Thalassaemia

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Haemoglobinopathies

- **Due to structural abnormality of one of the chains**
  - sickle cell ($\alpha_2\beta_2^6$valine for glutamic acid)
  - haemoglobin C ($\alpha_2\beta_2^6$lysine)
  - haemoglobin E ($\alpha_2\beta_2^{26}$lysine for glutamic acid)

- **Due to reduced synthesis of one globin chain and resulting in imbalance**
  - Thalassaemia α and β

Thalassaemia syndrome

is **characterised by decreased synthesis of one of the two types of polypeptide chains**

- **β thalassaemia** – β chains are reduced and α α chains are in excess (which precipitate in red cell precursors – ineffective erythropoeisis)

- **α thalassaemia** – α chains are reduced and β chains are in excess

β thalassaemia

- **One affected allele** (11 chromosome) heterozygous carrier or trait/minor

- **Two affected genes** – Phenotypes thalassaemia major and thal. intermedia

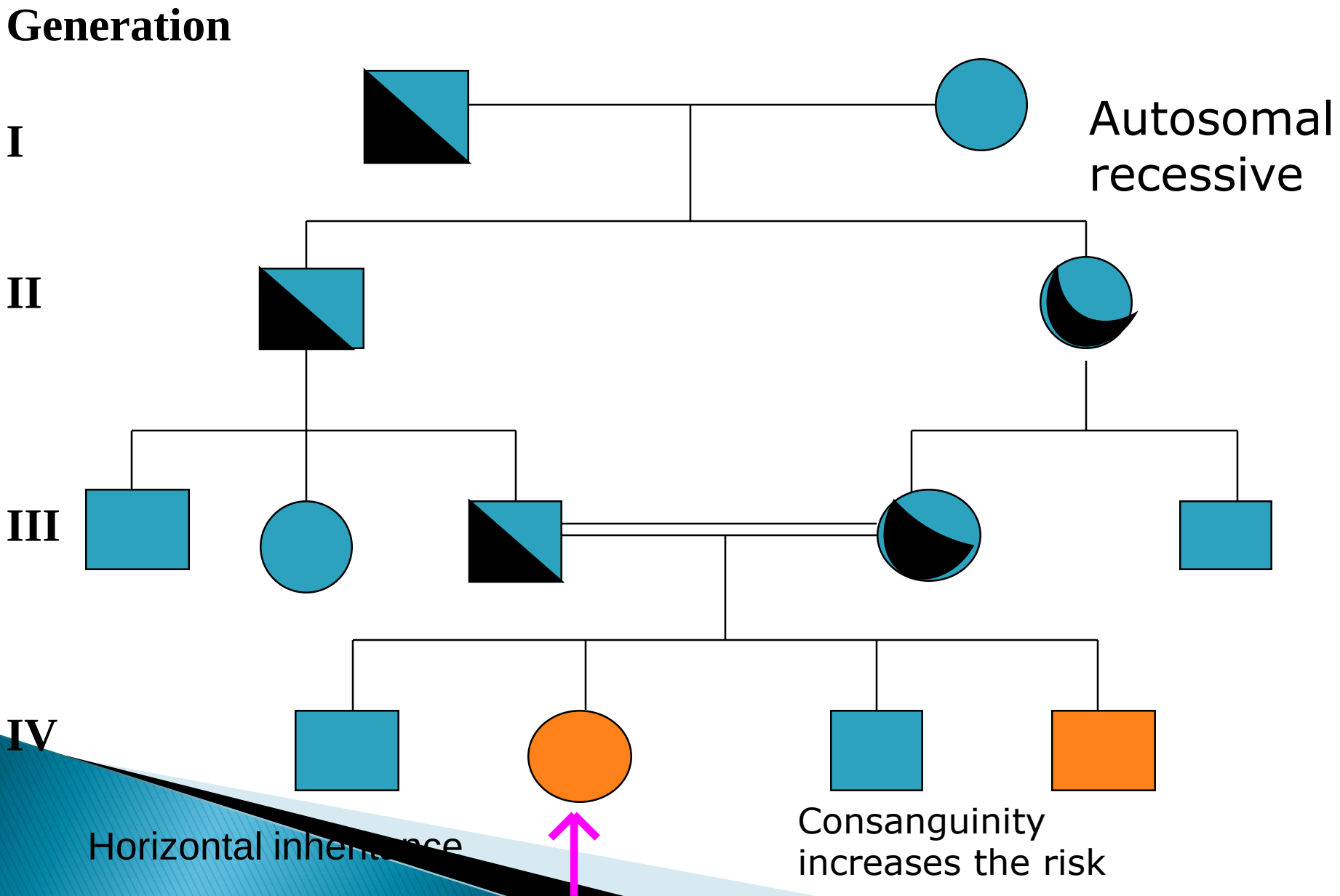
  β^0, β^+, β^{++} in thal. Major

- **Other β structural Hb**

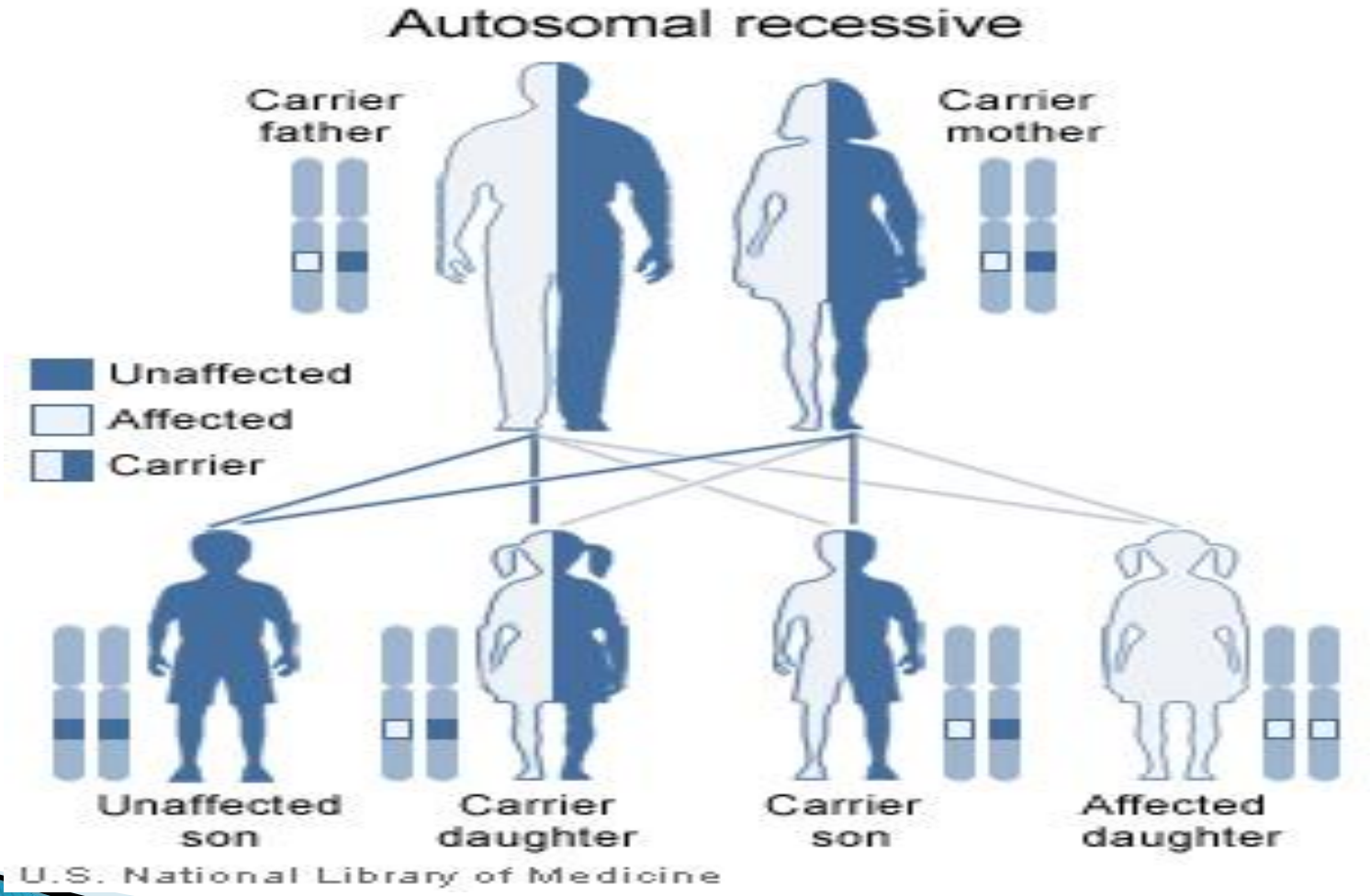
  Variants behaving similar to thal. such as HbE and HbE β thalassaemia

