HARRISON

EDITION 22nd

HAEMATOLOGY

Haematology

Chapter 101 Hematopoietic Stem Cells	Completed
Chapter 102 Iron Deficiency And Other Acquired Anemias Due To Decreased Erythrocyte Production	Completed
Chapter 103 Disorders Of Hemoglobin	Completed
Chapter 104 Megaloblastic Anemias	Completed
Chapter 105 Hemolytic Anemias	Completed
Chapter 107 Bone Marrow Failure Syndromes Including Aplastic Anemia And Myelodysplasia	Completed
Chapter 108 Polycthemia Vera And Other Myeloproliferative Neoplasms	Completed
Non Hodgkin Lymphoma Part 1	Completed
Non Hodgkin Lymohoma - Part 2	Completed
Non Hodgkin Lymohoma Part 3	Completed
Hodgkin Lymphoma	Completed
Plasma Cell Disorders	Completed
Plasma Cell Disorders Part 2	Completed

Acute Myeloid Leukemia	Completed
Acute Lymphoblastic Leukemia	Completed
Chronic Myeloid Leukemia	Completed
Transfusion Medicine	Completed
Disorders Of Platelets And Vessel Wall	Completed
Von Willebrand Disease	Completed
Coagulation Disorders	Completed

HEMATOLOGY

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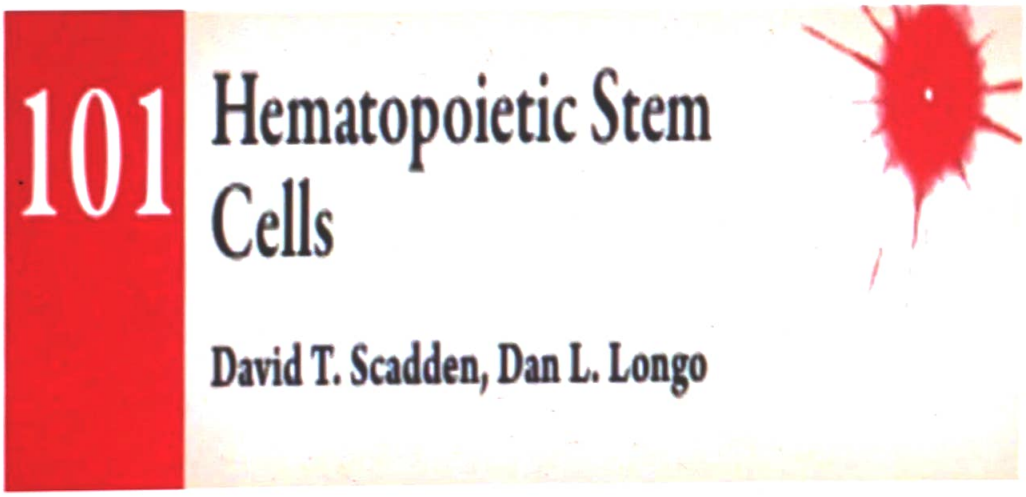
TOPICS FOR TODAY

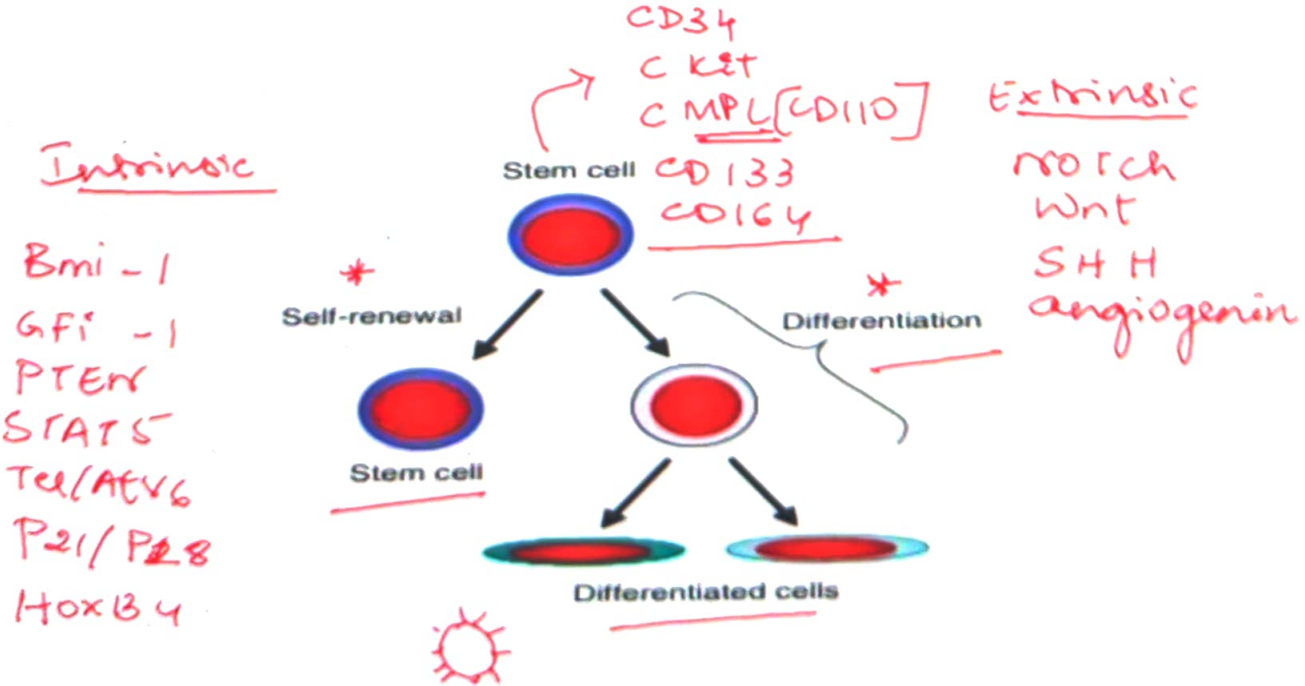
1. Hematopoietic Stem Cells .
2. Iron Deficiency and Other Acquired Anemias Due to Decreased Erythrocyte Production
3. Disorders of Hemoglobin
4. Megaloblastic Anemias
5. Hemolytic Anemias
6. Anemia Due to Acute Blood Loss
7. Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia .

