# APPROACH TO THALASSAEMIA

## HISTORY

**Chief complaint** … by disease itself or transfusion related complications

**HOPI**

a. symptoms of anaemia, jaundice, pigmentation, growth retardation, delayed puberty,

b. features of hypermetabolic state such as poor musculature, reduction in body fat, recurrent fever, poor appetite, and lethargic

c. Features of hypersplenism – bleeding,fever, worsening anaemia

d. CVS - s/s of CCF with or without Arrhythmia

e. Resp – features of pulmonary hypertension , Pulmonary embolism

f. GI - N,V, protruded of mass in abdomen, constipation,

g. GEU- nocturia, polyuria ,development of sex, impotence,

h. MS - arthralgia, myopathy, back pain, osteoporosis,fracture

***PMH***
***Disease or iron overload C'*** – worsening of anaemia,Gall stones, Cardiac C', Thromboembolism, COL, Gout, Endocrine C' such as DM, Adrenal insufficiency, Hypothyroidism, Splenectomy,cholecystectomy

***Transfusion*** - age of onset-(first year of life Major) (later- consider Intermedia), total units of blood transfusion, regularly or intermittent, duration between each transfusion, last transfusion, chelation therapy or not, transfusion related infection … HBV, HCV, HIV, MALARIA, Transfusion reaction,

**Drug H** - current – chelation, vaccine
**Personal** - school performance,Job, intelligence
**OG** - delayed puberty, poor breast development, oligo or amenorrhoea

**OE -** General appearance - short stature, low BMI ,skin pigmentation due to excess melanin and harmosiderin. **A, J**

***Characteristic facial appearance*** - frontal bossing, prominence malar bone, depressed nasal bridge, dental malocclusion
***LIMBS*** – shorten limb esp arms due to premature fusion of epiphysis
***Abdomen*** - splenectomy scar, hepatosplenomegaly, free fluid, sign of subcutaneous chelation ***CVS&RESP*** - AF, Murmur, signs of heart failure, pulmonary hypertension **D*elayed secondary sex characteristic***

**Fundus**

**Spine** – scoliosis, kyphosis, tenderness,

**MANAGEMENT**

**I. Investigation for Diagnosis / for complication**

**II. Treatment – supportive / curative**

**I. Investigation for Diagnosis**

**Laboratory Diagnosis**

**Blood for CP**

- degree of anaemia, decreased Hct and RBC count, decreased MCV,MCH and MCHC , increased RDW, RBC histogram shift to right and abnormal shape due to normal and abnormal RBC

- morphology –hypochromic, microcytic with marked aniso- and poikilocytosis,target cells,schistocytes, moderate basophilic stippling

**Rectic count** - increased 5 to 10 %

**Iron study** - serum iron –normal/increased, TIBC –normal/decreased, ferritin – increased/normal, transferrin saturation –increased

**Haemoglobin electrophoresis**

| **Disorder** | **genotype** | **electrophoresis** |
|---|---|---|
| **Beta - Trait** | β / β ° | **Hb A decreased**<br>**Hb A2 increased**<br>**Hb F slightly increased to normal** |
| **Beta - Intermedia** | β + / β + and others | **Hb F 10-50% (upto 100%)**<br>**Hb A 10 – 20%**<br>**HbA2 – variable (>4%)** |
| **Beta - Major** | β ° / β ° | **Hb A absent** |

| | | |
|---|---|---|
| | | **Hb F > 98%,**<br>**HbA2 normal/ <4%** |

- **unconjugated bilirubin and lactate dehydrogenase** - increased
- **low levels of haptoglobin**
- **Mentzer Index** – MCV/RBC - (<13 -thalassaemia trait ) & ( >13 – IDA)

# Imaging

**Skull X ray**

- "hair-on-end" radiographic appearance of the skull,prominent frontal bossing, delayed pneumatization of the sinuses, and marked overgrowth of the maxilla
- extramedullary erythropoiesis mass in Skull ( may present with convulsion)

**Spine X ray**

- continuation of active erythropoiesis of spine lead to compressive fractures and paravertebral expansion of extramedullary masses or tumor.
- These changes lead to complications such as back pain, spinal asymmetry and scoliosis, cord compression from intraspinal collections of hematopoietic tissue, and intervertebral disc degeneration
- Osteopenia with cortical thinning, increased trabeculation of the spine, severe osteoporosis with fractures,