  Both common in SE Asia and Indian subcontinent

Thalassaemia – Inheritance



Thalassaemia – Inheritance

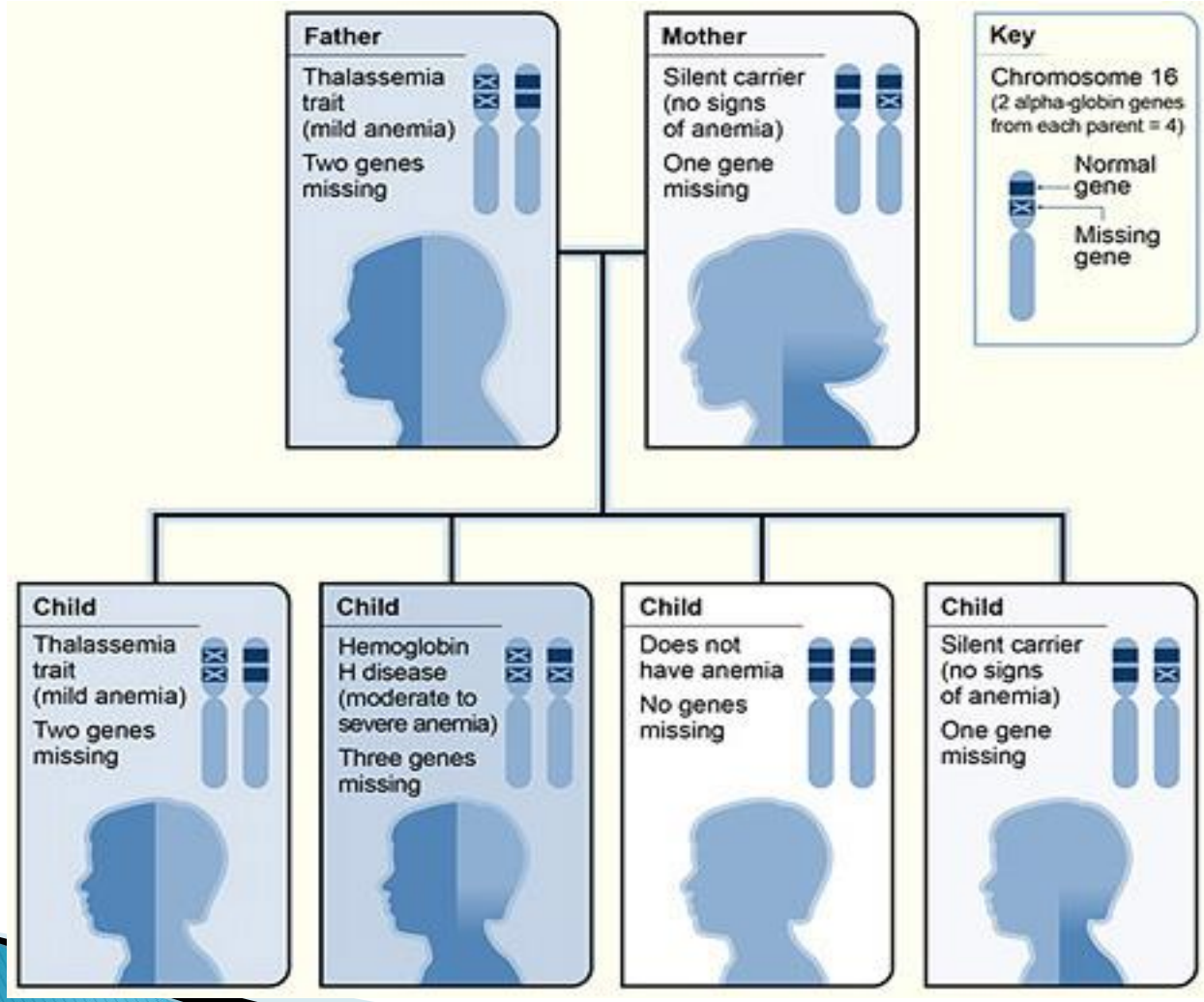


α thalassaemia

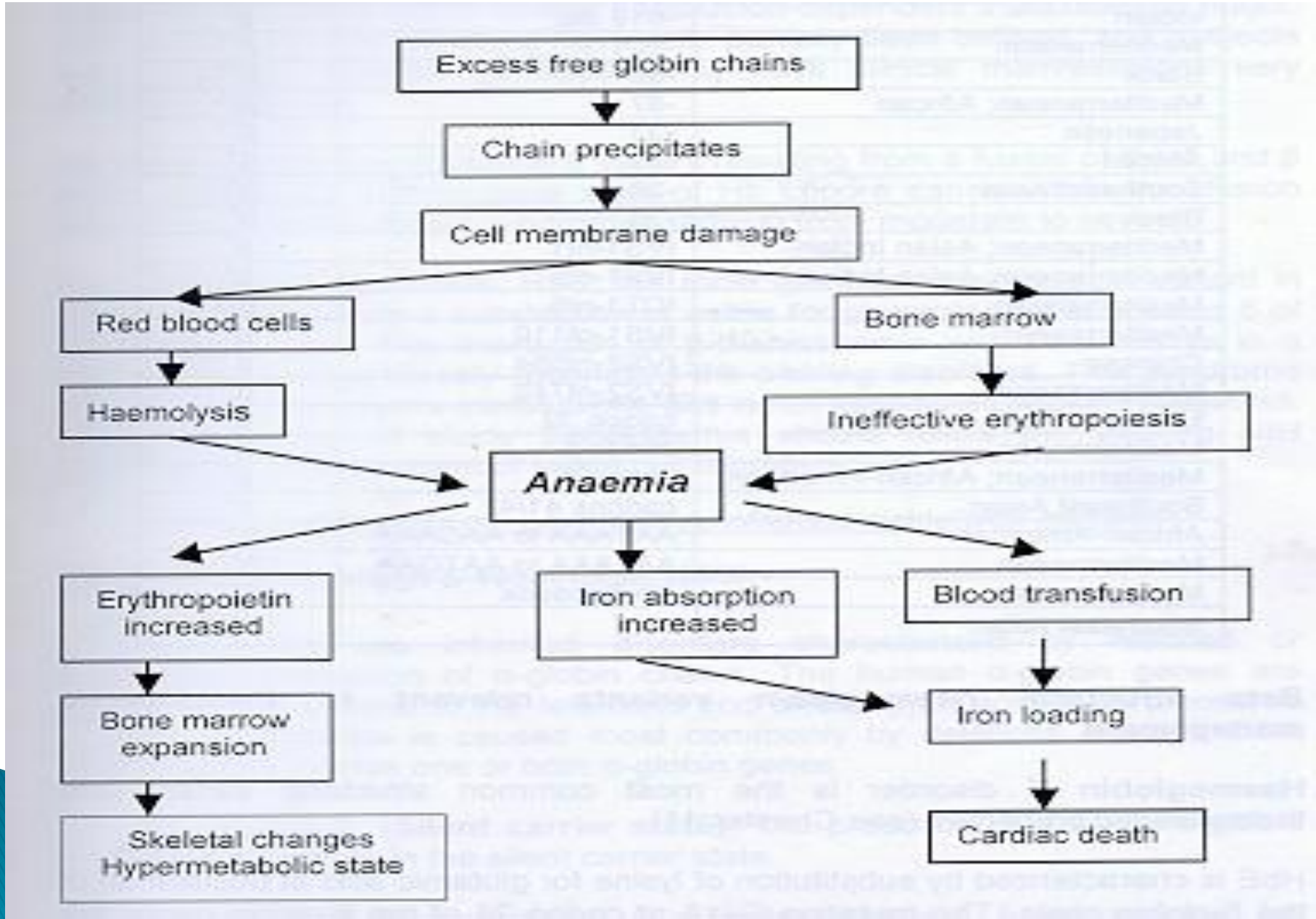
Human α genes are duplicated and located in chromosome 16.

- αα/αα — normal
- −α/αα — silent carrier, haematology is normal
- −−/αα or −α/−α — α thalassaemia trait
- −−/−α — HbH disease (mod. anaemia, splenomegaly, haemolytic crisis with drugs and infections)
- −−/−− — Hb Bart disease (hydrops fetalis)

Alpha thalassaemia inheritance



β thalassaemia – pathophysiology



Clinical features β thalassaemia

- Presents at 2nd 6 months of infancy with features of progressive chronic haemolytic anaemia including mild jaundice & failure to thrive
- Progressively enlarging spleen and liver
- Skeletal deformities
- Features of iron overload