8. Polycythemia Vera and Other Myeloproliferative Neoplasms
9. Chronic Myeloid Leukemia

SUBTOPICS

- PATHOPHYSIOLOGY
- CLASSIFICATION
- CLINICAL FEATURES
- LAB FEATURES
- PROGNOSTICATION
- TREATMENT
- COMPLICATIONS





Haematopoiesis

HSC < self
diff.
→ GEMML

BM
10,000 - 20000
1 stem cell dendritic

HSC → pleuripotent
HPC → comitted
→ more proliferative.

HGF — EPO
TPO
GCSF

Signalling
GATA2 CEBPA
RUNX1 PAX5
Ikaros

EPO → → Dosha epoetin AOCD, MDS
TPO → → ITP, aplastic, liver cirrhosis
GCSF → marrow stromal cells → neutropenia.
→ stem cell

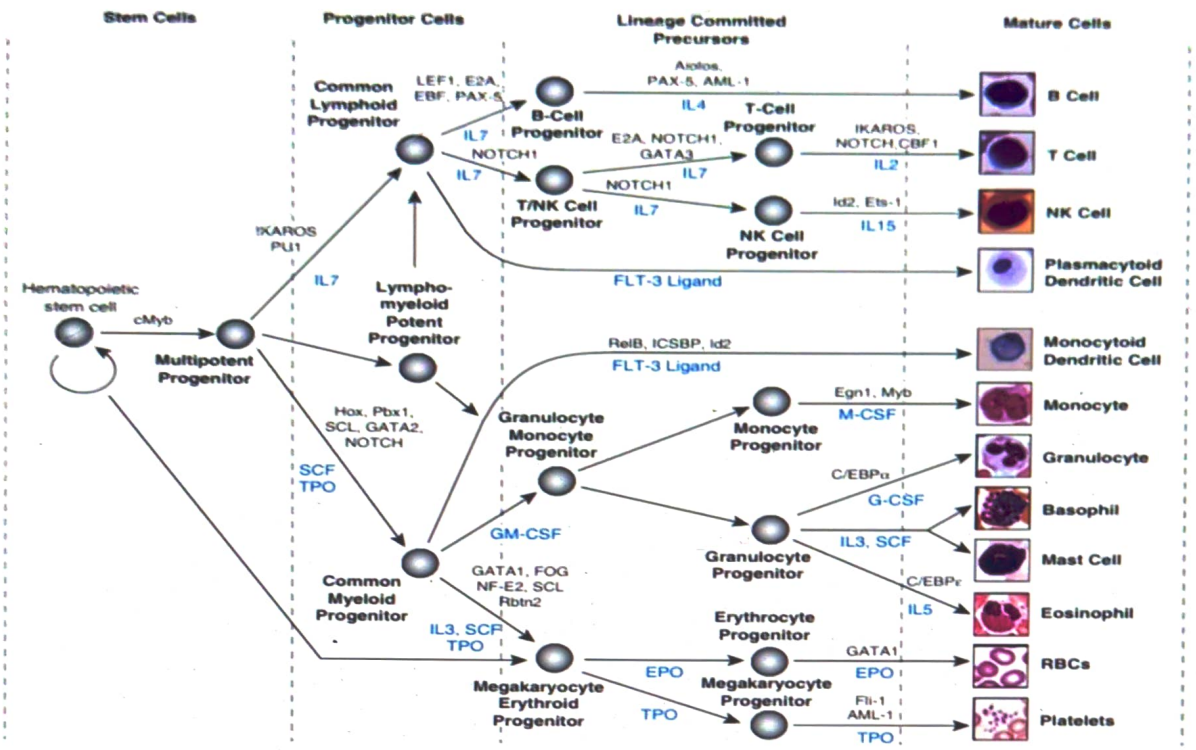
HSC

Surface

Immunophenotyping

flow / IHC

CD34+ CD38-*
CD45RA- CD90+



Yolksac 3-5 weeks GA ~ 3 months

AGM 4-6 weeks

→ 2 month - 6 month

BM → 4 months → post natal life.

Chemokine interaction

CXCL12
CXCR4

G-CSF ↑ inhibitor

Plerixafor

Stem cell niche

fat stromal HSC progenitor → mature

Perivascular space

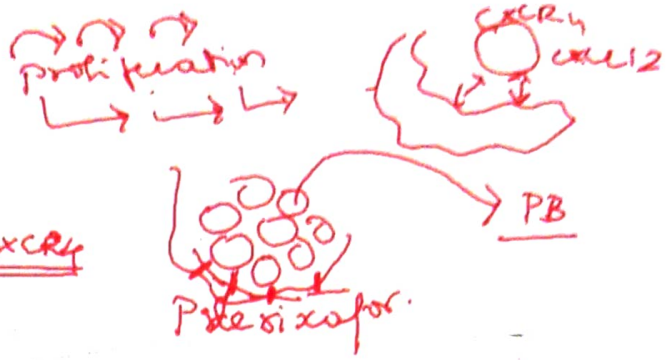
Various therapeutic uses

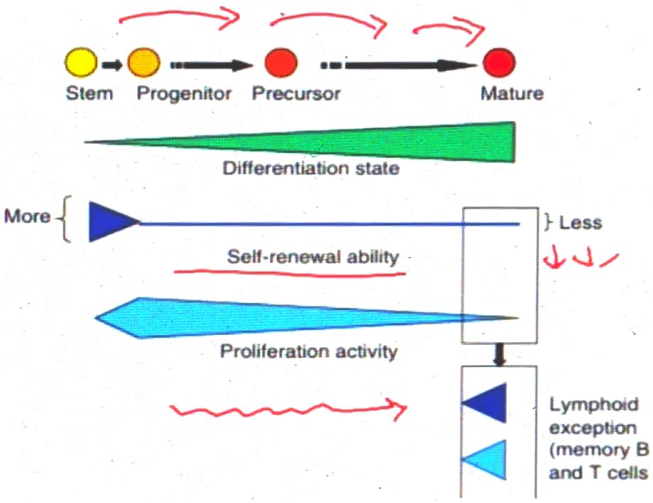
① Stem cell transplant
↳ BM niche

② GCSF & plerixafor → CXCR4
Haevest stemcells.

