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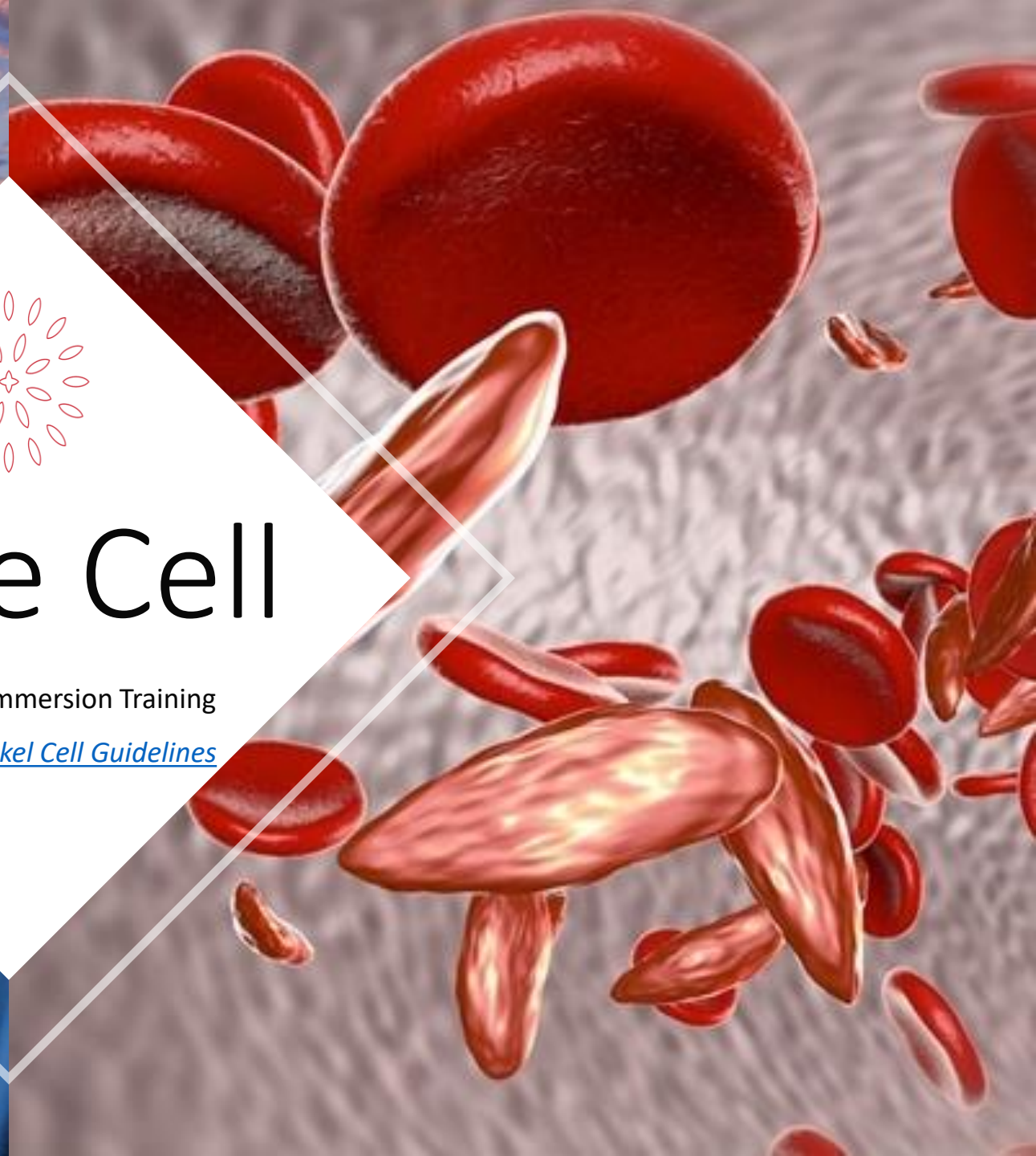
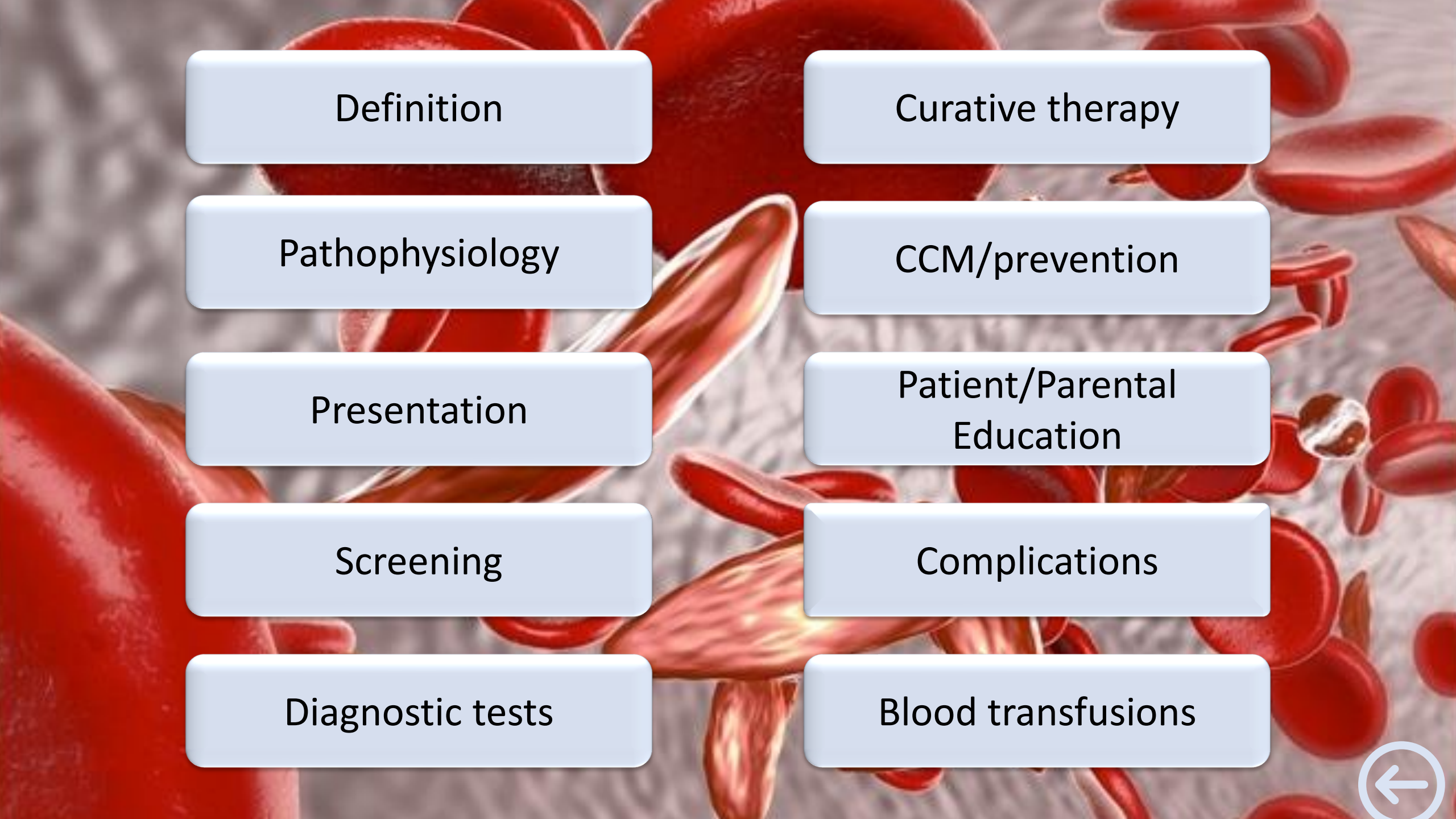
Sickle Cell

Seed Educator Immersion Training

Zambia 2020 Sickel Cell Guidelines

Quick reference

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- Surgery
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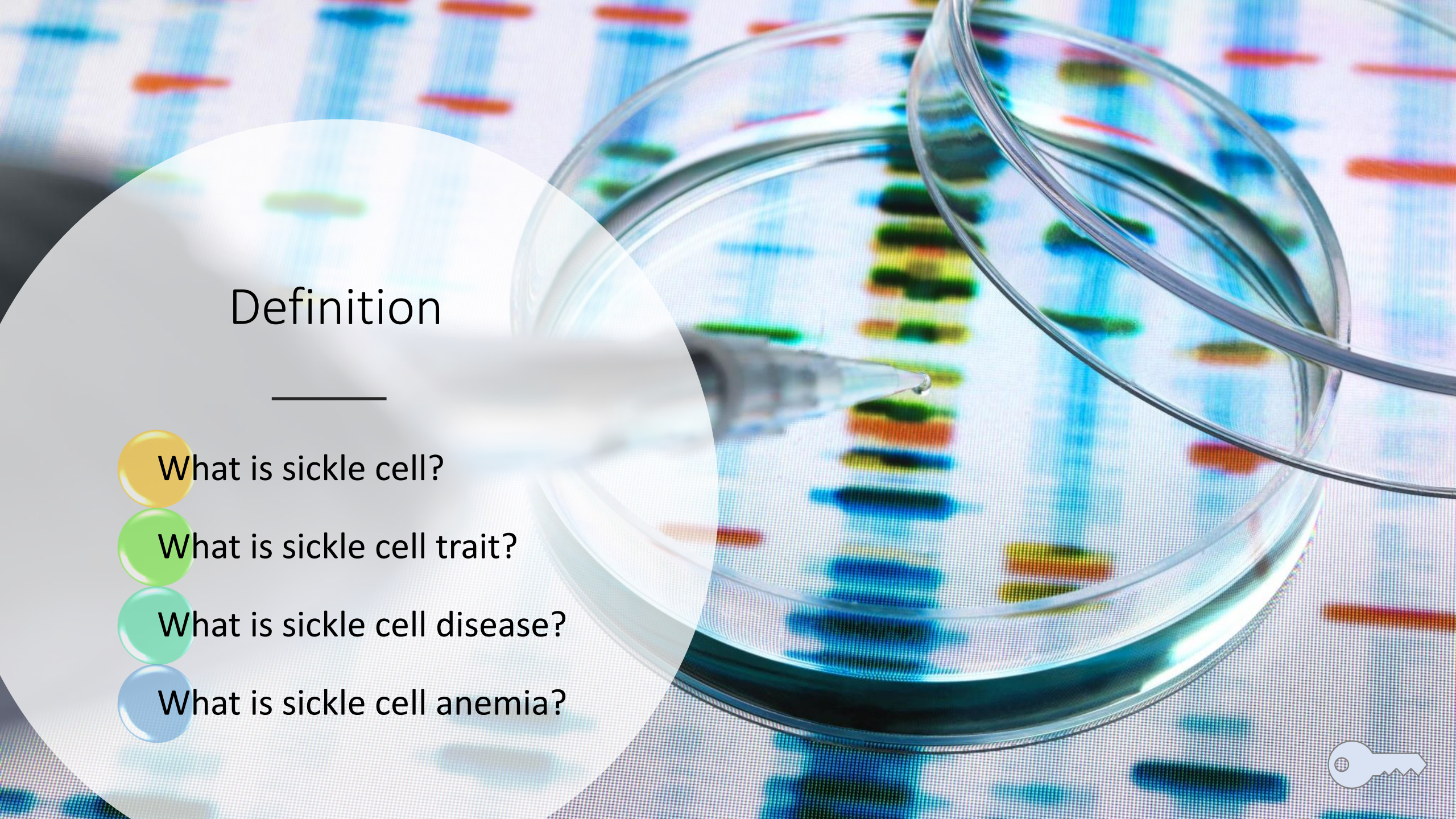
Definition

- What is sickle cell?
- What is sickle cell trait?
- What is sickle cell disease?
- What is sickle cell anemia?