**Bone marrow**

- erythroid hyperplasia with dyserythropoiesis. Stainable iron is increased but rare ring sideroblast

## I. Investigation for Complications

**For transfusion complication**

Blood borne infection - HBV,HCV,HGVHIV,Malaria

**For long term complications**

**LIVER**

- main causes – HCV and hepatic siderosis – liver injury/HCC/Gall stones
- LFT,ALT,AST, USG,CT, MRI, Liver biopsy, liver iron concentration > 3 to 7 mg Fe/ g dry weight

**CARDIAC**

- ECG- non specific, CXR, ECHO – decreased EF, Pulmonary pressure, diastolic dysfunction
- 24 hr Holter monitoring, Cardiac T2* MRI <20 milliseconds,

**ENDOCRINE**

- DM – RBS/ OGTT, Uric acid/urea/creatine
- Thyroid function test,
- Ca,PO4, PTH for hypoparathyroidism
- Hypothalamic pituitary adrenal gonadal function (GnRH,LH,FSH)

- Sex steroid – testosterone, 17-B Estradiol
- Pelvic USG
- Growth hormone stimulation test in selected cases
- IGF1, IGFBP3 in some cases

**OSTEOPOROSIS** – bone mineral density measurements by DEXA or SXA

**TREATMENT**

## Blood transfusion

**Rational** - to correct anaemia and clinical manifestation of disease (cardiomegaly,organomegaly,

bone deformity,

- to suppress ineffective endogenous erythropoiesis

- to promote growth and development

**Indication of transfusion: when to transfuse?**

to maintain a "steady state" hemoglobin level of 9 to 10 g/d

**Before transfusion therapy**

full blood group genotype should be established to prevent allo-sensitization, **HBV vaccine**

**How to transfuse**

**Dose –** 10-15ml/kg of packed red cell over 4-6 weeks to maintain steady state Hb.

- larger amounts of blood at longer intervals for difficult follow up (risk of iron overload+)

**Rate –** not exceed 4-5ml/kg/hr to avoid volume overload but should complete within 4 hrs.

- For patients with heard d/s- transfusion should be reduced to once a week and

rate of transfusion not more than 2ml/kg/hr

**Type of blood products**

- no place for use of whole blood because of danger of transfusion reaction
- *leucoreduction*: reduction of leucocyte to 5x 106 to prevent febrile non-haemolytic transfusion reaction and HLA alloimmunization
- Ideally blood transfusion should be ABO and Rh compatible
- *Neocyte transfusion* – transfusion with young red cell(mean age being 120 days) to reduce amount of blood required and prolonging the interval between transfusion

**Regular folic acid 5mg/day**

**SPLENECTOMY**

**Indication –** increased in yearly requirement of packed cell more than double the basal

i.e. packed cell 200 cc/kg/year or more

- hypersplenism (splenomegaly+anaemia+symptomatic leucopenia and thrombocytopenia)

All splenectomy patients should receive pneumococcal vaccine, H.influenza and meningococcal vaccine 4 weeks before surgery.Prophylatic antimalarial treatment in endemic area. Prophylactic penicillin therapy must be continued life-long.

**Complication**- overwhelming infection/ thrombotic complications in longterm/progressive hepatic enlargement

**MANAGEMENT OF IRON OVERLOAD**

**Assessment of iron overload**

Iron overload is caused by repeated blood transfusion (each unit of blood contain 200-250mg of iron) and increased GI absorption secondary to ineffective erythropoiesis due to inappropriately low hepcidin level

**Methods for assessment of iron stores**

***Serum ferritin*** – indirect estimate of body iron store/ lack sensitivity and specificity

- broad correlation between ferritin level and liver iron store

- it alone lead to inaccurate assessment of body iron store in individual patient

***Serum transferrin saturation*** – lacks sensitivity

***Serum non-transferrin bound iron*** – can be measured directly and useful for monitor of iron chealation Rx

***Deferoxamine or deferiprone induced urine iron excretion test***- poorly correlated with hepatic iron concentration

**Assessment of tissue damage caused by iron overload**

**Heart -** Echo/cardiac T2* by MRI for T2* relaxation time <20 milliseconds (relation between MRI and EF)

- No significant correlation between LVEF and serum ferritin or liver iron

- can be assessed by biopsy but not routine part due to invasiveness

**Liver -** MRI show variable correlation with hepatic iron concentration.

- LIC measured by liver biopsy is regarded as reference method for estimating iron load. It provide direct assessment of body iron burden, severity of fibrosis and inflammation.