③ CD34+ selection

④ hematological malig.
Genetic disorder
Immunodefecien





① Immunophenotype for HSC
CD34+ CD38+ CD45RA−

−	+	−
+	−	+
+	+	+

② Genetic alterations
transcription
CEBPA ✓
RUNX1 ✓
GATA /
PAX 5 ✓
1, 2, 4.

③ Stem cell mobilisation
GCSF, Plerixafor
- VLA-4
- CXCR4 ✓
- CXCR4-CXCL12
neutrophil

④ Not a locati
BM
AGM

anemia ↑ → Retic index (< 2) → Retic % ×

HCT/45 × 1/maturation time

(M) 120 days (F) 90 days

CM Progenetors → G ↓ E ↓ M ↓ M ↓

102 Iron Deficiency and Other Acquired Anemias Due to Decreased Erythrocyte Production

→ hypoproliferative anemia

Clara Camaschella, Domenico Girelli

cMP → Erythrocytes → Hb ↑↑↑ enucleation ♀

Reticulocytes

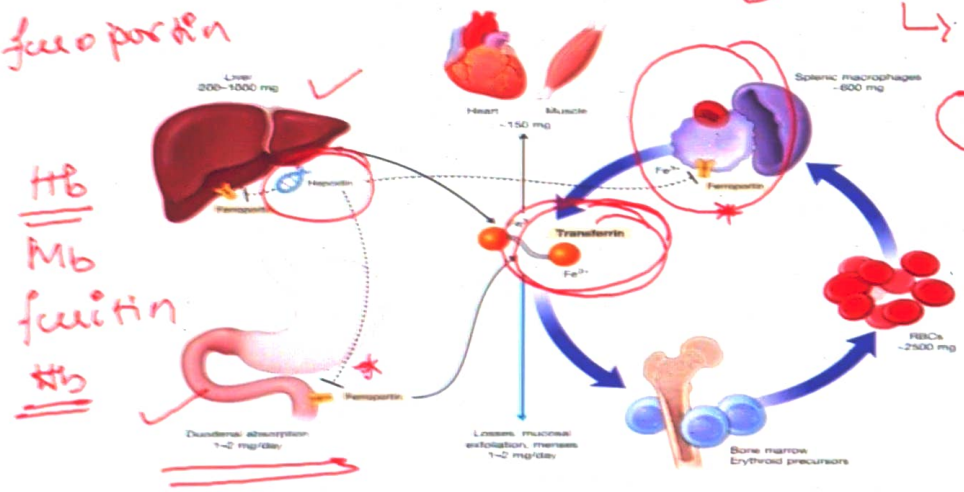
EPO

1–2 mg ♀

free portion

tightly regulated.

Iron store adequate ♀ → hepcidin ♀ → ♀ → Solu tr



Hb

Mb

ferritin

Hb

↓ intake

↓ absorptions

→ Inflammat

Bariatric

↓ gastric acidity

+ phytates, tannins, Calcium diet

Restless leg.