Pathophysiology

- What is sickling?
- Why is anemia common?

Presentation

- What are common symptoms?
- How do patients typically present?

Screening

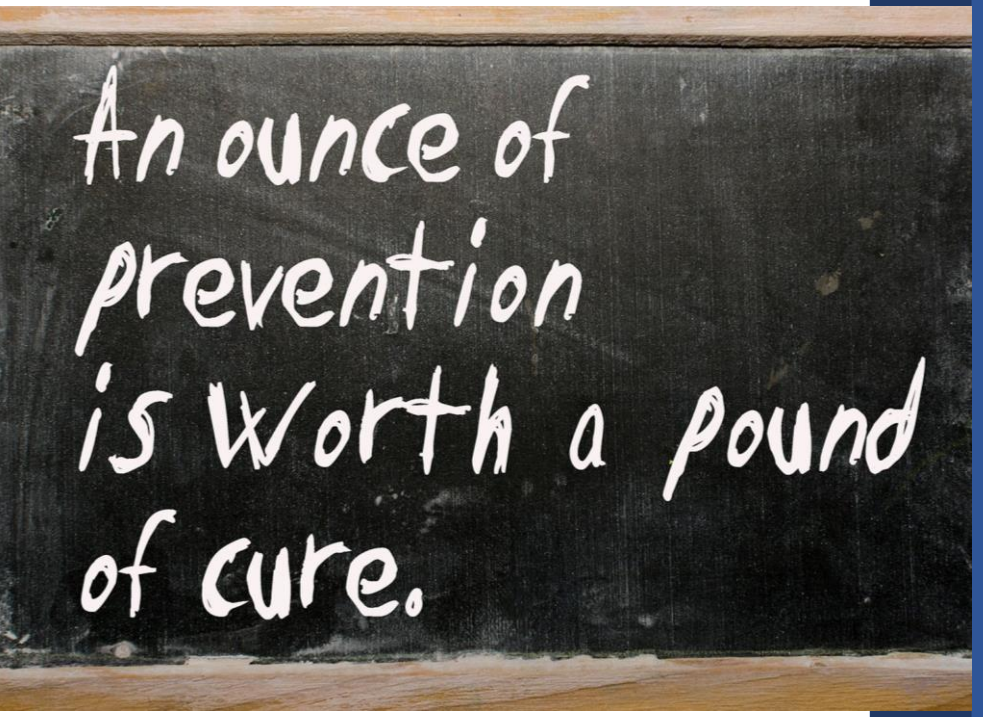
- Why screen for sickle cell disease?
- Who should be screened for sickle cell disease?
- What screening tests are available?

Diagnostic testing

- When is diagnostic testing indicated?
- What diagnostic tests are available?

Curative therapy

- What are curative options for sickle cell disease?
- What options exist in Zambia?
- When should curative therapy be considered in Zambia?



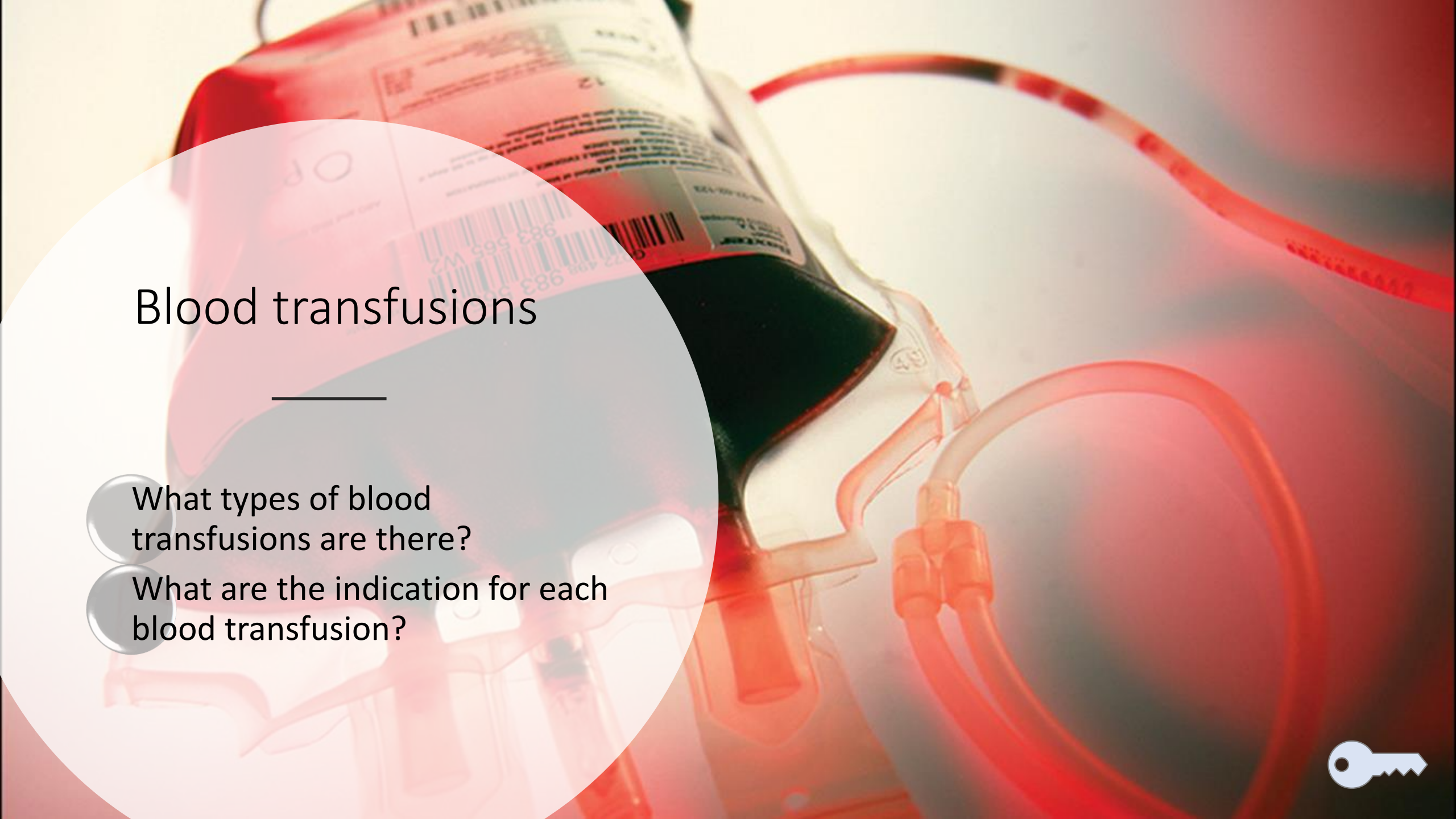
CCM/Prevention

What is on the sickle cell chronic care management checklist?

What are the indications, frequencies, doses, etc. of the interventions?

Patient/parental education

What are key aspects of counseling patients/parents with sickle cell?



Blood transfusions

- What types of blood transfusions are there?
- What are the indication for each blood transfusion?

Complications

- What are common complications/admissions for sickle cell?
- What is the work up?
- What is the treatment?
- Are there preventive measures?

Definition

Pg 1, 4-5

Sickle cell is a major genetic disease causing a hemoglobinopathy by inheritance of 2 abnormal genes, one has to be HbS.

Sickle cell trait (SCT): HbAS (A is normal)

