Current Management of Thalassemia

Positive Note

- Thalassemia is a treatable disorder that can be managed well with transfusion and chelation therapy

- If the disease is managed by optimal treatment, thalassemics can enjoy a near-normal lifestyle and experience regular physical and emotional development from childhood to adulthood and beyond…....

Thalassemia

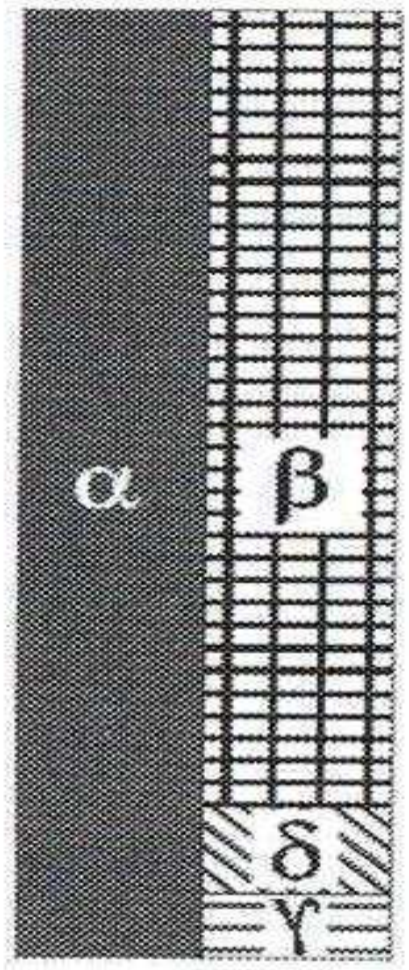
Inherited disorder of hemoglobin synthesis characterized by chronic anemia resulting from reduced or complete absence of production of one or more of the globin chains

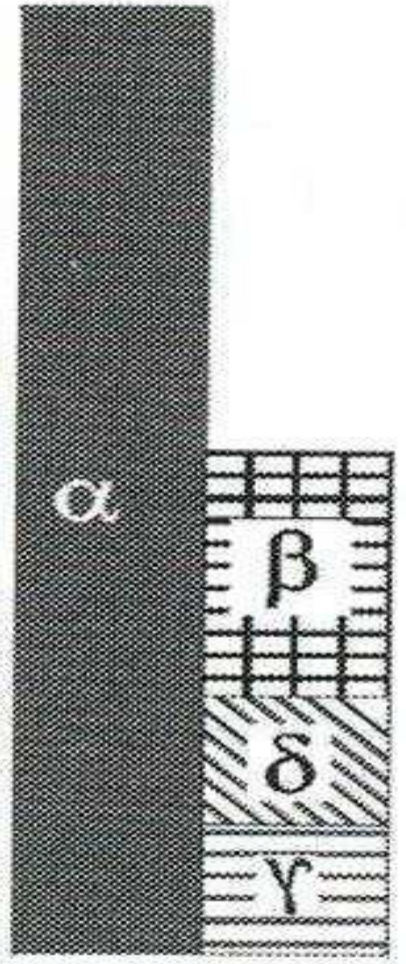
Thalassemia minor

NTDT Thal intermedia

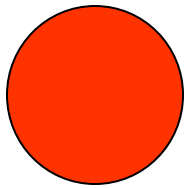
Thalassemia major

Molecular Basis of β-Thalassemia





Pathophysiology of β-Thalassemia



Decreased or absent β globin chain synthesis

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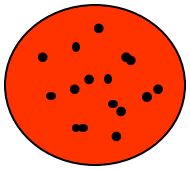
Imbalance of globin chains (α : non α chains)



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Accumulation of unpaired α globin chains

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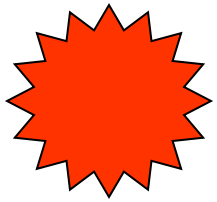