Pica

* Excess blood

menorrhagic

GI bleed

frequent blood donor

* ↑ demands → Pregnancy/Lactation

MCV ↓

low serum fe + sat

↑ TIBC

low ferritin

acute inflammat

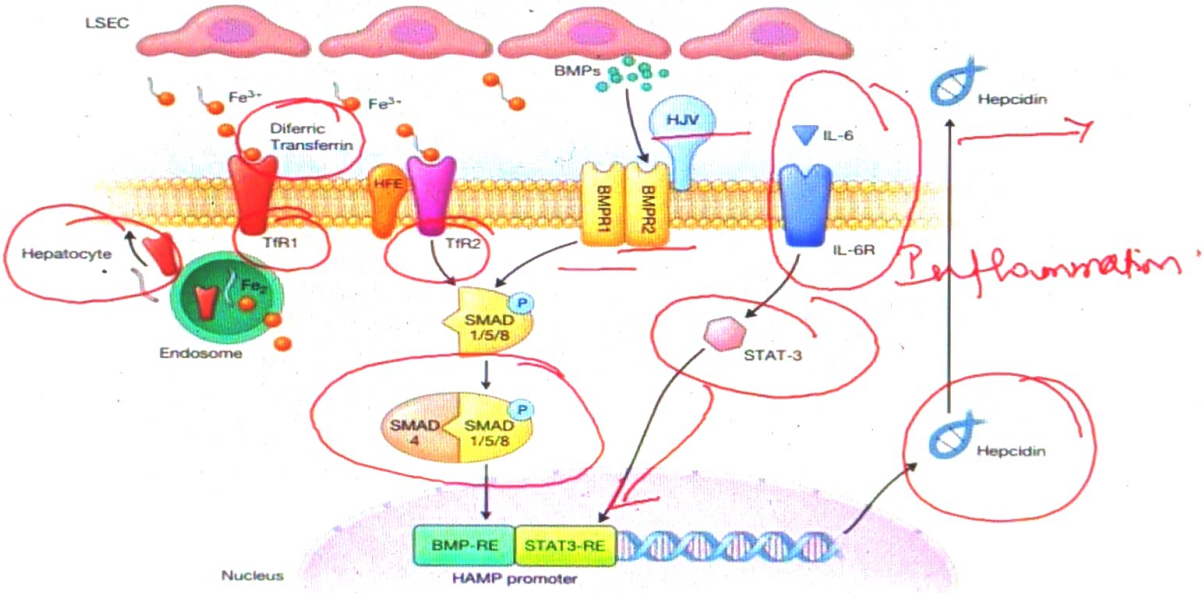
STFRI – STR ↑↑

ferritin

BM

Mentzer MCV/RBC <13 thal

>13 IDA



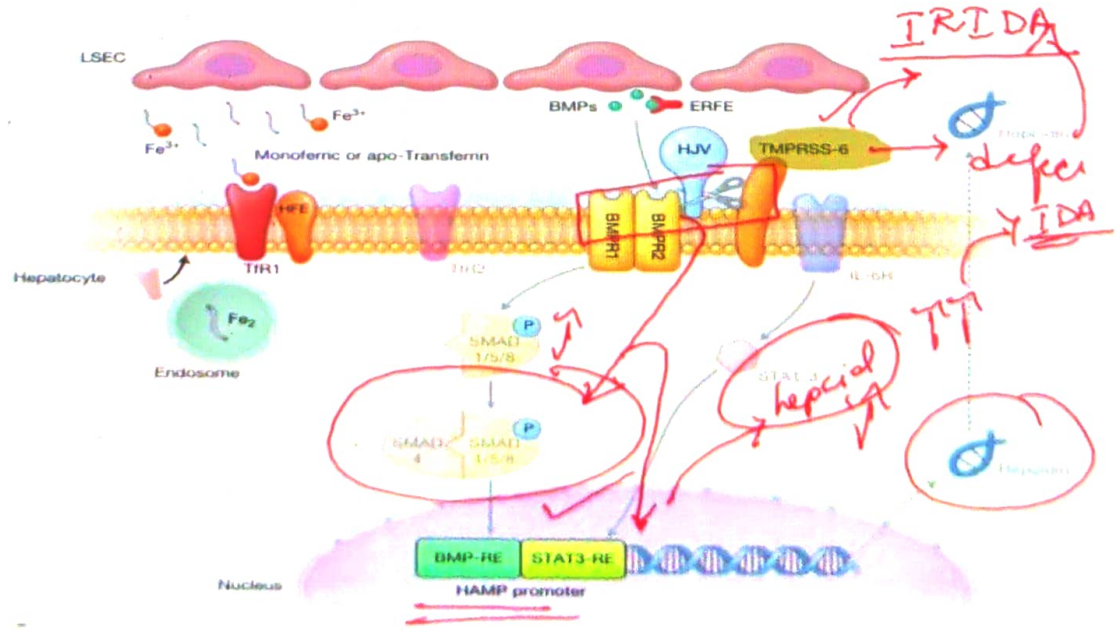


TABLE 102-1 Daily Iron Requirements (mg) According to Age and Gender	
Children	0.5–1.0
Adolescents	1.2–1.5
Adult males	1.0
Females (fertile age)	1.20–1.50
Pregnancy second trimester	2.8–3.0
Pregnancy third trimester	4.0–5.0
Breastfeeding	1.0–1.15
Females (postmenopausal)	1.0

Symptomatic
↳ End organ damage
Treatment RBC

Body wt × Hb deficit × 2.145
+ 500 mg

TABLE 102-2 Causes of Absolute Iron Deficiency With or Without Anemia	
MECHANISM	**CONDITIONS**
Increased iron needs	• Children, adolescents (growth spurt) • Pregnancy and breastfeeding • Treatment with erythropoiesis-stimulating agents
Inadequate iron intake	• Vegan or vegetarian diet • Malnutrition, poverty • Prolonged breastfeeding
Decreased iron absorption	• Gastrectomy, bariatric surgery • Celiac disease • *Helicobacter pylori* gastritis • Atrophic/autoimmune gastritis • Proton pump inhibitors* • Excess consumption of iron absorption inhibitors (e.g., tea, calcium) • IRIDA (*TMPRSS6* mutations)

Chronic blood losses	*Gastrointestinal* • Erosive esophagitis/gastritis • Peptic ulcer • Large hiatal hernia • Antral gastric ectasia (watermelon stomach) • Benign lesions (e.g., large polyps) • Meckel's diverticulum • Angiodysplasias (including Heyde's syndrome with concurrent aortic stenosis and acquired von Willebrand disease) • Malignancy (especially right colon cancer) • Large hemorrhoids • Inflammatory bowel diseases • Parasites (hookworms, others) *Gynecologic* • Heavy menstrual bleeding[b] • Fibroids • Uterine cancers *Urinary* • Intravascular hemolysis (e.g., PNH, prosthetic heart valves, march hemoglobinuria) • Urinary schistosomiasis (*Schistosoma haematobium*) • Bladder or renal cancer *Pulmonary* • Pulmonary hemosiderosis • Severe hemoptysis *Iatrogenic* • Hemodialysis • Surgical blood losses • Excess blood drawn for diagnostic testing • Drugs inducing or facilitating GI bleeding (aspirin, nonsteroidal anti-inflammatory drugs, corticosteroids, antithrombotic drugs) *Bleeding disorders* • von Willebrand disease, other coagulation defects, platelet disorders • Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) *Frequent blood donors* *Self-inflicted in psychiatric disorders* (Munchausen's syndrome)

TABLE 102-3 Laboratory Biomarkers for Differential Diagnosis of Iron Deficiency

	IRON DEFICIENCY	ANEMIA OF INFLAMMATION	MIXED FORMS	THALASSEMIA TRAIT
Ferritin (μg/L)	Low (≤15–30)	Normal to high (>100)	Low to normal (<70–100)	Normal to high
Serum iron (μmol/L)	Low	Low	Low	Normal to high
Transferrin saturation (%)	Low (<10)	Low (<20)	Low (<20)	Normal to high
MCV (fL)	Low (<80)	Low to normal	Low to normal	Low
RDW	High	Normal	Normal to high	Low to normal
% HYPO	High (>6%)	High	High	High
CHr	Low	Low	Low	Low
sTfR	High	Low to normal	Normal to high	Normal to high
sTfR/log ferritin	>2	<1	>2	NA
Hepcidin[a]	Very low	Normal to high	Low	Low to normal
Zn-PP[b] (μM/mol heme)	High (>80)	Normal to high	High (>80)	High