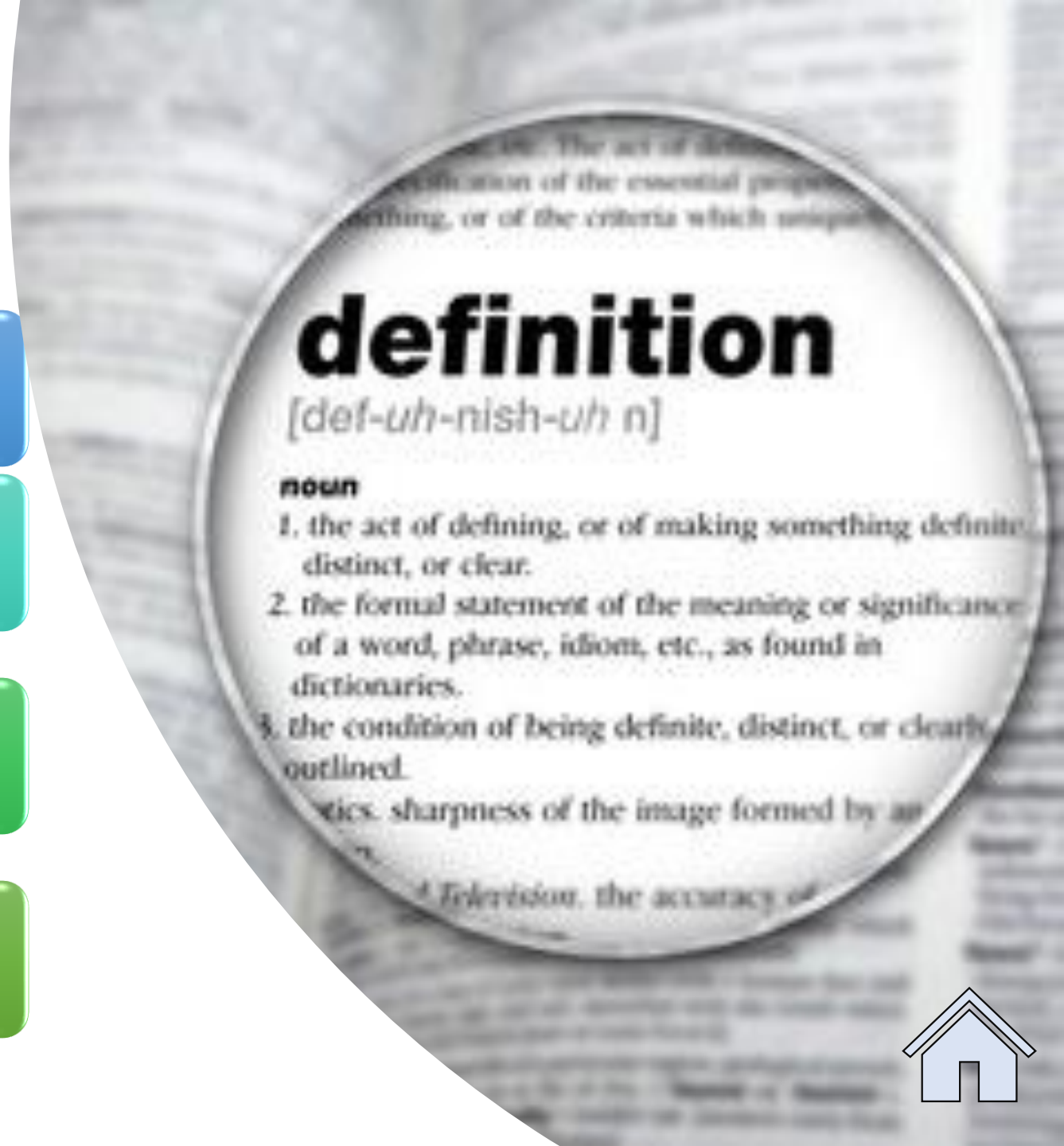
- Asymptomatic

Sickle cell disease (SCD): HbS + Other abnormal (C/D/thalassemia)

- Milder form

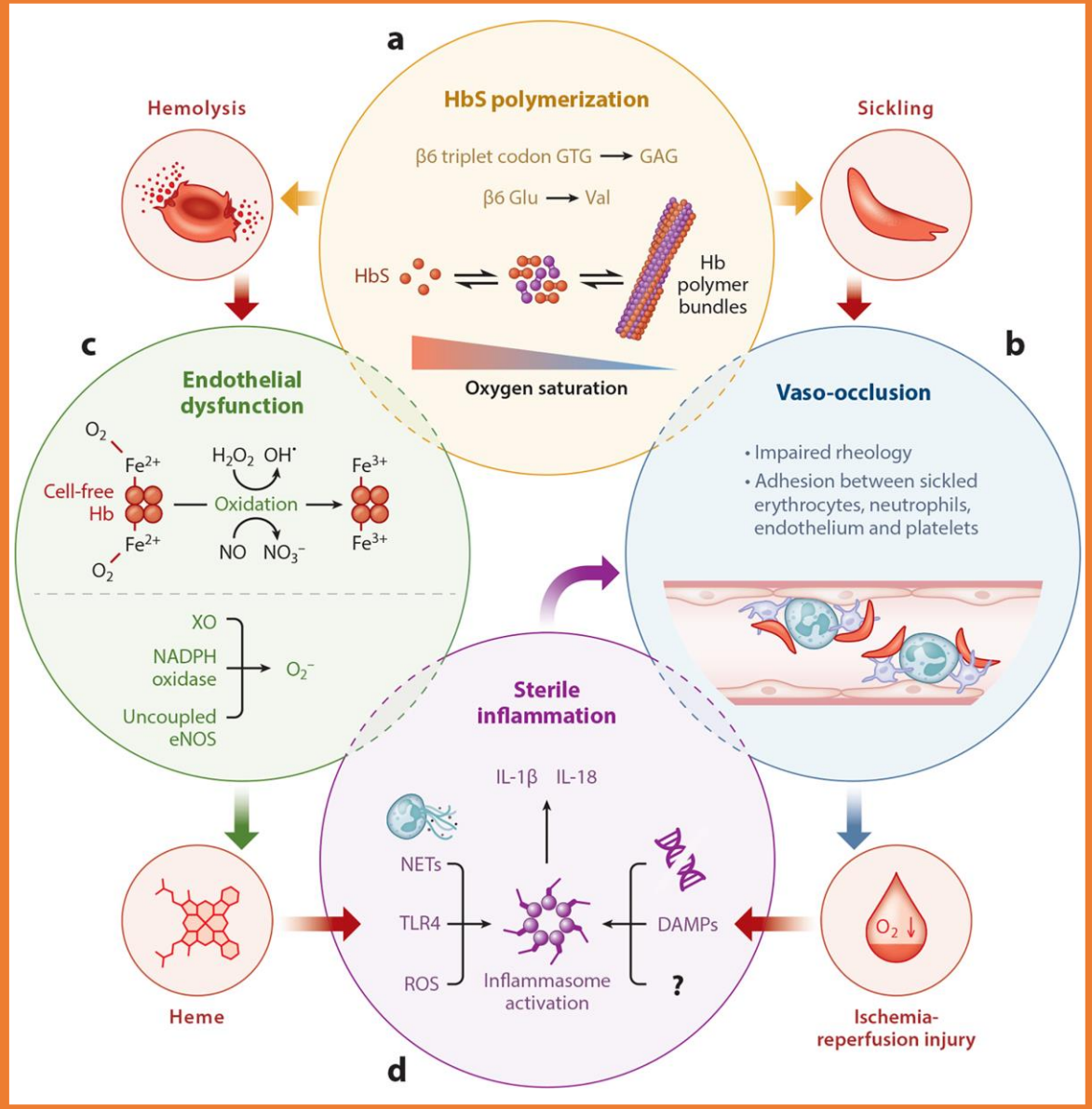
Sickle cell anemia (SCA): HbSS

- Earlier presentation tends to be more severe



Pathophysiology

Pg 1,4-5



RBCs deform and clump when oxygen deprived and occlude small blood vessels producing vascular damage, organ infarcts, painful episodes, anemia and other complications.

RBCs have a shorter life span and are easily hemolyzed

- HbS life span is 10 - 40 days

Average hemoglobin is 6 – 8g/dL

Presentation

Pg 5

Most children present after 3 months when fetal hemoglobin diminishes

Infancy: recurrent jaundice, dactylitis, and abdomen pain with anemia

Most commonly hospitalized for vaso-occlusion

- Could also present with splenic sequestration or aplastic anemia

Screening

Pg 1, 6-9

SCD trait affects 18% of Zambia, 12% of all cause admissions to UTH and is 4th cause of mortality in children

Early detection allows upstream interventions that are simple, proven and low cost which decrease morbidity and mortality

Screen all children and pregnant women

- <5yo, pregnant, post-natal if not tested
- Older children and adults if present with: bone/joint pains, recurrent abdominal pain, anemia, jaundice, stroke, heart/lung/kidney disease, gallbladder disease, avascular necrosis of femoral head, osteomyelitis, FH

Sickle SCAN: qualitative POC assay that detects A, C and S.

Sickling test: screens for RBC sickling. Cannot distinguish between heterozygous (disease) and homozygous (anemia)

Solubility test: distinguishes between heterozygous and homozygous

Newborn screening with heel stick dry blood spot tested (DBS) with IEF or HPLC (see diagnosis)

Diagnostic tests

Pg 6,9

NBS in infants <3 months of age

- DBS with IEF or HPLC

Confirmatory testing 3 months after the last transfusion

If screening test is positive a confirmatory test is needed

- Hemoglobin electrophoresis
  - Quantify amounts of hemoglobin
- Iso-electric focusing (IEF)
- High performance liquid chromatography (HPLC)
  - Quantifies amounts of hemoglobin

Curative therapy

Pg 65

Hematopoietic stem cell transplant (HSCT) - not available

Bone marrow transplant (BMT) – not available

Indications for BMT in children

- Stroke or silent cerebral infarction, recurrent acute chest syndrome or frequent VOC despite hydroxyurea with good compliance

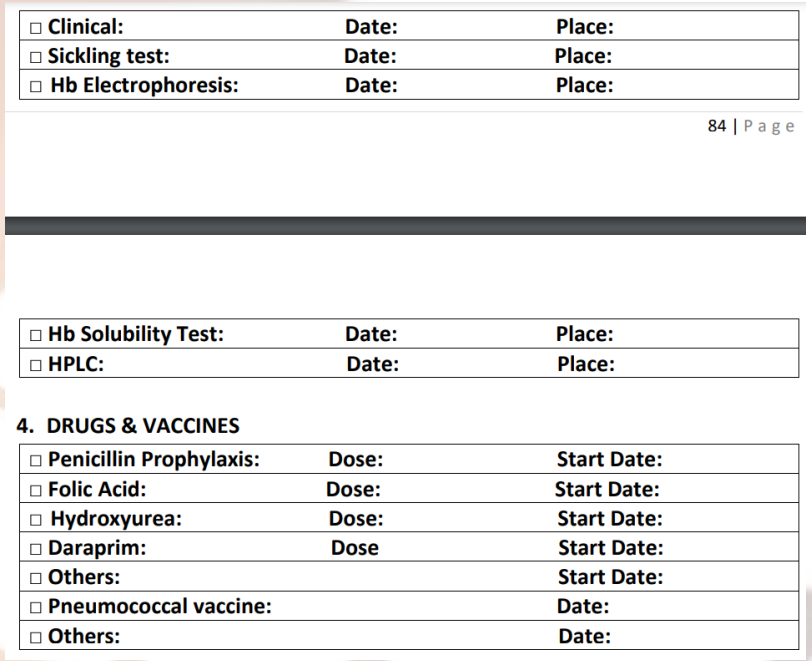
For Zambia consider treatment abroad in patients:

