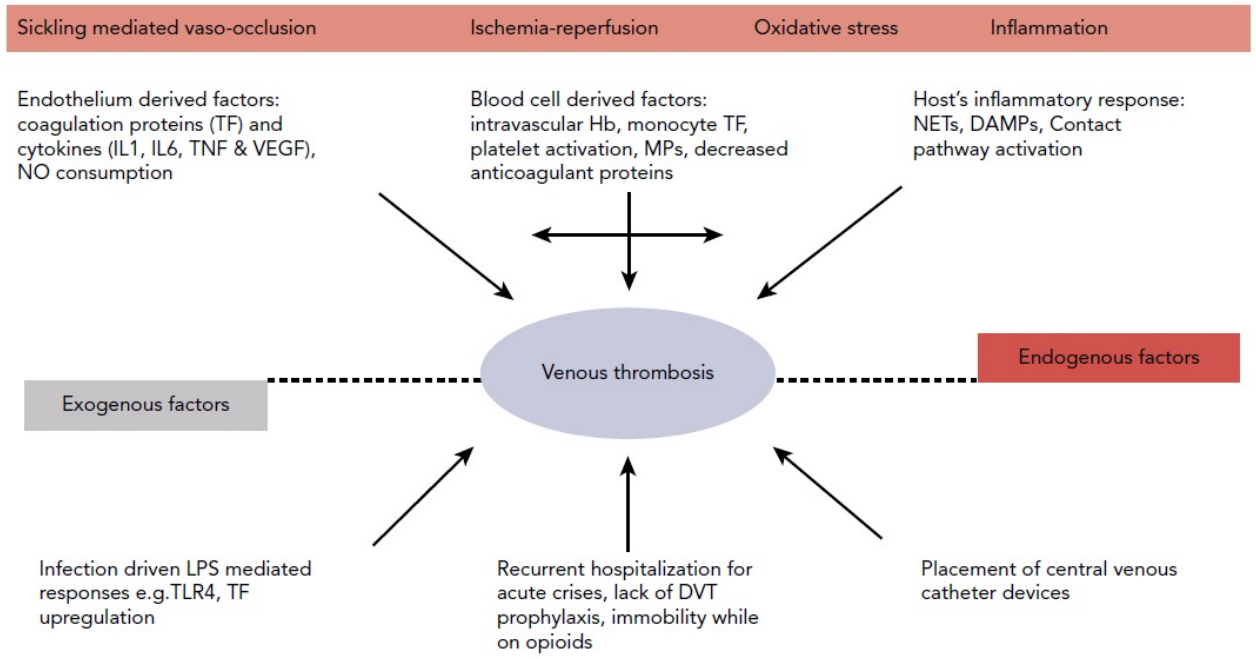
- The inherited disorders of hemoglobin (Hb) production are the most common human monogenic disorders affecting the adult β globin gene (HBB)
  - An estimated 7% of the world's population carries a mutation for a monogenetic disorder of hemoglobin
    - 250 000 individuals born each year with clinically significant sickle cell disease
    - 300 000 born each year with thalassemia
- β globin is encoded by a structural gene found in a cluster with the other β-like genes on chromosome 11 (11p 15.15)
  - Each expressed at distinct stages of development through a process referred to as hemoglobin switching (embryonic → fetal → adult)
- β thalassemia and sickle cell disease (SCD) are the most clinically significant inherited disorders of hemoglobin (Hb) production
  - Sickle Cell Disease
    - A homozygous hemoglobin [Hb] SS, or compound heterozygous HbS/b-thalassemia or HbS/HbC is the most common inherited blood disorder in the United States
    - Characterized by abnormal polymerization of Hb tetramers upon deoxygenation resulting in acute and chronic end-organ damage
  - Sickle Cell Trait (SCT)
    - Heterozygous form HbAS
    - Sickle cell hemoglobin C disease, hemoglobin S/beta thalassemia (Sβthal) have a milder course compared with HbSS
    - SCT is highest in Africans and is seen mostly in people of African descent in other parts of the world
  - β thalassemia
    - Results from a relative excess of a chains due to reduced production of β globin chains and, in some instances, increased dosage of a globin

Sickle Cell Disease (SCD): Signs and Symptoms

- **Sickle cell crisis**
  - Intermittent painful episodes
  - Hemolytic anemia
  - Vascular inflammation
  - Vaso-occlusion

Eventual end organ damage

- **Hypercoagulability** due to activation of prothrombotic factors or decreased antithrombotic proteins
  - Cerebrovascular disease: strokes, transient ischemic attacks, thromboembolic events
- **Cardiopulmonary disease**
- **Renal disease**
  - Hyposthenuria, proteinuria, episodic hematuria and papillary necrosis, renal tubular disorders, glomerulonephropathy, acute renal injury segmental glomerulosclerosis, chronic kidney disease, and chronic renal failure
- Sickle hepatopathy
- Bone infarcts and eventual osteonecrosis
- Sickle retinopathy



DAMP, damage-associated molecular pattern; IL, interleukin; LPS, lipopolysaccharide; MP, microparticle; NET, neutrophil extracellular trap; TF, tissue factor; TLR, Toll-like receptor; TNF, tumor necrosis factor a; VEGF, vascular endothelial growth factor.