- Direct noninvasive method of hepatic iron store is possible with the technique of Superconducting quantum interference device (SQUID). It has excellent correlation with biopsy determined.

**Endocrine – MRI** is the only method available to imagine pituitary iron.

**Indication**

After the first 10 to 20 transfusions have been given,

Serum ferritin is greater than 1000 mcg/L, and/or

Liver iron concentration (LIC) is greater than 3 to 7 mg Fe/g dry weight

**Dosing –** should be tailored to achieve serum ferritin levels <1000 mcg/L,

- LIC <7 mg Fe/g dry weight, and cardiac T2* by MRI >20 milliseconds

**Intensification of treatment**

LIC >15 mg Fe/g, serum ferritin >2500, a cardiac T2* MRI <20 milliseconds, or a fall in the left ventricular ejection fraction (LVEF) because of cardiac siderosis, cardiac failure, or arrhythmia indicates inadequate chelation, requiring intensification of treatment

**DRUG**

**Desferrioxamine (DFO)**

**Mechanism of action**

DFO is a hexadentate iron-chelating molecule, meaning that one molecule of DFO can bind one iron atom. DFO promote iron excretion by dural mechanism

1. it enter hepatocytes, chelating iron in situ and is excreted in bile.

2. it may interact with circulating NTBI or iron released from RE cells and other organs.

It more chelate liver iron. DFO has a relatively short half-life in the body and needs continuous infusion.

**Dosage and administration**

40mg/ over 8-12 hrs, 5-7 days weekly, subcutaneous infusion via pump or continuous IV infusion

Vitamin C 200mg/day is given to increase iron excretion**.**

**Side effects**

costly, poor compliance for patients,

Local cutaneous reaction, allergic or severe sensitivity reactions.

Systemic – Ocular – cataract and retinal damage

- Ototoxicity – high tone deafness
- Bone abnormalities and growth retardation
- Infection susceptibility esp Yersinia enterocolitica

**Deferiprone (DFP/Kelfer)**

**MOA** -orally effective iron chelator, three molecules are required in order to bind one atom of iron and causing predominantly urine iron excretion. It can be used alone or combined with DFO. It has additive or synergistic effect on iron excretion. It has better ability to penetrate cell membranes and may have a better cardioprotective effect than DFO

**Dosage** – 50-120mg/kg/day orally

**Side effect** – arthropathy, agranulocytosis (0.6% of patients per year) and leucopenia (6%),GI disturbance.

## Combination Therapy with DFO and DFP

Sequential combined administration of DFO and DFP. Used in patients not complying with SC DFO or experiencing toxicity or not excreting sufficient amounts of iron with use of either drug alone

**Shuttle hypothesis –** Experimental evidence suggests that intracellular iron chelated by DFP is transferred in the plasma to the more powerful chelator, DFO.

**Advantages of combination therapy**

**1.** Avoide excessive high dose of either drug

2. Improve compliance by reducing the number of DFO infusion needed

3. Increase iron excretion in patients who are inadequately chelated by either drug

4. Reduce the time of exposure of the heart and other organs to non transferrin binding iron

by daily chelation

5. Extract iron from the heart with DFP and from the liver with DFO.

**Deferasirox**

MAO – newest oral chelator, causes fecal iron excretion only.
Two molecules are required to bind one iron atom. It has prolonged plasma half life.

**Dosage –** 20-40mg/kg Once daily.

**Side effect –** rare, skin rashes, rise in liver enzyme and creatinine

**ENDOCRINE THERAPY**

- Either replacement because of end organ failure or to stimulate the pituitary if puberty is delayed

**OSTEOPOROSIS**

- Ca and vitamin D supplementation, Bisphosphonate

**EXTRAMEDULLARY ERYTHROPOIESIS TUMOUR**

- hypertransfusion regimen usually reduce tumor masses.

- Radiotherapy in neurological lesions complicated by mass in spinal canal

- Hydroxyurea successfully cure in some cases.

**BONE MARROW TRANSPLANTATION**

Allogenic SCT offers the prospect of permanent cure.
Three most important prognostic factors for survival and event free survival are
1. Hepatomegaly(>2cm below costal margins),2.liver fibrosis 3.iron overload.
Success rate is 80-90% in well chelated younger patients without fibrosis or hepatomegaly.