- Developing/with end organ damage despite chronic/prophylactic blood transfusion and/or maximal disease modifying therapy
- With silent or overt stroke
- With iron overload and cannot continue chronic transfusions
- Recurrent severe forms of VOC despite chronic/prophylactic blood transfusion and/or maximal disease modifying therapy

CCM/Prevention Checklist

Pg 12, 81-84

- Vaccinations
- Height and weight
- Blood pressure
- Pulse oximetry
  - If abnormal referral for echo and lung function
- Urinalysis
- FBC, KFTs, LFTs
- Blood group, HIV, Hepatitis status
- Hemoglobin electrophoresis
- Transcranial Doppler
- Prophylactic folic acid
- Prophylactic anti-malaria
- Prophylactic penicillin
- Hydroxyurea



□ Clinical:	Date:	Place:
□ Sickling test:	Date:	Place:
□ Hb Electrophoresis:	Date:	Place:

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□ Hb Solubility Test:	Date:	Place:
□ HPLC:	Date:	Place:

4. DRUGS & VACCINES

□ Penicillin Prophylaxis:	Dose:	Start Date:
□ Folic Acid:	Dose:	Start Date:
□ Hydroxyurea:	Dose:	Start Date:
□ Daraprim:	Dose	Start Date:
□ Others:		Start Date:
□ Pneumococcal vaccine:		Date:
□ Others:		Date:

Vaccinations

Pg 63

Table 12.2: Additional Recommended Immunization Schedule for SCD

Age group	Pneumococcus	Meningococcus
Under 2 years	Routine vaccination together with other childhood vaccinations[a] **PCV 10** or 13 starting at 6 weeks, given every 4 weeks for 3 vaccinations, followed by the 4th dose between 12-15 months	**Menveo vaccine** Dose 1 at age 8 weeks: 4-dose series at 2, 4, 6, 12 months Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after age 12 months)
Age 2–5 years (fully immunized)	Single dose **PPV**	Administer booster dose 3 years after completion of primary vaccination and then subsequent booster doses every 5 years
Age 2–5 years (unvaccinated or partially vaccinated)	Two doses of **PCV 10** given 2 months apart, followed 2 months later by PPV	Dose 1 at age 24 months or older: give 2-dose series at least 8 weeks apart
Age >5 years (fully vaccinated)	Single dose **PPV**	Administer booster doses every 5 years.
Age >5 years (unvaccinated)	Single dose **PPV**	Children without a history of Meningitis vaccination should receive 2 primary doses of Menveo at least 8 weeks apart (administer at least 4 weeks after completion on PCV13 series)
Reinforcing immunization	**PPV** every 5 years	Administer Menveo booster doses every 5 years.

Investigations

Pg 13

Age	Clinical Visit Frequency	Investigation
0 - 6 months	Monthly	FBC
6 months – 2 years	Every 3 months	FBC
2 – 5 years	Every 6 months	FBC LFTs and RFTs Yearly UA
Over 5 years	6 – 12 months	FBC LFTs and RFTs Yearly Urinalysis
Adolescents	Yearly Age-appropriate counselling	FBC LFTs and RFTs Urinalysis
Adults	Yearly	

Hydroxyurea

- How does hydroxyurea work?
- What effect on morbidity and mortality does it have?
- Who should be on hydroxyurea?
- How is hydroxyurea dosed?
- When should the dose be decreased?
- What if hematologic toxicity occurs?

Hydroxyurea

Increases fetal hemoglobin, reduces neutrophils, alters adhesion of RBCs to endothelium, increases water content of RBCs,

Reduces rate of sickle-cell crises, vaso-occlusive episodes, acute chest syndrome, transfusions, and hospitalization

Splenic preservation and long-term prevention of organ damage

Reduced mortality

All patient with sickle cell anemia (HbSS)

- Infants ≥ 9 months, children, adolescents with SCA regardless of severity
- Exclusions: acute liver disease, history of severe hydroxyurea toxicity or hypersensitivity, pregnancy or sexually active and unwilling to use contraception

Hydroxyurea

Pg 58

Baseline investigations

- FBC w/ diff, Hemoglobin electrophoresis with quant HbF%, chemistry profile, KFTs, LFTs

Dosing

- 20-25mg/kg daily, increased by 3-5mg/kg/day every 4-6 weeks as tolerated with a target absolute ANC of 2.0 - 3.0, max dose of 35mg/kg/day.
- Typically 26-28mg/kg/day but ranges from 20-30mg/kg/day.

Thresholds for reductions

- Check an FBC every 4-6 weeks and decrease if:
  - ANC <2, retic count <80, Platelets <80 or Hgb <7
  - Once on a stable dose check FBC every 3-6 months

If hematologic toxicity occurs

- D/c hydroxyurea until counts recover (5-7 days) then restart same dose
  - If threshold is reached again then reduce to previous dose

Folic acid

- Patients with SCA
- 5mg PO daily
- Prophylaxis in chronic hemolytic states

Anti-malaria prophylaxis

Deltaprim (pyrimthamine 12.5mg/dapsone 100mg) weekly

- < 5 years: 28.125mg
- 5 – 10 years: 56.25mg
- >10 years: 112.5mg

Proguanil

Malarone

TREATMENT

- Artemether-Lumefantrine (AL) given BD for 3 days, first two doses given 8 hours apart
  - <15kg: 20+120
  - 15-25kg: 40+240
  - 25-35kg: 60+360
  - ≥ 35kg: 80+480