Clinical features β thalassaemia

Clinical features of β thalassaemia

Beta Thalassemia Major – bone changes

Skeletal deformities

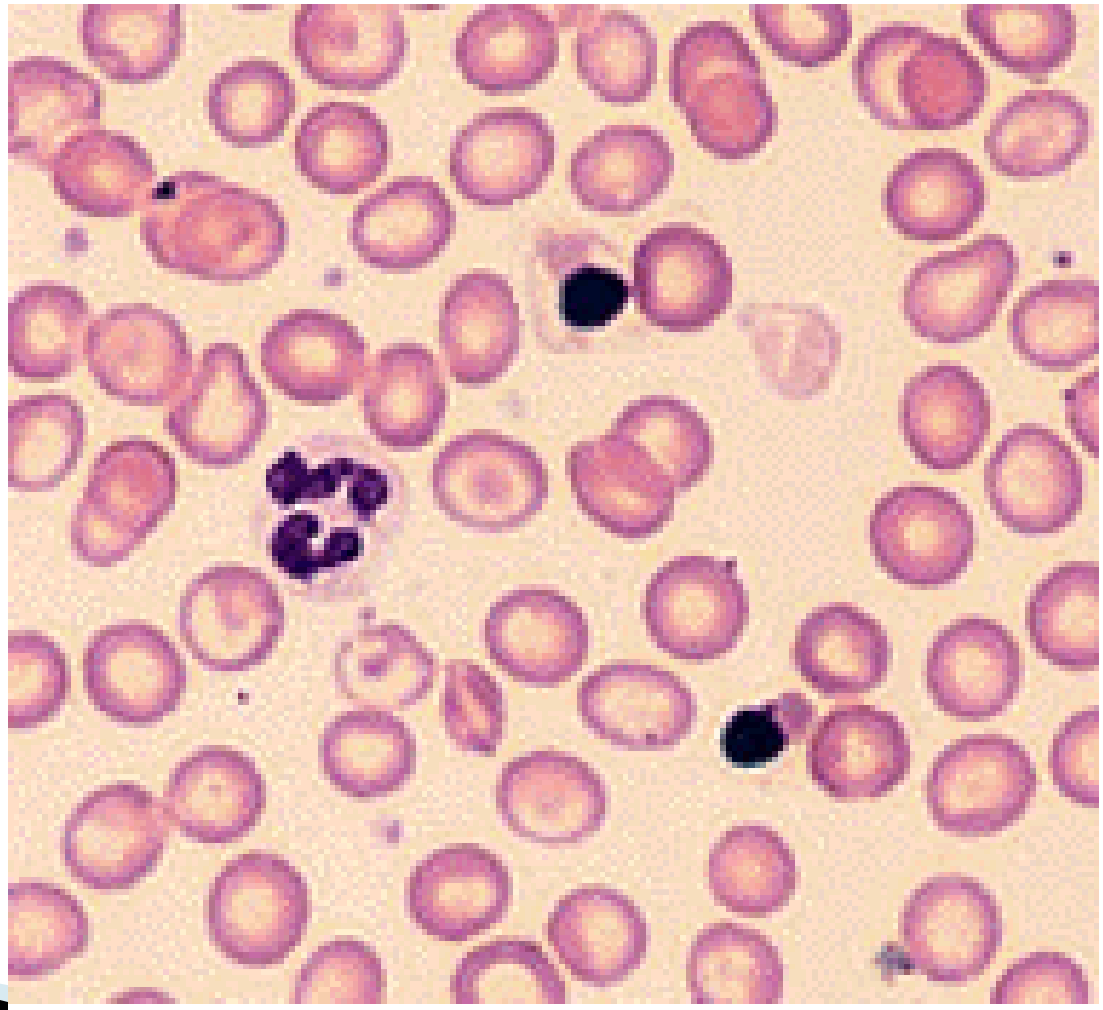
- skull bossing
- scaphocephaly
- prominent maxilla
- flat nasal bridge
- malocclusion of teeth
- pigmentation of the skin
- bone tenderness and fractures
- deformities in legs similar to rickets

typical thalassaemic facies

Investigations

- FBC including Hb
- Blood picture
- Reticulocyte count
- HPLC (high performance liquid chromatography)/Hb electrophoresis

Thalassaemia blood picture



X-ray changes β thalassaemia

Hair on end appearance

HPLC / electrophoresis

- HbF ~70% at birth
- By 6-12 months only traces are present
- Normal child - HbA 98%, HbF traces, HbA_2 2%

Hb electrophoresis

Type	HbA	HbF	HbA_2
β^0	Nil	>90%	↑
β^+	~10%	~80%	↑
β^{++}	~40%	~60%	↑

Management of thalassaemia (transfusion dependent chronic haemolytic anaemia)

- Regular blood transfusions
- Iron chelation therapy
- Splenectomy
- General management
- Management of complications
- Genetic counselling
- Prevention