TABLE 102-4 Iron Preparations for Replacement Therapy

Oral Compounds

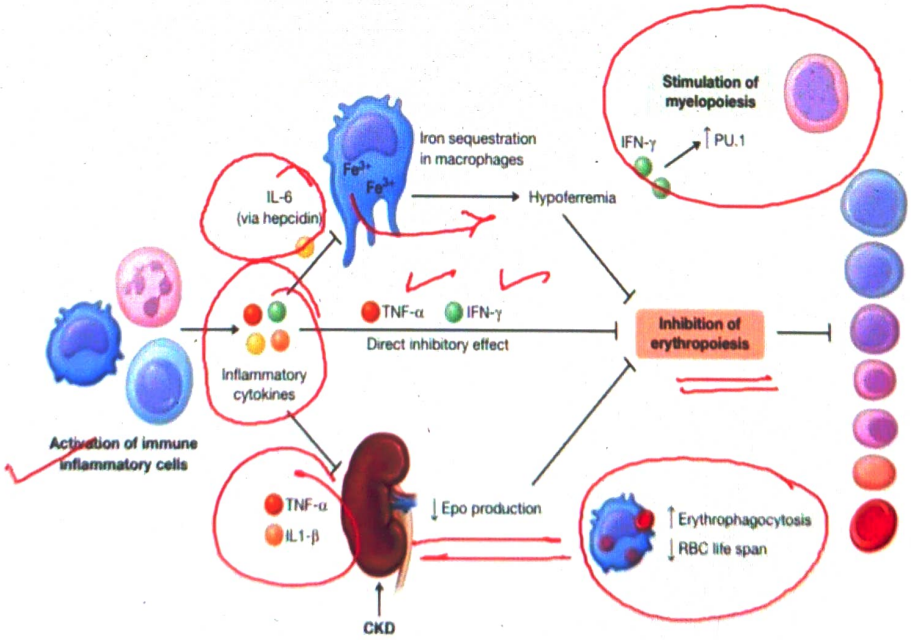
	ELEMENTAL IRON CONTENT,[a] mg	DOSAGE
Iron sulfate	65–105	65–100 mg 1–2 times a day or 65–100 mg on alternate day
Iron gluconate	27–38	1–2 doses per day
Iron fumarate	29–105	1–2 doses per day
Sucrosomial iron[b]	30	30 mg/d
Polysaccharide iron complexes (tablet or elixir)	50–200 15/mL 125/mL	50–200 mg/d
Ferric maltol	30	30 mg 2 times a day
Ferric citrate	45–210	3 doses per day in chronic kidney disease patients with hyperphosphatemia

Intravenous Compounds

	IRON CONTENT, mg/mL	MAXIMUM SINGLE DOSE
Iron sucrose	20	200–300
Iron gluconate	12.5	125, slow infusion
Low-molecular-weight dextran	50	1000, over 1 h
Iron carboxymaltose	50	750–1000, over 15 min infusion
Iron derisomaltose	100	Up to 20/kg, rapid infusion
Ferumoxytol	30	510, rapid infusion

Systemic

- → nutritional
- → hypothyroid
- → Inflammatory
- → CKD
- → Myelophthisic condition



Chronic inflam.

↑ hepcidin

↓ release

blunted

↑ apoptosis

shortened RBC lifespan

↑ ferritin

↓ serum iron

↑ TIBC ↓

- Autoimmune
- infection
- malig
- IBS
- Heart failure
- DM, CKD, COPD

Lab: normocytic

MCV ~ (N)

MCH ↓↓

ferrit (N)

Str (N)

& StrI (N) → >2 s/o IDF

<1 s/o ADCD

StrI = Str / ferrit

IDA > 2

ACD < 1

Rx: treating the underlying disease

↝ ESA

EPO → ↓ hepcidin

Serum > 100 ng/ml

RBC tx

ACD ↺ relative def.

0.45 - 0.75 mcg/kg.

~ 10 g/l.

ESA { risk of thrombosis stroke, MI, HF, HTN.

>11 g/l.

103 Disorders of Hemoglobin

Vijay G. Sankaran, Martin H. Steinberg

TABLE 103-1 Disorders of Hemoglobin

I. **Hemoglobinopathies**—hemoglobin variants with amino acid sequence variants that alter the physical, chemical, or functional properties of hemoglobin
   - A. Common variants with unusual properties
     1. HbS—polymerization
     2. HbE—reduced biosynthesis
     3. HbC—hemoglobin-membrane interaction
   - B. Altered oxygen affinity
     1. High affinity—erythrocytosis
     2. Low affinity—cyanosis, anemia
   - C. Hemoglobins that oxidize readily
     1. Unstable hemoglobins—hemolytic anemia, jaundice
     2. M hemoglobins—methemoglobinemia, cyanosis

II. **Thalassemias**—defective biosynthesis of globin chains
   - A. α Thalassemias
   - B. β Thalassemias
   - C. Complex thalassemias

III. **Hereditary persistence of fetal hemoglobin**—persistence of higher than normal levels of HbF into adult life
   - A. Deletions within the *HBB* cluster—15–30% HbF in heterozygotes, pancellular HbF
   - B. Point mutations in *HBG2/1* promoters—5–30% HbF in heterozygotes; pancellular or heterocellular HbF

IV. **Acquired hemoglobinopathies**
   - A. Methemoglobin due to toxic exposures
   - B. Sulfhemoglobin due to toxic exposures
   - C. Carboxyhemoglobin
   - D. HbH in erythroleukemia
   - E. Elevated HbF in myelodysplasia

Thalassemia — quantity defect — Imbalance

α β

α^0 β^0

α^+ β^+

$\alpha_2 \beta_2$

β thal → α thal — Middle sympt

HPFH

Middle phenotype

Ineffective erythropoiesis

↓ Hb production

↓ RBC survival

Excess → heterotetramers

β thal → α triplicon / quadrip

severe

α thal

↳ SEA

Middle east-

North Africa

Non deletional variants are very rare.