Penicillin

Reduces risk of S. pneumoniae

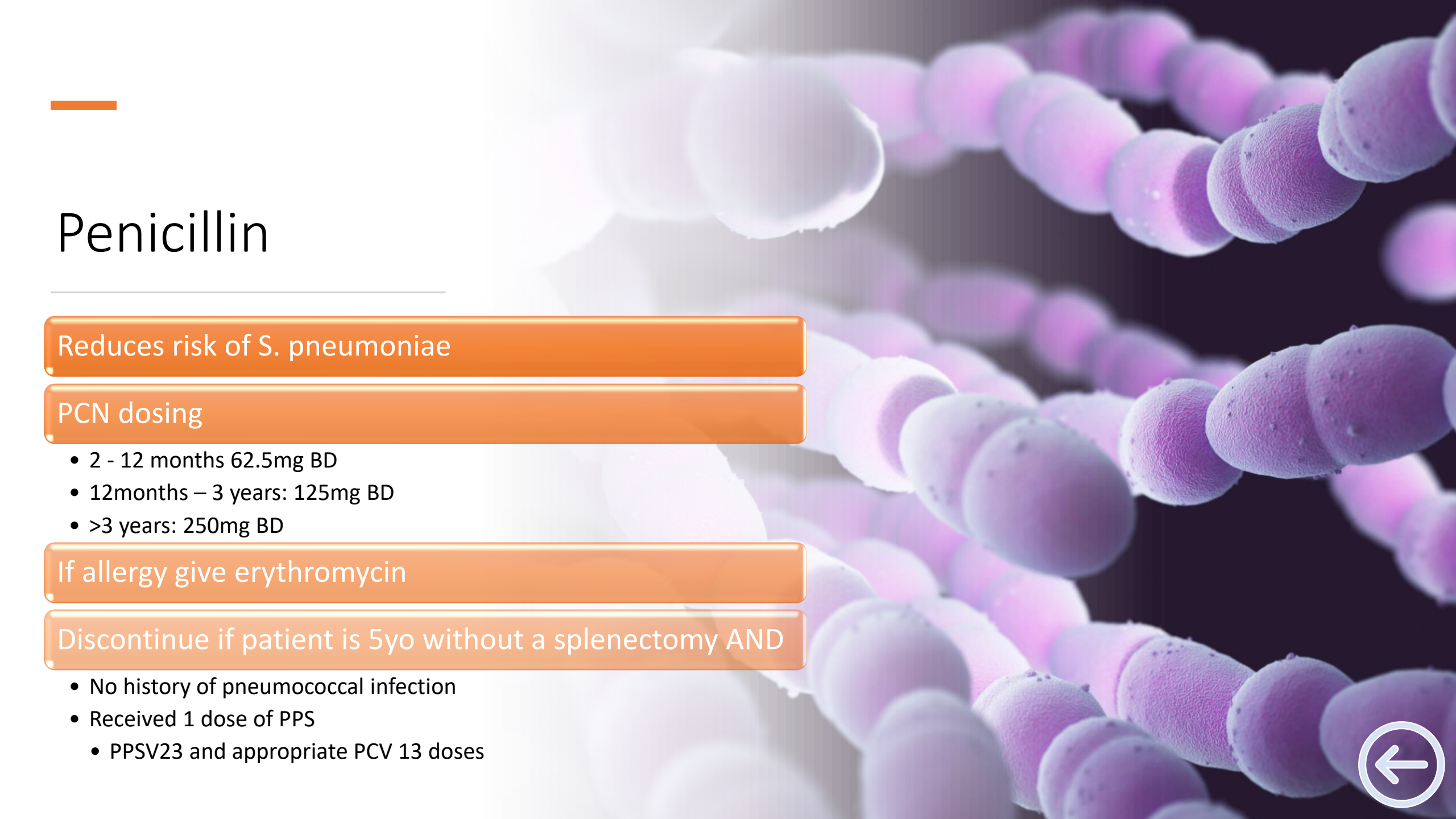
PCN dosing

- 2 - 12 months 62.5mg BD
- 12months – 3 years: 125mg BD
- >3 years: 250mg BD

If allergy give erythromycin

Discontinue if patient is 5yo without a splenectomy AND

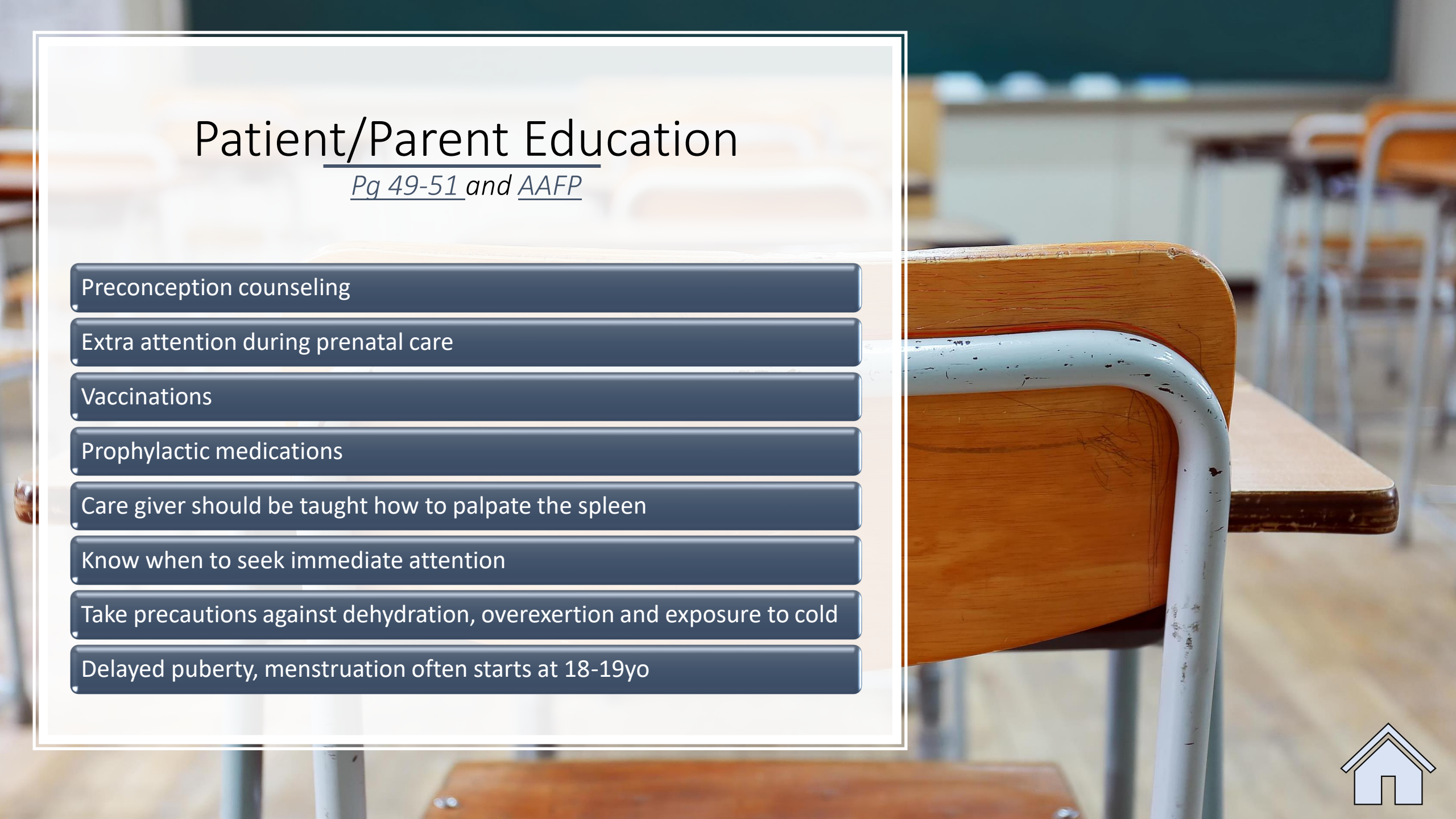
- No history of pneumococcal infection
- Received 1 dose of PPS
  - PPSV23 and appropriate PCV 13 doses



Patient/Parent Education

Pg 49-51 and AAFP

- Preconception counseling
- Extra attention during prenatal care
- Vaccinations
- Prophylactic medications
- Care giver should be taught how to palpate the spleen
- Know when to seek immediate attention
- Take precautions against dehydration, overexertion and exposure to cold
- Delayed puberty, menstruation often starts at 18-19yo



Know when to seek immediate attention

AAFP

- An enlarging spleen
- Temperature elevation
- Pallor of the skin, lips or nail beds
- Respiratory symptoms
- Signs of pain or inability to move extremities
- Earliest symptoms will most likely be painful swelling of the hands and/or feet (hand-foot syndrome)

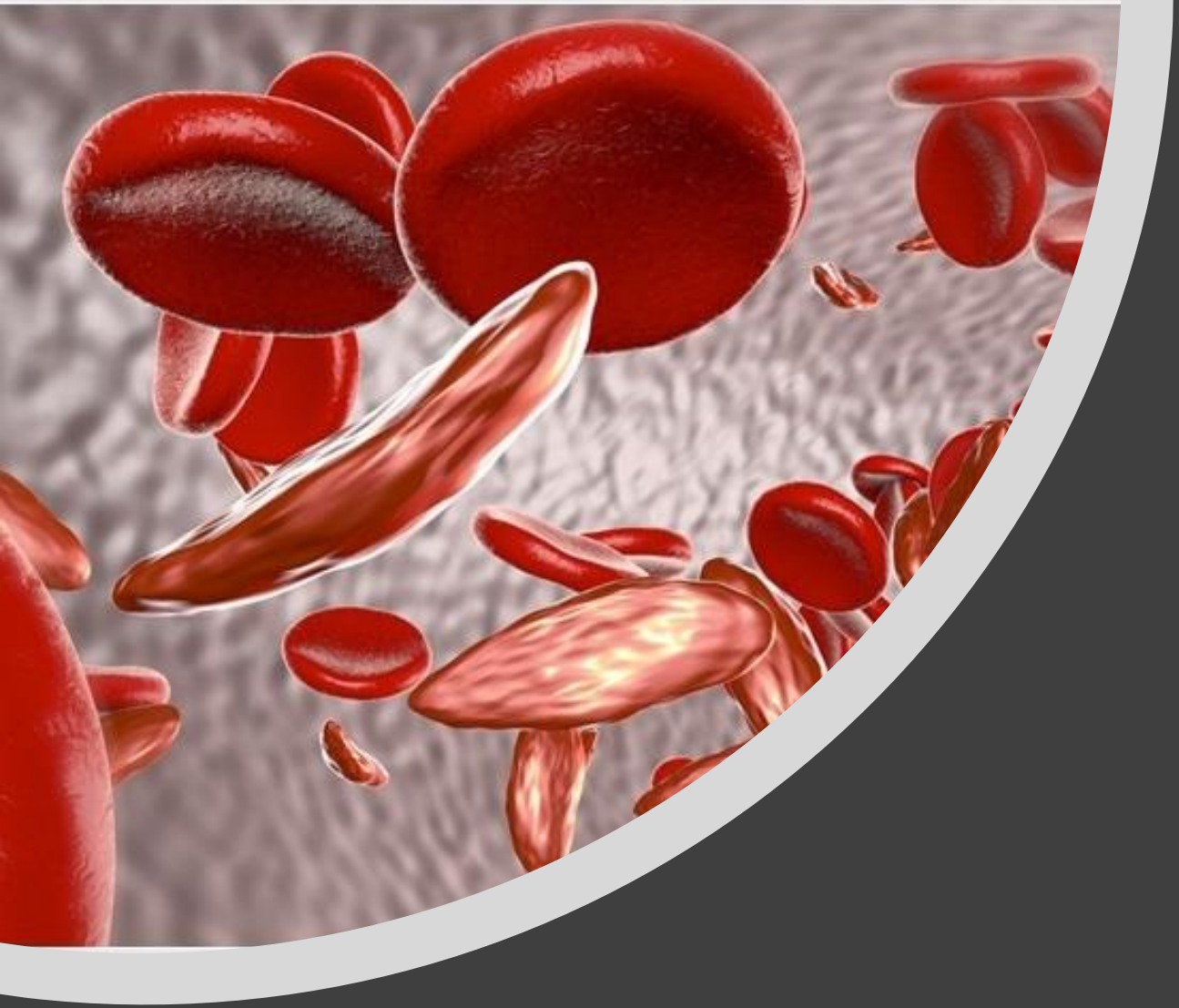
Complications

- Acute abdomen
- Acute anemia
- Acute chest syndrome
- Avascular necrosis
- Chronic skin ulcers
- Cholecystitis/cholelithiasis
- CNS infections
- Infections
- Osteomyelitis
- Painful crisis
- Priapism
- Renal disease
- Stroke
- Surgery
- Thrombocytosis

Painful crisis

Pg 14-16

- Vaso-occlusive pain usually in hands and feet in young children
- Long bones in older children
- Abdominal pain can mimic an acute abdomen
- IV access, IVF with 5% dextrose 1.5x maintenance, pulse, RR, pulse Ox
- Assess cause and severity of pain
  - IV abx if febrile
  - Reassurance, warm packs, reposition, massage, distraction
  - Mild: Paracetamol 15mg/kg QID or adult 1g qid
  - Moderate: mild + ibuprofen 5mg/kg TDS OR diclofenac 1mg/kg TDS
  - Severe: moderate + oral morphine 0.2-0.3mg/kg q4prn, Adult 5-10mg q4prn
    - Night dose 1.5-2x higher
- Stop fluids when stable and pain is controlled, weigh child daily



Acute anemia

Pg 17-18

Precipitous fall of Hb by 2.0g/dL below baseline

Acute splenic sequestration: EMERGENCY. Pallor, tachycardia, signs of hypovolemic shock, enlarged tender spleen.