Shet AS, et al. *Blood*. 2018;132(17):1761-1769; Thein SL, et al. *Blood*. 2018;132(17):1750-1760.

Sickle Cell Disease (SCD): Cardiopulmonary Disease

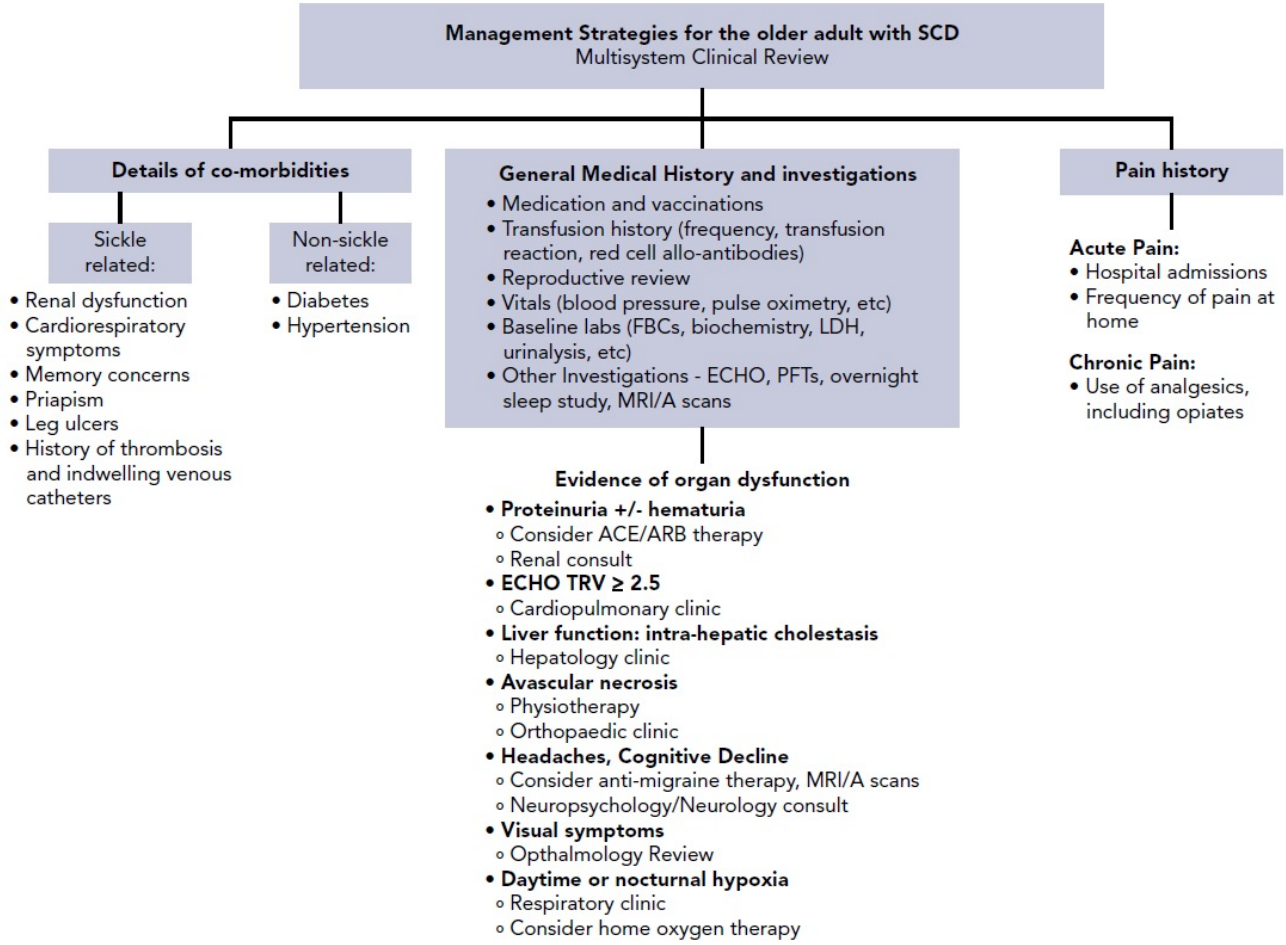
- Asthma
- Acute chest syndrome (ACS)
  - Acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest x-ray
  - Severe hypoxia is useful predictor of severity and outcome
  - Signs and symptoms in adults
    - Fever
    - Cough
    - Chest pain
    - Dyspnea
    - Tachypnea
    - Wheezing
    - Skeletal pain
    - Hypoxia
    - Hemoptysis
- Pulmonary hypertension
- Left ventricular hypertrophy