MHA but HbA_2 (or)

DNA analysis.

β severe anemia tx.

β — minor — TDT

Inter — major — or TDT

αα

-α αα → mild anemia MHA

--α Hb H

---- Hydrops fetalis

β ε (HbG2 HbG1)

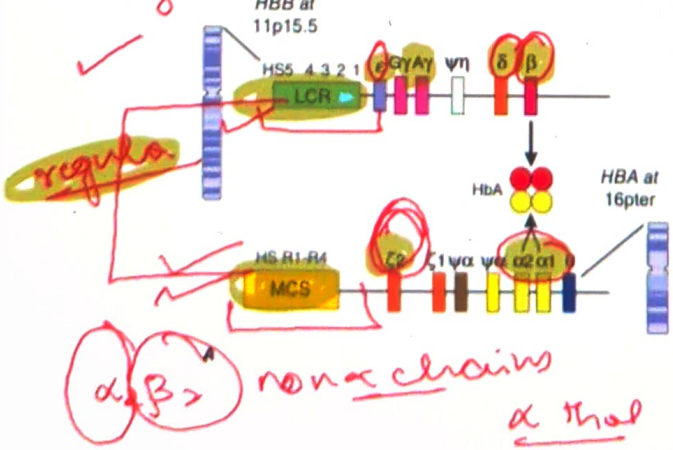
γ

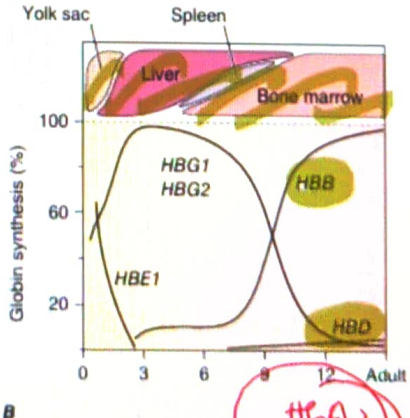
β HbB

δ HbD

G_2E_2 → Gower 1 $G_2\gamma_2$ → Portland

$\zeta_2\epsilon_2$ → e-2





$\alpha_2\beta_2$ non α chains

α thal ↓ α chain

$Hb A_2$ $\alpha_2\delta_2$

β thal

↳ variably ↑ HbA₂ & ↓ HbF

δ & β ⟹ HbA₂ (N) falsely low.

→ ↝ 10 5 bone heal ↓ chelation of iron

→ HSCT MSD < 17 yrs

→ Gene therapy

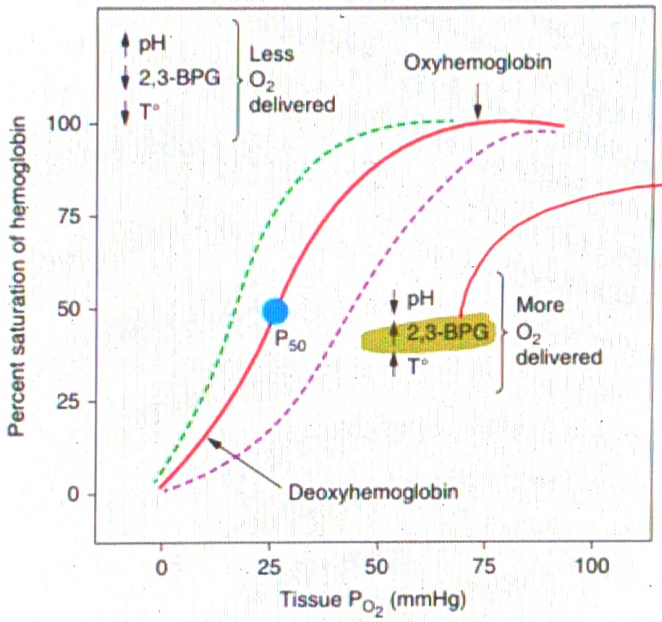
→ Transplacept.

TDT

> 500

Trans LD

Extended antigen match Rh & Kell match.



fetal Hb

↓↓ 2 3 BPG

affinity high

Sickle cell disorder (qualitative)

Point mutation

↓

Codominant

HbS + HbA

HbSA

* CO inheritance HbF ↑ Improved outcome

Hb → deoxygenated

HbS → Conformational chang.

↓ Solubility ↑ polymerisation.