- FBC, retic count, urgent transfusion of 20mL/kg of whole blood
- NS if no blood is not available while transferring to higher care
- Splenectomy when stable

Aplastic Crises (TRCA): Suppression of erythropoiesis from parvovirus B19

- Complications: BM necrosis, stroke, ACS, glomerulonephritis, sequestration
- FBC, retic count, Parvovirus B19 IgM
- Packed red cell transfusion and monitor retic count

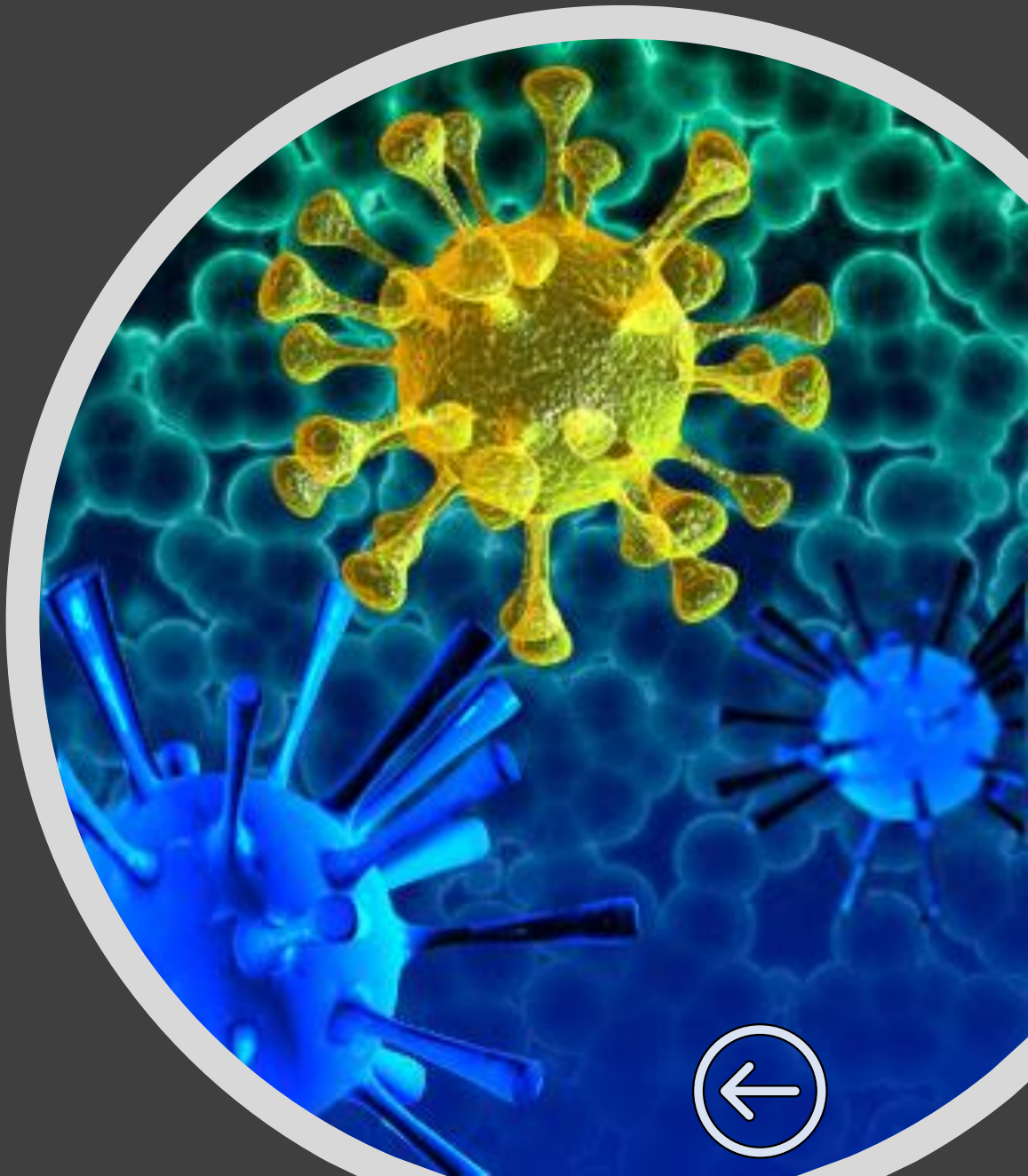
Hyper-hemolytic crisis: massive intravascular hemolysis

- Commonly precipitated by infections including malaria and drugs
- FBC, retic count, LDH, Bili, DAT, look for precipitating cause
- Transfuse if needed, treat underlying anemia, withdraw offending agents

Infections

Pg 19

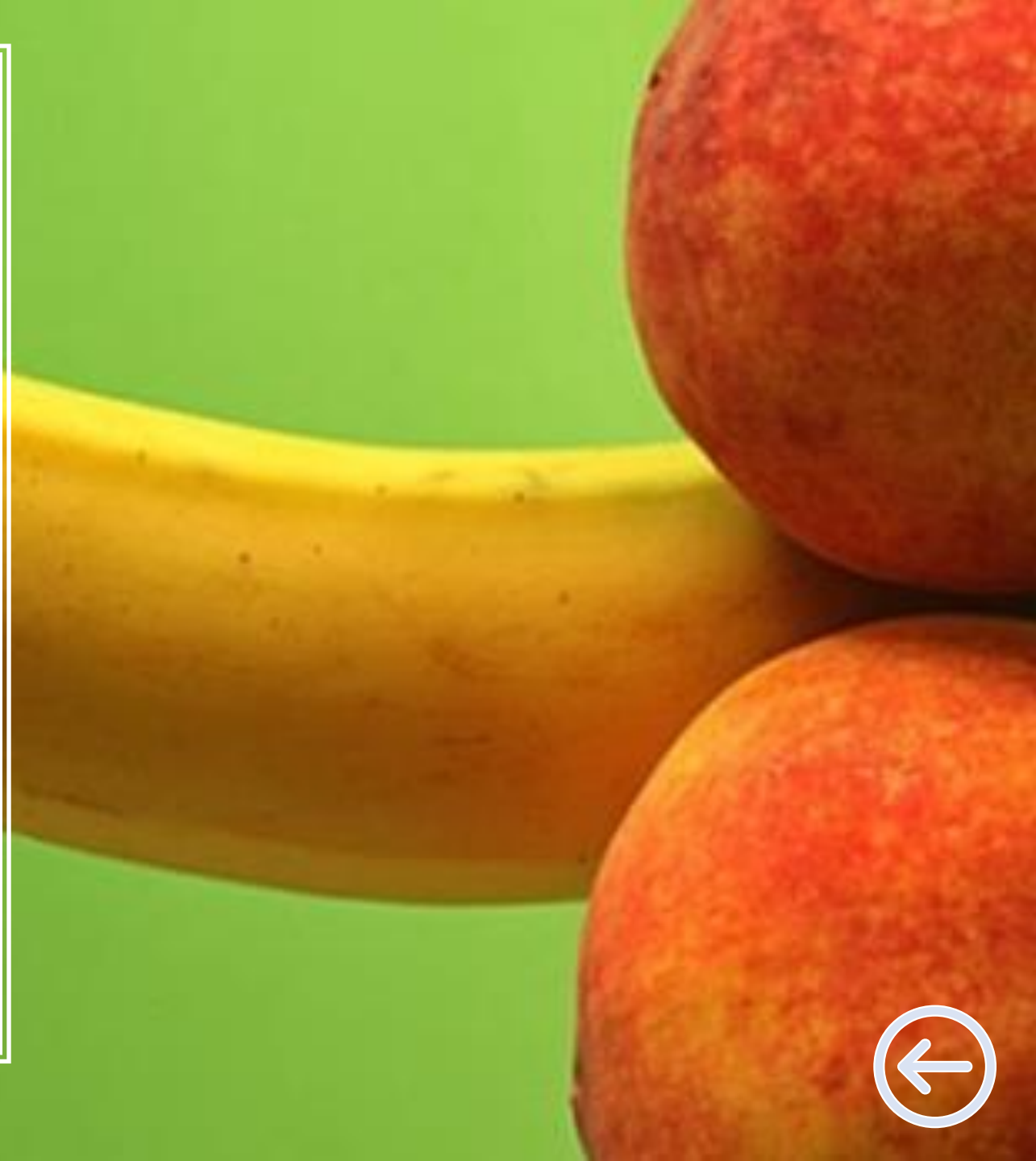
- 20-50% of SCD deaths
- Higher risk due to functional asplenia, default in complement, micronutrient deficiencies, genetic, mechanical factors
- Pneumococcal septicemia, meningitis, pneumonia, salmonella osteo
- Fever, bone tenderness, DB, CP, D/V, jaundice, stiff neck/HA, lymphadenopathy
- Temp ≥40 should be in-patient, < 38 observation
- FBC, malaria, UA, blood cx, sputum cx, CXR, LP if indicated
- Hydration, O2 prn, blood transfusion if Hb <5, paracetamol
- Abx: PCN, chloramphenicol or cefotaxime for at least 7 days
- If not improving after 48hours of abx and investigations think TB, PCP, mycoplasm



Priapism

Pg 21-22

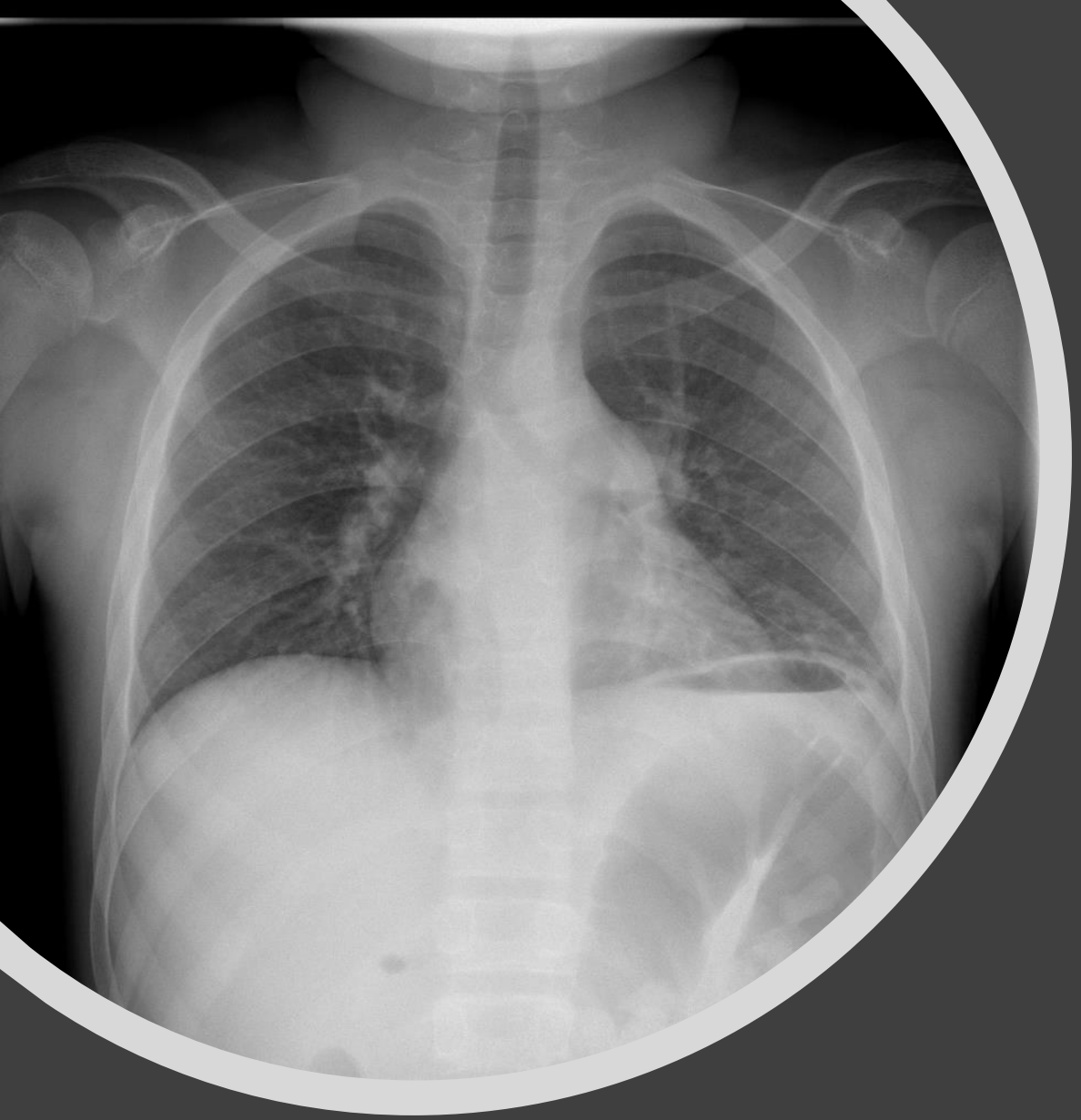
- 80% of males with have 1 episode by 20yo
- Prolonged: painful erection > 4 hours unrelieved by ejaculation
- Stuttering: repeated erections > minutes but < 4 hours
- Onset: oral fluids, attempt to urinate, oral analgesics, walking/warm baths
- > 4 hours: IV 1.25x maintenance fluids, opiods, anxiolytics, simple pRBC transfusion 10-15mL/kg, urology consult for aspiration
- If detumescence not achieved within 1 hour need to aspirate