Altered red cell membrane function

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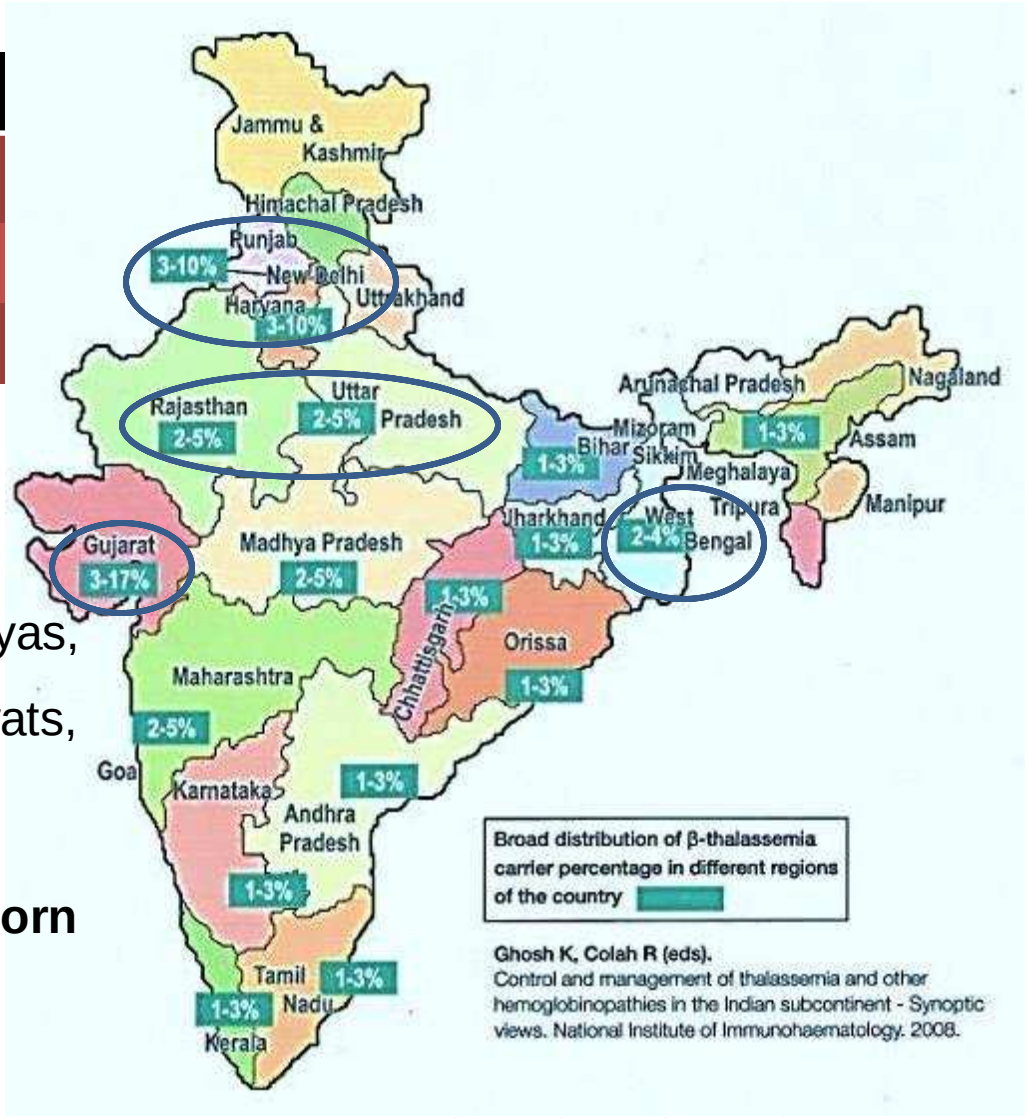
Shortened RBC life span

Beta-Thalassemia in India

Thal minors	
Number	35.6 – 47.5 million
Prevalence	1 – 17%
Mean	3.3%



Commonly involved communities :

- Sindhis, Punjabis, Lohanas, Baniyas, Gujaratis, Bengalis, Gaurs, Saraswats, Banushalis and Rajputs