Sickles → chronic hemolytic anemia. 1/7 ~ 17 days

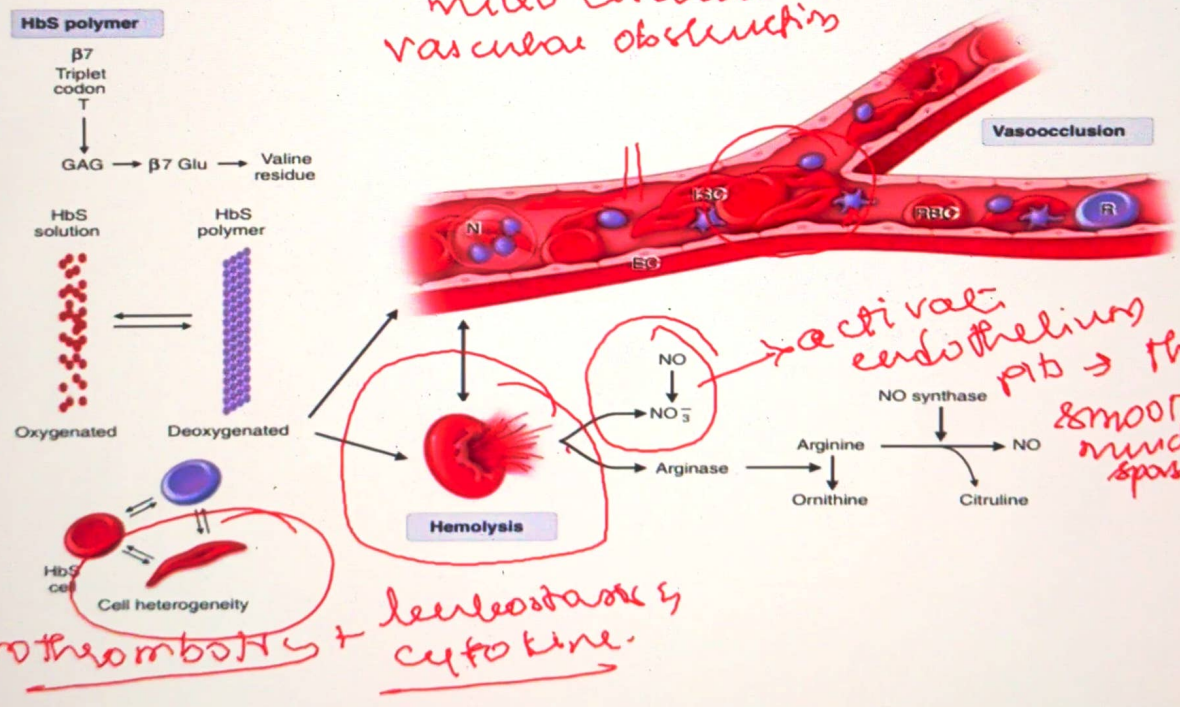
SSD → homozygous HbSS

↳ Compound heterozygous

β C, D, E, O Arab, Lepore.

TABLE 103-2 Common Sickle Hemoglobinopathies

GENOTYPE	CLINICAL ABNORMALITIES	HEMOGLOBIN LEVEL, g/L (g/dL)/MCV, fL	HEMOGLOBIN FRACTIONS (%)
Sickle cell trait (HbAS)	8% of African Americans; hematuria, papillary necrosis, hyposthenuria, increased incidence of chronic kidney disease; 2–4 times increased VTE risk;? stroke; splenic infarction at altitude; rhabdomyolysis	Normal	HbA: 60–70 HbS: 30–40 Percent HbS dependent on presence or absence of α thalassemia
Sickle cell anemia (HbSS)	Vasoocclusion related: pain, acute chest syndrome, osteonecrosis, splenic infarction Hemolysis related: stroke, pulmonary and systemic vasculopathy, nephropathy, leg ulceration gallstones, priapism	70–100 (7–10)/80–100	HbS: >75 HbF: 2–25 HbA_2: 3–4
HbS-β^0 thalassemia	Rate of complications similar to HbSS	80–100 (8–11)/60–85	HbS: >75 HbF: 2–15 HbA_2: 5–6
HbS-β^+ thalassemia	Rate of complications about half the rate of complications of HbSS depending on percent HbA	100–140 (10–14)/70–80	HbS: 60–90 HbA: 5–40 HbF: 1–10 HbA_2: 5–6
Hemoglobin SC disease (HbSC)	Nearly asymptomatic to disease as severe as HbSS; about half the rate of complications as HbSS. Increased risk of retinopathy	100–140 (10–14)/70–100	HbS: 50 HbC: 50
HbSE	Resembles clinically HbS-β^+ thalassemia; symptoms delayed; often Asian/Indian ancestry	90–130 (9–13)/65–75	HbS: 65 HbE: 35 HbF: 1–5
HbSS-α thalassemia	Present in 30% of HbSS; phenocopies HbS-β^0 thalassemia because of microcytosis and high HbA_2; like HbSS but with fewer strokes and leg ulcers and less pulmonary vascular and renal disease	80–100 (8–11)/60–85	HbS: >75 HbF: 2–15 HbA_2: 4–5



SCD

HbF ↑ HPFH ↓↓↓
Hydroxy

HbS / αThal — hemolytic ↓↓
→ vaso occlusive
complication ↑↑↑
→ Priapism
osteonecrosis