Thrombocytosis

Pg 23

- Reactive and benign
- Differential: clonal thrombocytosis, CLL, CML, polycythemia vera, TTP
- FBC, ESR or CRP, MPS, PBS, LFTs, U&Es, Iron studies, ANA, RF, cytogenic analysis, BM aspiration, biopsy, Abd U/S
- Treated underlying cause
- If platelets ≥ 1,000 consider low dose aspirin



Acute chest syndrome

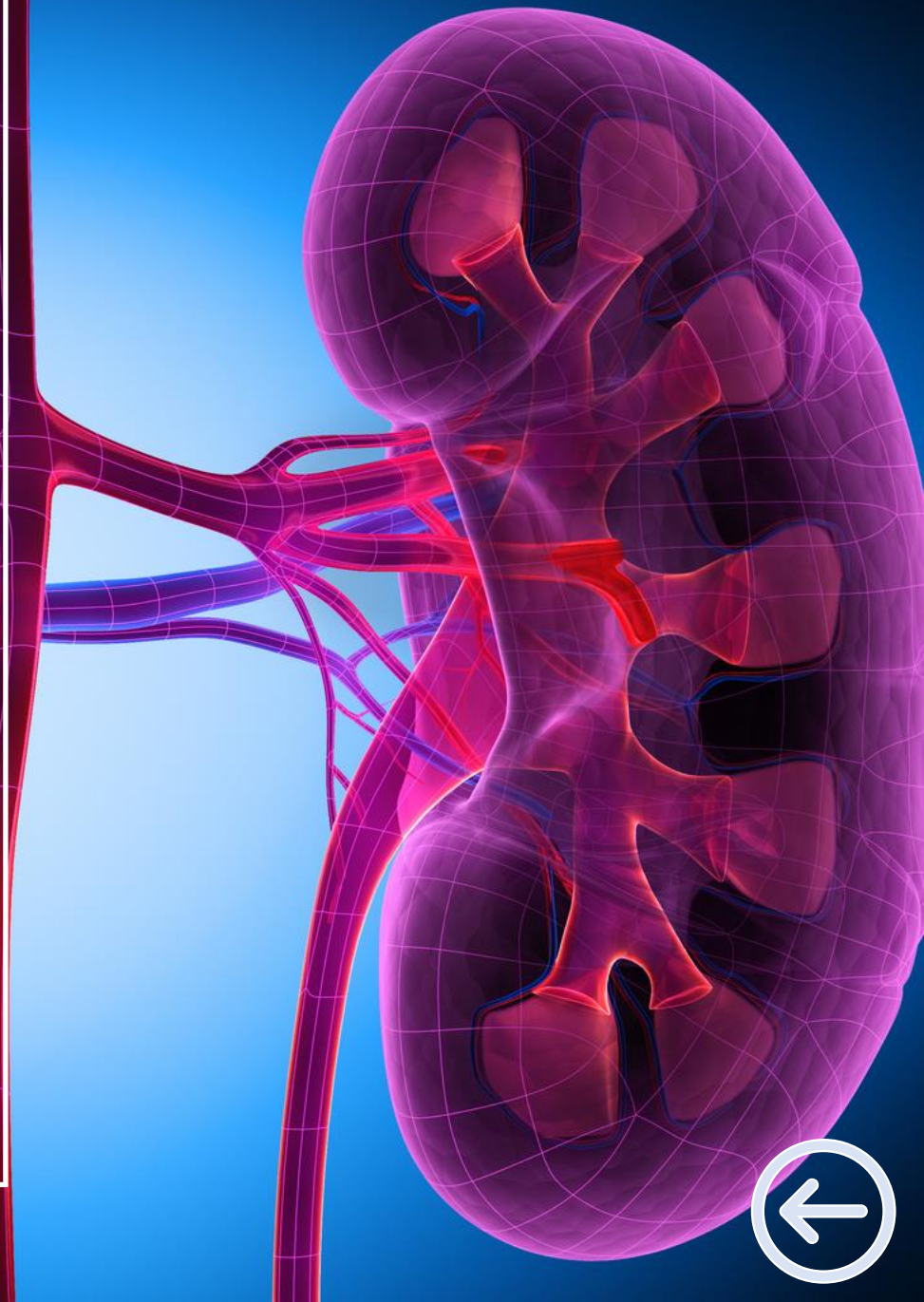
Pg24-25

- Mimics severe pneumonia, usually due to infection
- Most common cause of death, 2nd cause of hospitalization
- Sudden onset cough, SOB, nasal flaring, CP, hypoxia <95%, retractions
- RF: young age, low HbF, high steady state Hb, high steady state WBC, > episodes of VOC in year, asthma/airway hyperactivity, tobacco smoke/exposure, recent surgery
- FBC, retic count, group and match, blood cx, total bili, LDH, CXR (60% have infiltrate with normal PE), CRP/ESR, U&Es, LFTs, pulse ox
- Hydration IVF @ max of 2/3 maintenance if needed. Overhydration can lead to pulmonary edema
- Continuous monitoring of pulse, RR, O2 sats (maintain >94%), BP
- Blood transfusion: simple pRBC at 10-15mL/kg if severe anemia (<7 or drops > 2 from baseline), significant hypoxia, worsening respiratory status
- Antibiotics for pna: cefotaxime 200mg/kg q8 IV + Erythromycin 10mg/kg q4 for PO 10-14 days
- Bronchodilators if wheeze/reactive airway disease
- Complications from recurrent ACS: chronic hypoxemia, atelectasis, obstructive pulm disease, restrictive lung disease, fibrosis, Cor pulmonale, pulmonary hypertension

Renal disease

Pg 26-27

- Sickle cell nephropathy is associated with hypoperfusion
- UA, microscopy, renal function tests, Hep B and C, U/S
- Gross Hematuria: Usually self-limited. Bed rest, high urine flow rate, maintain UO >1mL/kg/min. +/- transfusions
- Proteinuria: No specific treatment slows or prevents progression of sickle cell nephropathy. ACEI and ARBs are used to reduce proteinuria
- Anemia in SCA with CKD: Hb goal no higher than 10 because sickling (VOC) is more likely at higher Hb levels
- ESRD: all forms of dialysis are acceptable and transplant is possible although outcomes are not as good as patients without SCA.



Stroke

Pg 29-30

Progressive occlusion leads to narrowing. Transcranial doppler (TCD) ultrasound can quantify fast and turbulent flow

PRIMARY PREVENTION

TCD should be preformed in children 2-16yo

- Abnormal TCD: >200 cm/sec
  - Chronic blood transfusion, repeat in 6 months
  - Then hydroxyurea (or if blood transfusion not feasible)
- Conditional: 170-199 cm/sec. Repeat in 1-3 months
- Normal TCD: <170 cm/sec. Repeat yearly

MANAGEMENT

- CTH
- Immediate simple blood transfusion with pRBCs or exchange transfusion within 4-6 hours of admission followed by hyper transfusion protocol. Hb should be maintained around but no greater than 11. Start hydroxyurea at 20-25mg/kg/day

CNS infections

Pg 33

Present with: HA, vomiting, neck stiffness, photophobia, febrile seizures, altered mental status

Investigations: FBC, renal function tests, liver function tests, blood culture, malaria, LP if not contraindicated, neuroimaging if indicated

Empiric antibiotics: with coverage for encapsulated organisms like x-pen and chloramphenicol or 3rd generation cephalosporin

Surgery

Pg 34-36

- Surgery can precipitate sickling
- 25-30% will have post-op complications
- Investigations: FBC, retic count, CXR, group and cross match, CMP
- Simple transfusion to reduce sickled cells and achieve a Hb of 9.5 - 10 and rehydration with 1.25x maintenance fluids the night prior to surgery
- Keep patient warm
- Hydrate during fasting periods
- Prevent hypothermia