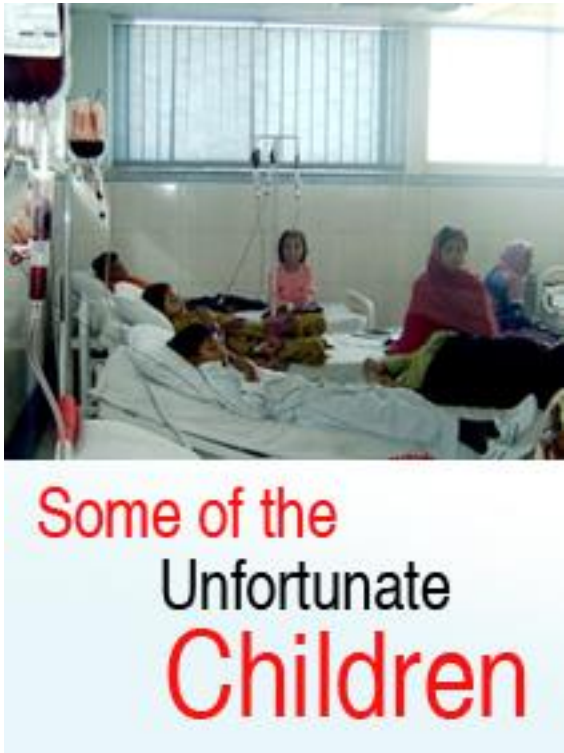
Regular blood transfusion

- Why?

To correct anaemia

To improve physical and mental well being

To suppress extramedullary erythropoiesis



Regular blood transfusions ctd

- Every 3-4 weeks
- Pre-transfusion Hb at 9 g/dl – 10.5 g/dl
- ABO, Rh & other blood group compatible, if not available O blood can be given
- Red cell phenotype should be done at the beginning for future reference

Regular blood transfusions ctd

- Blood should be < 2 weeks old , Packed cells , PCV at least 75%
- Leucodepleted (leucoreduced) blood is used most of the time
- Irradiated and CMV free blood to be used if planning for bone marrow transplantation
- Washed red cells are given for children had febrile reactions

Regular blood transfusion ctd

- Deficit(14-pre transfusional Hb) x wt (kg) x 4
- Maximum amount of blood to be given on a day – 15 ml/kg/day
- Better to give with a midway IV furosemide 1 mg/kg
- Hb drops by 1 g/dl/wk

Complications of blood transfusion

- Iron overload
- Transfusional reactions
- Transfusion transmitted infections

Iron overload

- As a result of regular blood transfusions (500 ml of blood will give 200 mg of iron)

- Increased intestinal absorption of iron due to anaemia

Why iron is toxic to the body

free iron (non transferrin bound)

causes cell death and fibrosis by free radical formation

Features of iron overload

- **Liver:** Organomegaly, cirrhosis, hepatic fibrosis
- **Heart:** Cardiomegaly, Cardiomyopathy, CCF & Arrythmias
- **Endocrine organs :**

Pancreas	– Diabetes mellitus
Pituitary failure	– hypothyroidism
	– growth failure and delayed puberty
Parathyroid	– Hypoparathyroidism

Skin pigmentation

Investigations to assess iron overload

- **Liver** – Liver functions
  (derangement may be due to transfusion transmitted hepatitis, iron chelation related side effects, etc)
  - –Liver iron concentration (LIC) by **Ferriscan**
  - – **LIC by liver biopsy** – invasive . Can miss true level of iron overload due to patchy deposition of iron
  - – **SQUID** (super conducting quantum interface device)

Investigations to assess iron overload

- **Heart :**
  - 2D ECHO : To assess ejection fraction and chamber size

  -T2 MRI

Investigations to assess iron overload

- **Endocrine organs :**
  - RBS/FBS/OGTT
  - GH assay
  - Thyroid functions
  - FSH/LH
  - S Ca/ PTH

Iron chelation

- Starting point: From 10th transfusion or depending on serum ferritin levels >1000 µg/l

- Available medications
  - Desferrioxamine
  - Deferasirox
  - Deferiprone

Desferrioxamine

- Desferrioxamine is the drug of choice initially , first introduced in 1970s
- Chelates iron & has a very short half life (0.5 hours)
- It has a very poor bioavailability when give orally
- Administrating routes : SC / IV

Desferrioxamine therapy

- Ideally should be given as a slow infusion (subcutaneous) over 8-10 hours (up to 12-24 hours) daily for at least 5-7 days per week

- 30-50 mg/kg/day – subcutaneously
- 60 mg/kg/day – IV

- Should run over minimum of 6 hours
- Max rate 15 mg/kg/hour
- Vitamin C: 2-4 mg/kg/day just after starting infusion