Sickle

HbSA — sickle
HbSS — SCD ↑
HbSC — SC ↑
HbS β° ↑
HbS β+ → variable

Africa

HbSC ⇝ HbSS

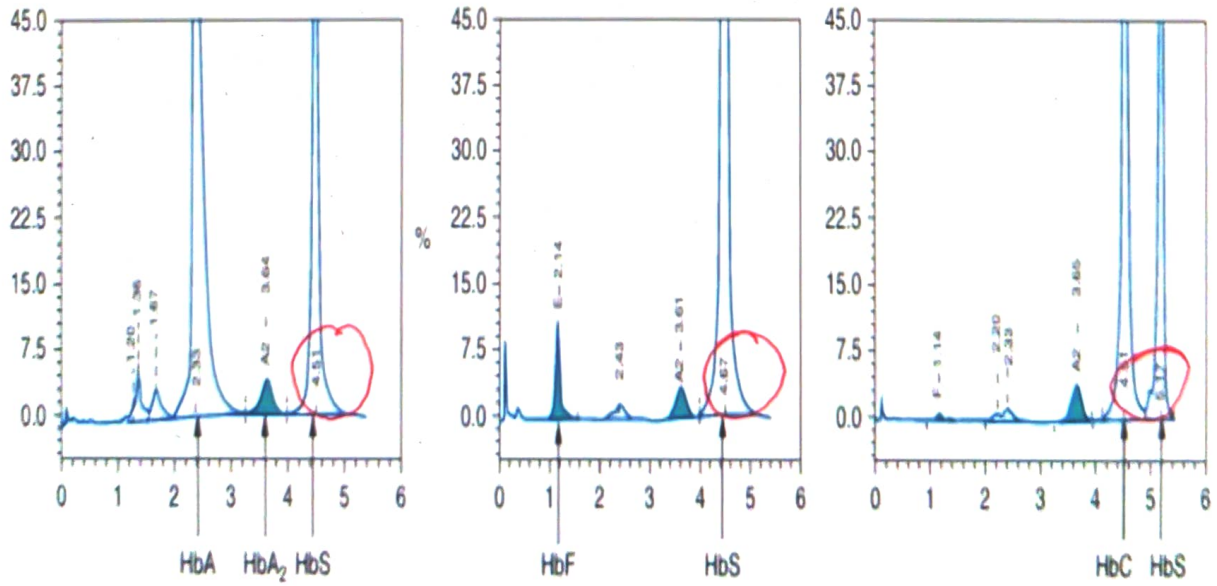
HbCC → mild anemia.
mild splenomegaly

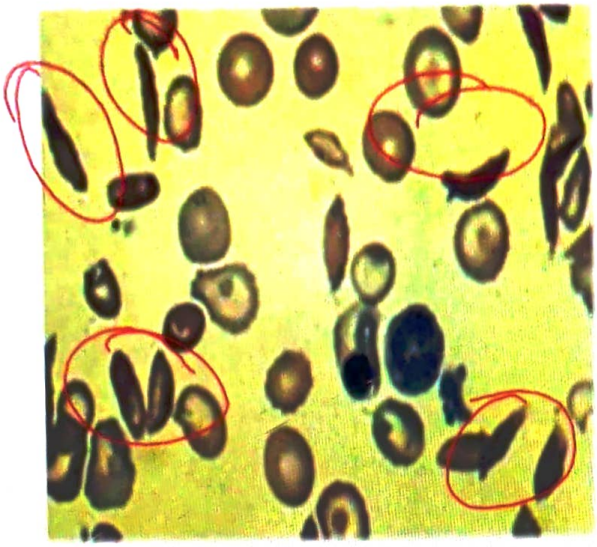
SCD Electrophoresis:

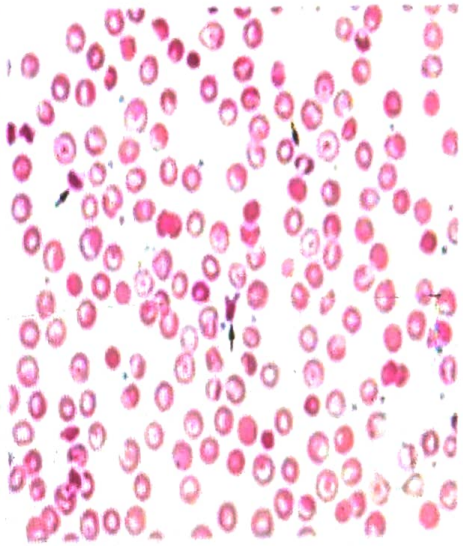
HPLC → quantification abnormal Hb

>40-1-S → SCD

HbSA	AS	60-1-A 40-1-S	asymptomatic
SS	SS	>90-1-HbS	Most severe dis.
HbS HbC	SC	50-1-S 50-1-C	severe disease
HbS β+	S β+	>50-1-S <50-1-A	mod
HbS β°		>90-1-S	SCD
HbS + F		15-25-1-HbF	moderate dis







manage acute episode

ACS hypoxia chest pain

50% ↓ fever

vaso occlusive episode

PE

fluid overload

Antibiotics

Incentive spirometer

O_2, IV fluids

Exchange tx

R/O ACS → Hydroxyurea · L-glutamine

crizanlizumab

ab P selectin

chelate TCD · ↑↑ transfusion

Retinopathy

proteinuria

TABLE 103-3 Complications of Sickle Cell Disease

COMPLICATION	INCIDENCE, DIAGNOSIS, AND FEATURES	TREATMENT
Priapism	~30% of males; can be episodic and short duration (stuttering); severe episodes can cause impotence; associated with markers of hemolysis	Many therapies including α-adrenergic agonists, stilbesterol; consult urology for treatment, which is time-critical
Stroke and silent infarction	10–15% of all cases; infarction in early childhood into adulthood; hemorrhagic in adults; neurocognitive abnormalities in adults even without apparent stroke; associated with markers of hemolysis	Transcranial Doppler screening in children ages 2–16; transfusion for at-risk patients; hydroxyurea
Gallstones/surgery	~40% of patients; bilirubin levels and stones related to polymorphisms of *UGT1A*; in surgery requiring general anesthesia, simple preoperative transfusion to a hemoglobin of 10 g/dL is recommended	If asymptomatic, usually let be; otherwise, laparoscopic cholecystectomy
Hepatic disease	>80% of patients have hepatomegaly; intrahepatic cholestasis can have bilirubin ~100 mg/dL; viral hepatitis, iron overload, RBC sequestration, extrahepatic cholestasis also contribute	Exchange transfusion for intrahepatic cholestasis; transplant for end-stage liver failure
Nephropathy	~30% of adults age >30 years; hyperfiltration in children, renal failure in adults; early albuminuria, later nephrotic-range proteinuria; associated with markers of hemolysis	Screen for microalbuminuria by age 10 years; avoid NSAIDs; use ACE inhibitors or receptor antagonists for albuminuria; erythropoietin for symptomatic anemia; dialysis or transplant for renal failure
Lung/pulmonary hypertension	Restrictive disease; asthma common; 5–10% have pulmonary hypertension by right heart catheterization; 30% have increased TRV that portends poor prognosis; associated with markers of hemolysis	Consult expert pulmonologist; screen yearly by echocardiography measurement of TRV
Retinopathy	20% in HbSC disease; 3% in HbSS*; develops in peripheral retina; vitreous hemorrhage and retinal detachment can cause blindness	Screen annually starting at age 10 years with fluorescein angiography; laser photocoagulation for proliferative disease
Acute anemic episodes	B19 parvovirus infection, folic acid deficiency, splenic sequestration, delayed hemolytic transfusion reaction with destruction of transfused and sometimes autologous red cells	RBC transfusion if symptomatic; splenectomy if more than 1 or 2 episodes of sequestration; anti-parvovirus IgM positive in acute infection, IgG in past infection
Multiorgan failure	Can accompany severe acute chest syndrome; often confused with sepsis and can coexist with sepsis; CNS liver, muscle, lung, kidney affected	Exchange transfusion, ICU support
Pregnancy	Screening both partners for hemoglobin disorders with risk counseling is critical component of family planning	All pregnancies are "high risk", transfuse if sickle cell events increase, if previous miscarriage, multiple fetuses