Acute abdomen in SCA

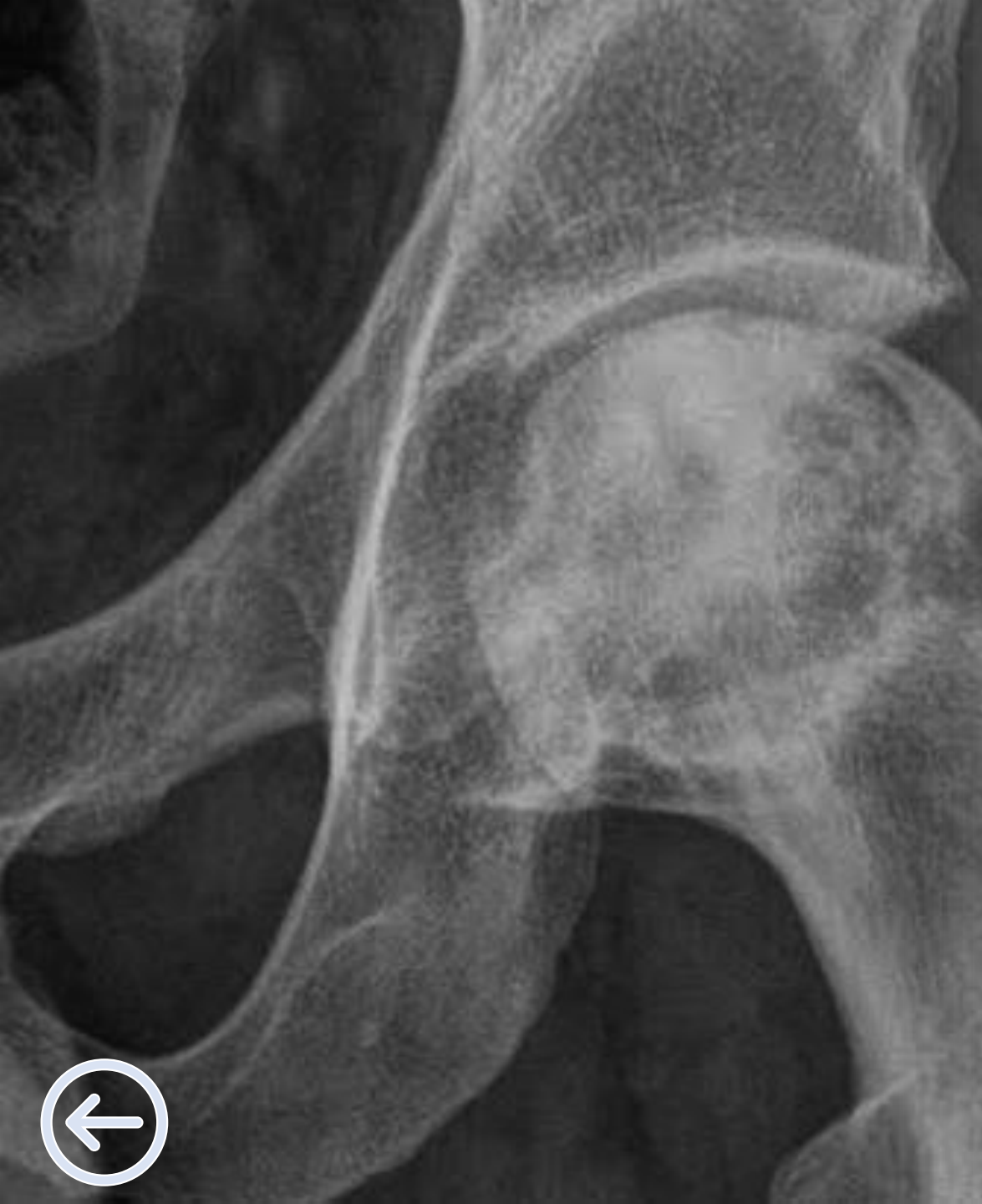
Pg 36-37

Presents as an acute abdomen and is difficult to differentiate between surgical cases

Investigations: UA, FBC, amylase, LFTs, blood culture, U/S, x-ray, CT/MRI

Treatment

- Abdominal VOC: conservative treatment with adequate hydration and pain control
- Antibiotics if UTI, appendicitis, cholecystitis, splenic abscess, peritonitis
- Surgical management if indicated



Avascular necrosis of femoral/humeral head

Pg 38

- Caused by intravascular sickling of red blood cells in the micro-circulation of the bone
- Develop chronic hip/groin pain with referred pain to knee/leg
- Investigations: FBC, blood cultures, U/S, x-ray, MRI
- Prevention: medical treatment to reduce VOC episodes
- Early evaluation of all cases of hip pain
- Conservative management: bed rest, traction, non-weight bearing, bracing and physiotherapy before AVN is radiographically present
- Surgical treatment for advanced cases
- Hydroxyurea and blood transfusion cannot reverse the process but can prevent progression to contralateral joint
- Pre-op and post-op transfusions for 3 months can maximize bone healing

Osteomyelitis

Typically in the lower limbs, tibia

Staph aureus is the most common organism

Salmonella is common as well

Need to differentiate between VOC induced bone infarct

Can present with F/C, irritability/lethargy, pain, swelling, warmth, redness, loss of movement, pyomyositis, pus, pathologic fracture or deformity

Investigations: FBC, blood cultures, CRP/ESR, x-ray, US/MRI, joint aspiration

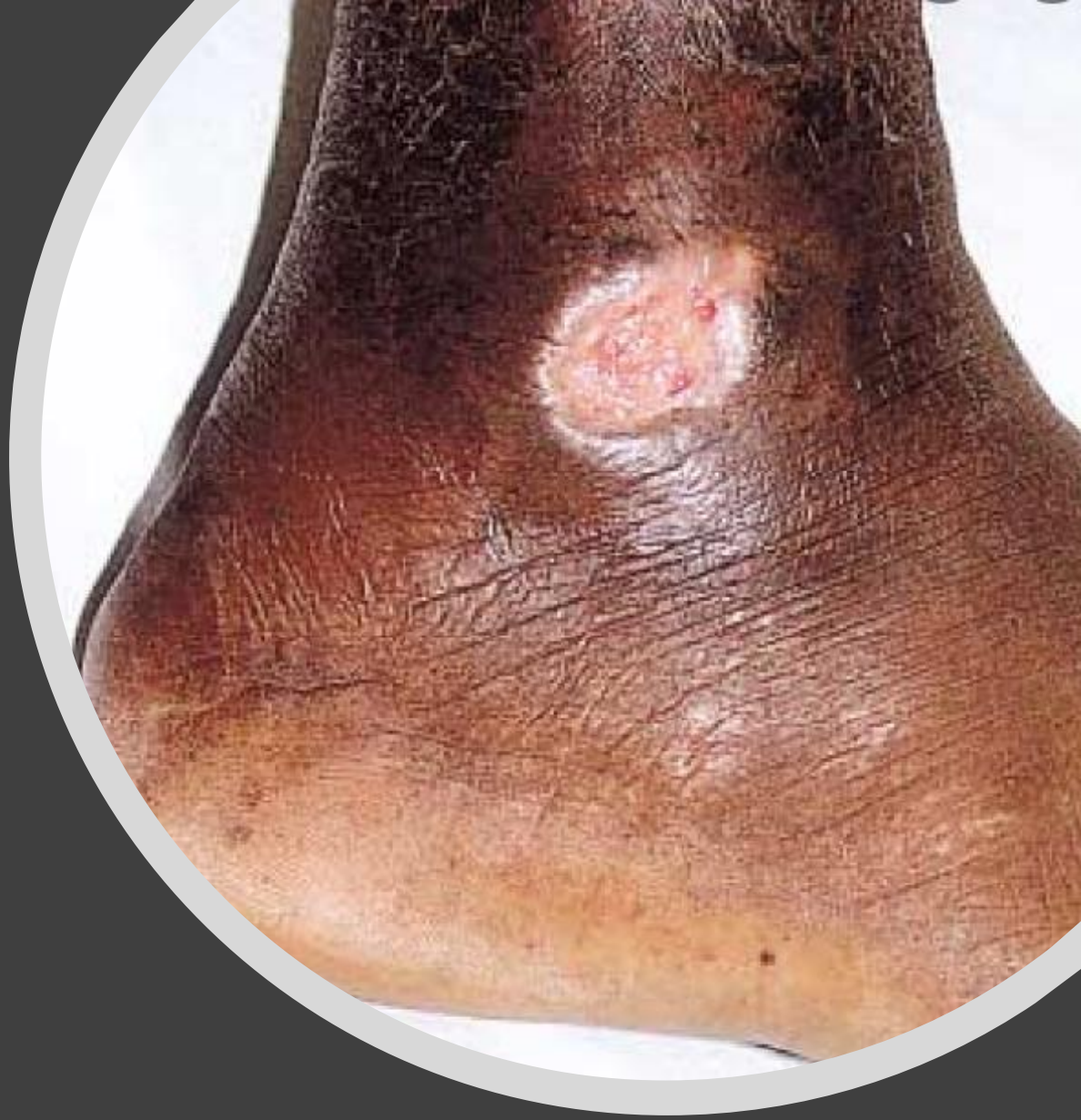
Management with cloxacillin, add a 3rd generation cephalosporin if gram negative and ciprofloxacin if salmonella is suspected

- 1 - 2 weeks of IV followed by oral for a total of 4 - 6 weeks

Serial infection markers, hydration, pain management, rest limb, ortho evaluation

Chronic skin ulcers

- Skin necrosis secondary to VOC or decub ulcers
- Presents with erythema, pain and dermal gangrene
- Investigations: FBC, ESR, pus swab
- Treatment is conservative aimed at keeping ulcer clean by regular daily dressings and patient education
- Bed red is essential
- Surgical debridement of thick slough with analgesia
- Surgical procedures reserved for those with unhealing ulcers >8 cm
- Hydroxyurea and recombinant human erythropoietin improving healing



Cholecystitis/cholelithiasis

Cholecystitis secondary to chronic hemolysis cholelithiasis although the stones are usually asymptomatic

Can precipitate a painful abdominal crisis

Manage initially with: metronidazole/cefotaxime

- Pain management
- Hydration
- Bowel rest

Once out of the acute phase will need cholecystectomy

Blood transfusions

Simple transfusions

- Blood Transfused = (Desired Hb – Actual Hb) x Total body weight x K
  - K=4 pRBC, 6 whole blood

Exchange transfusions

- Removal and replacement of patient blood by transfusion, decreases blood viscosity; preferred for cases requiring immediate or sustained reduction in complications of SCD without increase in blood viscosity
  - Volume of blood (mL) x 100 = (Desired Hb – Actual Hb) x Total body weight x 3
  - If above 50kg: Blood Transfused = (Desired Hb – Actual Hb)

Hypertransfusion therapy/Chronic blood transfusion

- Chronic transfusion is indicated when sustained low levels of HbS is required for primary or secondary prevention of SCD-related complications

Simple	Exchange	Chronic/hypertransfusion
Surgery	Acute chest syndrome	Prevention of stroke
Splenic/hepatic sequestration	Recurrent stroke	Prevention of repeat stroke
Aplastic episode	Multiorgan failure	Recurrent VOC
Sepsis		Recurrent ACS
Acute anemia		Pregnant SCD with previous OB complication
		Delayed growth and development in children with SCD

Blood transfusions