Diagnostics

- Chest radiograph
- Full blood count
- Complete metabolic panel
- Blood group and screen (or crossmatch)
- Blood cultures
- ABG measurement on room air in adults (if SpO2 ≤ 94% on room air). This should not be done on room air if patient is in obvious respiratory distress or if SpO2 saturations fall to < 85% if oxygen is stopped briefly.
- Serology for atypical respiratory organisms and urine for pneumococcal and *Legionella* antigen
- Sputum for bacterial culture and sputum and nasopharyngeal aspirate for immunofluorescence or polymerase chain reaction (PCR) for viruses in patients with coryzal symptoms

Howard J, et al. *Br J Haematol*. 2015;169:492-505.

Management Strategies for the Older Adult With Sickle Cell Disease



Thein SL, et al. *Blood*. 2018;132(17):1750-1760.

Comprehensive Health Maintenance at Specialized Centers That Provide Multidisciplinary Care Using Standard Guidelines

Preventive measures

- Regular monitoring and periodic comprehensive evaluations for common complications
- Frequency of visits and laboratory monitoring depends on the genotype, medication, and disease severity
  - Folic acid supplementation if diet inadequate
  - Genetic counseling
  - Immunization according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices
  - Education about complications of sickle cell disease

Comprehensive Health Maintenance at Specialized Centers That Provide Multidisciplinary Care Using Standard Guidelines (cont)

- Monthly complete blood count, reticulocyte count, percent hemoglobin S, CMP, and ferritin for patients on chronic transfusion and chelation
- Monitor vitamin D levels and supplement if < 30 IU
- Blood pressure measurement each visit
- Neurocognitive testing if imaging abnormalities, or school or work performance difficulties
- Ophthalmology evaluation for retinopathy biannually if normal, more frequent if abnormal
- Echocardiogram to evaluate pulmonary hypertension and diastolic dysfunction; brain natriuretic peptide if any symptoms of pulmonary hypertension
- Pulmonary function studies if history, signs, or symptoms of asthma or other respiratory disease
- Sleep study if history of snoring or other symptoms of obstructive sleep apnea
- Evaluate bone density if abnormal
- Radiographic evaluation of hips to assess femoral avascular necrosis if pain in hips, knees or low back. Avascular necrosis also seen in shoulder and knees.

CMP = comprehensive metabolic panel

Sickle Cell Disease: Therapeutic Landscape

Hydroxyurea

- Baseline: CBC/differential (ANC), reticulocyte count, hemoglobin electrophoresis (HPLC), creatinine, LFTs (ALT, bilirubin)
- Monthly toxicity laboratory tests: CBC with differential
  - Hold if ANC < 1×10^9/L or platelet count is < 100,000; reduce dose if ANC is 1 to 1.5×10^9/L or platelet count is < 150,000
  - Restart at lower dose once recovered
- Once maximum tolerated dose is reached, follow every 2–3 months and assess for compliance and toxicity (CBC with differential, mean corpuscular volume, creatinine, ALT, reticulocyte count)
- Monitor for leg ulcers

Voxelotor

- Allosteric modulation of Hb S shifts oxyHbC. Voxelotor prevents RBCs from forming sickle shape and binding together
- Approved by FDA in 2019 to treat SSD in adults and children 12 years and older
- How administered: 1500 mg once daily with or without food
  - Dose modification required for concurrent CYP3A4 inducers, strong CYP3A4 inhibitors, or in moderate to severe hepatic impairment
- Possible side effects include headache, diarrhea, abdominal pain, nausea, fatigue, and fever. Rarely, allergic reactions may occur, causing rashes, hives, or mild shortness of breath. Patients should talk to their doctors about other medicines they take.