Approx 10,000 thal majors born annually

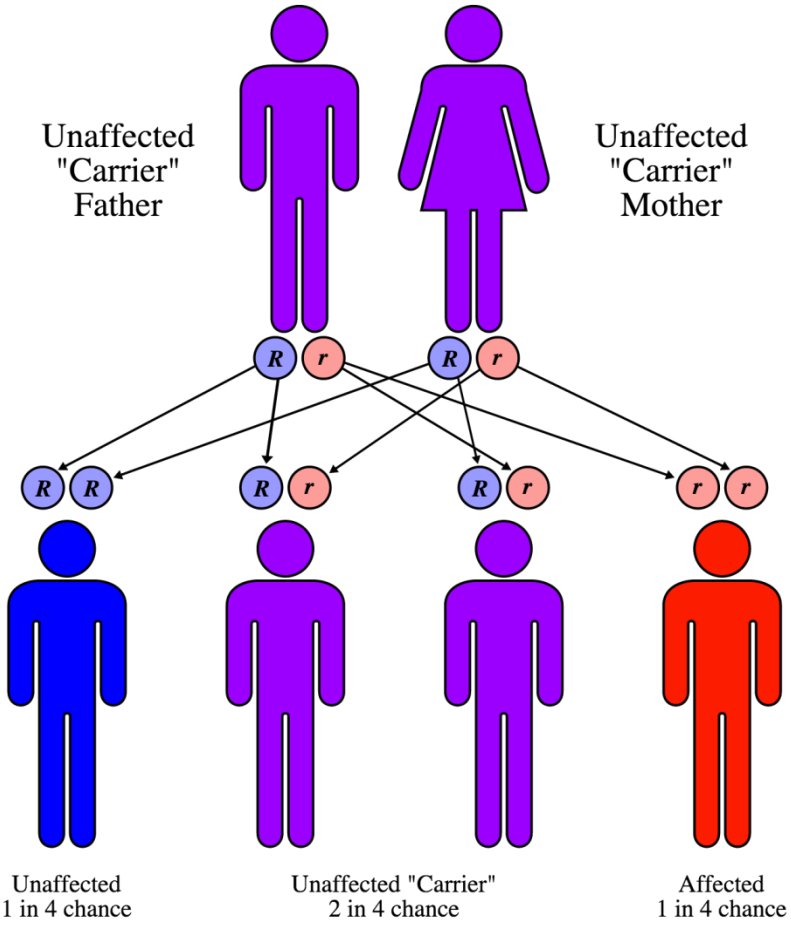
Grow K et al Int J Pharm Pharm Sci 2014;6:28-31

Types of Thalssemia

Production of normal Hb is controlled by a pair of genes, one acquired from each parent

- Thalassemia minor
- Thalassemia major

Inheritance of Thalassemia

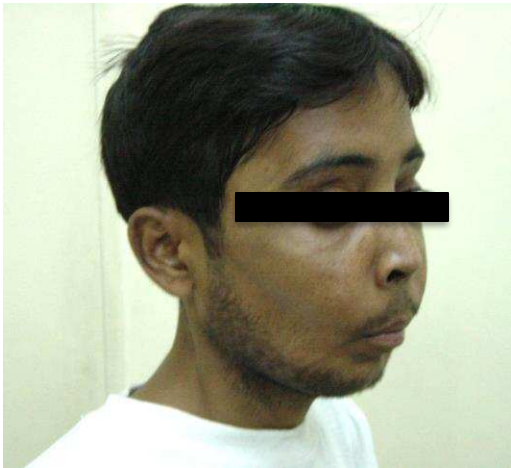


Thalassemia Minor (Trait or Carrier)

- One abnormal gene present
- Mild or no anemia
- **Normal life-span**
- **Can pass abnormal gene to next generation**
- RBC indices
  - **RBC count – normal / increased**
  - **MCV < 80 fl**
  - **MCH <27pg**
- Hb electrophoresis / HPLC
  - **Hb A2 increased(>3.5%)**
- *Thal minors can have iron deficiency additionally, which should be treated*