Desferrioxamine therapy

Desferrioxamine – side effects

Local pain and tenderness

Fat necrosis and abscess formation

Hypersensitivity

Infection with Yersinia

Visual impairment – eg maculopathy

Hearing defects

Skeletal abnormalities

Growth retardation

Side effects are more in children< 2 years and children with minimum iron stores

Iron chelation – Deferasirox

- Oral iron chelating agent
- High bioavailability with oral route
- Half life 12-16 hours enables once daily dosing
- Dispersible tablets
- Tablets are available in 100 & 400mg
- Used in children 2 years and over

Iron chelation – Deferasirox

- Starting dose – 20 mg/ Kg / day
- Can go up to 40 mg/kg/day
- Method of administration
  - Taken once daily
  - Taken on an empty stomach at least 30 minutes before or30 minutes after food
  - Preferably same time each day
  - Tablets are dispersed by stirring in a glass of water or apple or orange juice (100–200ml) until a fine suspension is obtained

Iron chelation – Deferasirox

- Method of administration

  - After the suspension has been swallowed , any residue must be re-suspended in a small volume of water or juice and swallowed

  - The tablets must not be chewed or swallowed whole

  - Dispersion in carbonated drinks or milk is not recommended due to foaming & slow dispersion respectively

Iron chelation – Deferasirox

- Contraindications
  - Creatinine clearance <40ml/min or serum creatinine > two times the age appropriate upper limit or normal
  - Hypersensitivity to the tablet

Iron chelation – Deferasirox

- Before starting Deferasirox
  - Liver functions (SGPT & SGOT)
  - Renal functions (S. Creatinine)

Iron chelation – Deferasirox

- Monitoring during treatment

TEST	FREQUENCY
S. Ferritin	Quarterly
S. Creatinine	prior to therapy and 3 monthly thereafter
Proteinuria	Monthly
Liver function	Monthly
Auditory and opthaimic	Prior to therapy and yearly thereafter
Growth	Yearly

- Weekly monitoring of serum creatinine is recommended in the first month after initiation or modification of therapy and monthly thereafter for patients with preexisting renal conditions or patients who are receiving medicinal products that depress renal function

Iron chelation – Deferasirox

- Side effects
  - Gastrointestinal disturbances (nausea / vomiting / diarrhoea / abdominal pain) 26%
  - Mild, non-progressive increase in serum creatinine
  - Skin rash 7%

    Above are dose dependent adverse effects
  - Elevated liver enzymes

    Not dose dependent

Iron chelation – Deferasirox

- How to manage side effects
  - GI : Advise to take Deferasirox in the evening rather than in the morning
  - Hypersensitivity : If angiodema or anaphylaxis develops discontinue the drug & appropriate medical intervention should be instituted
  - Skin rash : If mild- moderate continue the drug

Deferiprone

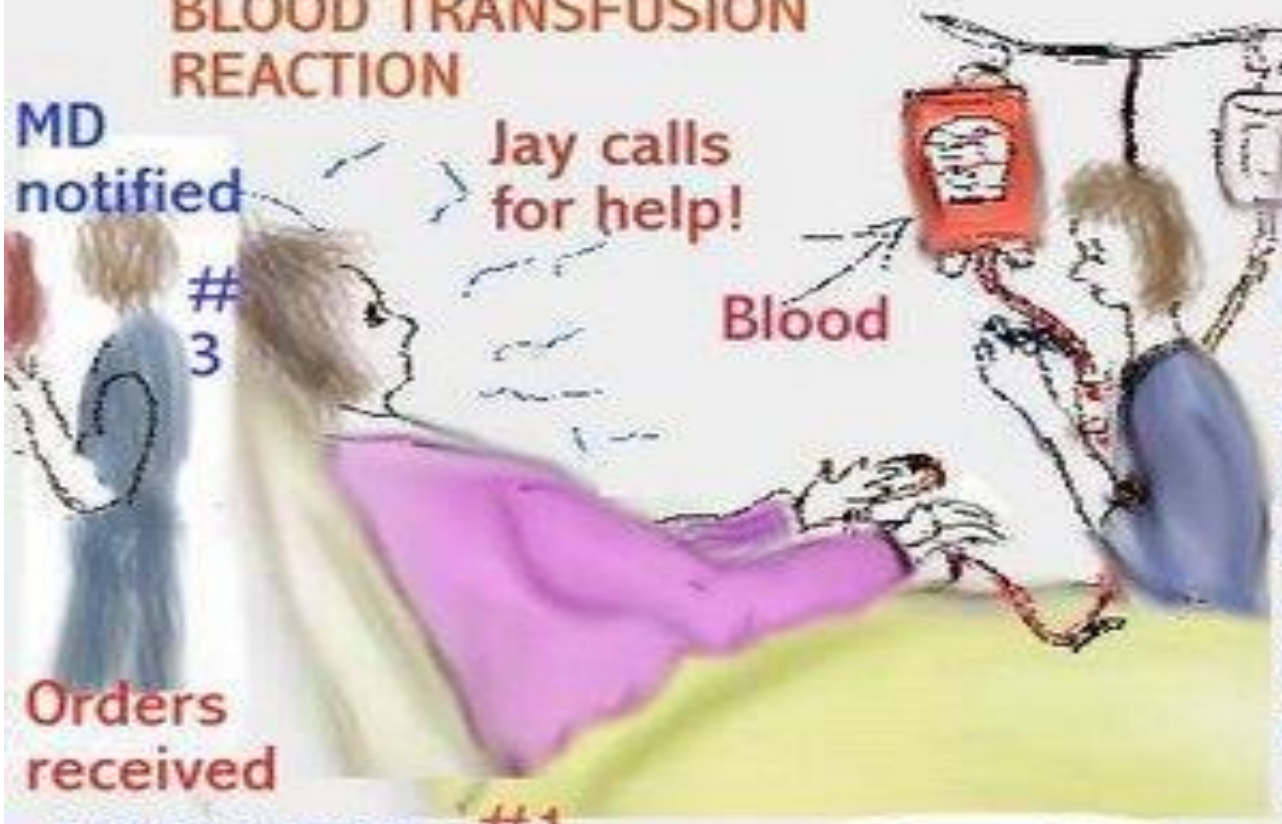
- registered in Sri Lanka in year 2000
- given orally as a second line therapy
- the dose varies from 50-75 mg/kg/d
- combine therapy with desferrioxamine is a method of current treatment mainly for cardiac iron overload