Crizanlizumab-tmca

- Indicated to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients, aged 16 years and older, with sickle cell disease
- Helps prevent blood cells from sticking to blood vessel walls and causing blood flow blockage, inflammation, and pain crises
- How administered: 5 mg/kg by IV infusion over a period of 30 minutes at weeks 0 and 2, then every 4 weeks
- Possible side effects: nausea, joint pain, back pain, fever

ANC = absolute neutrophil count; ALT = alanine aminotransferase; FDA = US Food and Drug Administration; Hb = hemoglobin; LFTs = liver function tests; oxyHbC = oxyhemoglobin C; RBCs = red blood cells; SSD = sickle cell disease

Characterization of Beta Thalassemia

β-Thalassemia Minor	**β-Thalassemia Intermedia**	**β-Thalassemia Major** (Cooley's anemia)
Patients typically have 1 normal functioning β-globin	Patients usually have partial β-globin function	Patients typically have no β-globin gene function
Patients have mild or no anemia (typically asymptomatic)	Patients may have mild-to-moderate anemia not dependent on transfusions	Patients have the most severe type of anemia
Patients usually do not require regular transfusions	May require regular RBC transfusions if anemia becomes severe	Patients require regular lifelong RBC transfusions

RBC = red blood cell

Ben Salah N, et al. *Hematology*. 2017;22(10):607-616; Cappellini MD, et al. *Blood Rev*. 2018;32(4):300-311; Rachmilewitz EA, et al. *Blood*. 2011;118(13):3479-3488; Rund D, et al. *N Engl J Med*. 2005;353(11):1135-1146.

Beta Thalassemia Complications

- Complications of beta thalassemia are numerous and include:
  - Growth failure
  - Bone disease
  - Cardiac abnormalities (pulmonary hypertension, heart failure, arrhythmias)
  - Predisposition to thrombosis
  - Extramedullary hematopoiesis (splenomegaly, masses with compression)
  - Endocrinopathies

Beta Thalassemia: Routine Monitoring in Adults

Test	Frequency of Monitoring
Alpha and beta globin genotyping	Once at diagnosis
High-resolution HLA typing	At diagnosis, when transplant is being considered
Pain assessment	Every 3–6 months
CBC with differential	Every 6 months if no transfusions
Comprehensive metabolic panel	Every 6 months
Iron panel	Every 6 months
Ferritin	Every 3 months or more often in transfusion-dependent disease
RBC genotype/phenotype	Once at start of transfusions
Liver iron concentration by MRI	When ferritin reaches 500 ng/mL in transfusion-dependent patient, then annually
Cardiac T2 MRI	Annually in transfusion-dependent patients

CBC = complete blood count; HLA = human leukocyte antigen; MRI = magnetic resonance imaging; RBC = red blood cell

Khandros E, et al. Hematol Oncol Clin North Am. 2019;33(3):339-353.

Beta Thalassemia: Routine Monitoring in Adults (cont)

Test	Frequency of Monitoring
Hepatitis A, B, C serology (PCR as indicated), HIV testing	Annually
Echocardiogram and EKG	Annually
TSH and free T4	Annually
FSH, LH, estradiol, prolactin (women), testosterone (men)	Annually
Vitamin D	Annually
Parathyroid hormone	Annually
Bone density by DEXA scan	Annually
Visual acuity and dilated ophthalmology examination	Annually for patients on iron chelation therapy
Audiology examination	Annually for patients on iron chelation therapy
Vitamin C level	Annually for patients on iron chelation therapy
Zinc level	Annually for patients on iron chelation therapy

DEXA = dual-energy x-ray absorptiometry; EKG = electrocardiogram; HIV = human immunodeficiency virus; FSH = follicle-stimulating hormone; LH = luteinizing hormone; PCR = polymerase chain reaction; TSH = thyroid-stimulating hormone

Khandros E, et al. Hematol Oncol Clin North Am. 2019;33(3):339-353.

Beta Thalassemia: Clinical Management

- Regular blood transfusions
- Chelation therapy for hemosiderosis
- Daily doses of folic acid
- Possible surgical removal of gallbladder
- No iron supplements
- Erythropoietin-stimulating agents
- Bone marrow transplantation

- Luspatercept
  - Trap-ligand: Binds to TGFβ ligands to suppress SMAD2/3 signaling; restores erythropoiesis by increasing the number and improving the quality of mature RBCs
- How administered
  - Once every 3 weeks by subcutaneous injection; titrated dosing
- Serious AEs included cerebrovascular accident and DVT
- Most common AEs: headache (26% vs 24%), bone pain (20% vs 8%), arthralgia (19% vs 12%), fatigue (14% vs 13%), cough (14% vs 11%), abdominal pain (14% vs 12%), diarrhea (12% vs 10%) and dizziness (11% vs 5%)