- 5% have side effects including GIT irritation, arthropathy, agranulocytosis

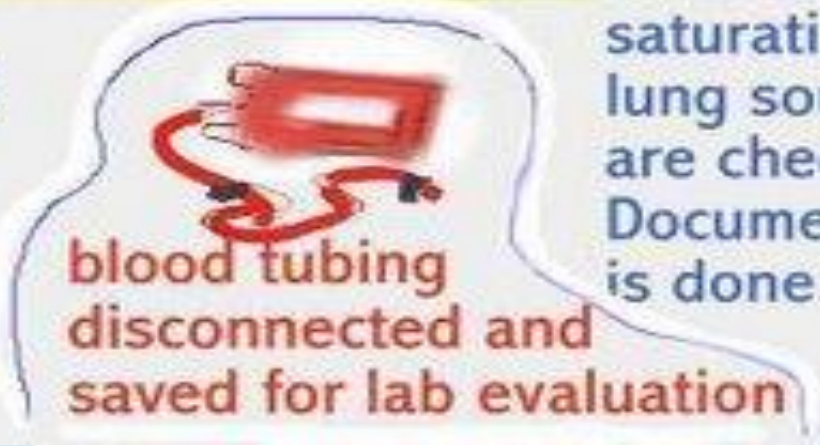
Transfusional reactions

- Acute intravascular – due to major blood group incompatibility
- Intravascular – delayed due to Ag Ab reaction
- Acute extravascular – due to IgG attached to red cells
- Febrile non-haemolytic due to donor lymphocytes cytokines (Leukocyte depletion)
- Allergic due to plasma proteins
- Autoimmune haemolytic anaemia

BLOOD TRANSFUSION REACTION



ASSESSMENT
The nurse arrives and quickly assesses the situation as a blood transfusion reaction.



INTERVENTION
-IV clamps are turned off and blood transfusion stopped.
-Normal Saline is hung using new IV tubing.
-Vital signs, O2 saturation and lung sounds are checked.
Documentation is done.

Infections through blood

- Hepatitis C
- Hepatitis B – vaccination is mandatory
- HIV
- CMV
- Malaria

Splenectomy

Indications

- Annual transfusion requirement > 200 (225-250) indicating hypersplenism
- Hb drop > 1.5 g/dl/wk
- Pancytopenia
- Marked enlargement ?
- Difficult to maintain iron balance with optimal chelation

Splenectomy

- Increasing pre transfusional Hb will help to 9.5 to 10
- Delayed until 5 years

General management

- No food very rich in iron, plain tea after meals
- Normal schooling & normal exercise
- Folic acid 1 mg/d
- More calcium
- Vitamin C – no excess and only during desferrioxamine therapy
- Hepatitis B vaccination
- Psychological support
- Social support group
- Genetic councelling

Other forms of therapy

- Bone marrow transplantation from a histocompatible donor
- Gene therapy
- Pharmacological modulation of fetal Hb