Thalassemia Major

- **Both genes abnormal**
- Appear normal at birth
- After 3-6 months:
  - Pallor, irritability, failure to grow, feeding problems
  - Prominence of facial bones
  - Enlargement of liver and spleen



Current Management of Thalassemia Major

- Diagnosis
- Transfusion therapy
- Assessment of iron overload
- Iron chelation therapy
- Management of complications
- Alternate approaches
- Bone marrow transplant
- Gene therapy

Confirmation of Diagnosis

- Hb electrophoresis / HPLC

- Molecular studies (mutation analysis)
  - **Recommended for all newly diagnosed cases**
    - Of more than 300 mutations identified worldwide, 28 mutations are reported from India and of these, 5 common mutations are responsible for 90% cases

  - **Benefits :**
    - Confirmation of diagnosis in a case who has already received blood transfusion
    - Prediction of severity of disease
    - Most common technique used for prenatal diagnosis

Pre-transfusion Therapy Evaluation

- Confirm diagnosis preferably by molecular analysis
- Extended RBC antigen typing
  - C,c, E,e, Kell antigens
- Baseline serological testing for HIV, HBV and HCV
- Hep B vaccination for patients who do not have immunity
- HLA matching with siblings

Transfusion Therapy

- **Initiation of transfusion**
  - Hb < 7 g/dl on 2 occasions > 2 wks apart (excluding all other causes such as infections)
- **5 ml/kg of packed cells (60%) increases Hb by 1 g/dl**
- **15 – 20 ml/kg of packed cells @ 5 ml/kg/hr every 2-4 weeks**
- In cases of heart disease or very low Hb(< 5g/dl), smaller aliquots of 5ml/kg @2ml/kg/hr
- **Pre-transfusion Hb : 9-10.5g/dl**

Regimen	Pre-transfusion Hb (g/dl)
Palliative	
Supertransfusion	12
Hypertransfusion	10
Moderate transfusion	9 – 10.5

Blood Safety

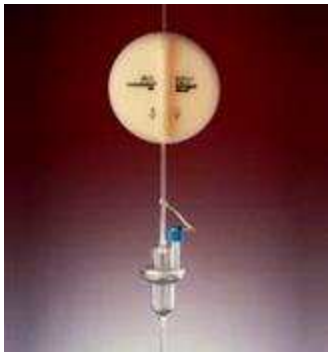
- **Thorough screening of donor blood**

  Screening for HIV, Hep B, Hep C, syphilis, malaria mandatory

  Nucleic Acid Testing (NAT)

  Detects early infection during window period and reduces the risk of transmission of HIV, Hep B and Hep C

- **Pathogen Inactivation**
  - Inactivation of viruses, bacteria and protozoa
  - In some European countries available for plasma and platelets
    - Intercept
    - Mirasol
    - Thermaflex
- **Leucodepletion**
  - **Bedside**
  - **Pre-storage**
    - Prevents release of cytokines
    - Reduces chances of CMV transmission
    - Expensive



Schlenke P Transfus Med Hemother 2014;41:309-25

Transfusion Therapy - Points to Remember

- Before blood units are attached to transfusion set, a medical officer must tally the cross-match slip for blood group, patient's name, blood bag no., expiry date and check blood for any evidence of contamination, clots or hemolysis

- Parents must check the blood before attaching the blood to transfusion set, for name of the patient and the blood group

- **Transfusion of blood from first degree relatives should be avoided** because of developing antibodies that might adversely affect the outcome of later bone marrow transplant

Transfusion Therapy - Points to Remember

- Blood for transfusion stored in CPDA solution should be less than 1 week old and blood with additional nutrients, less than 2 weeks from the date of collection

- **Can apply Emla/Prilox cream 60 minutes before fixing cannula to reduce pain**

- Routine use of Lasix, Avil or steroids before transfusion is not recommended

- After blood transfusion, thrombophob gel maybe applied at the site of cannula

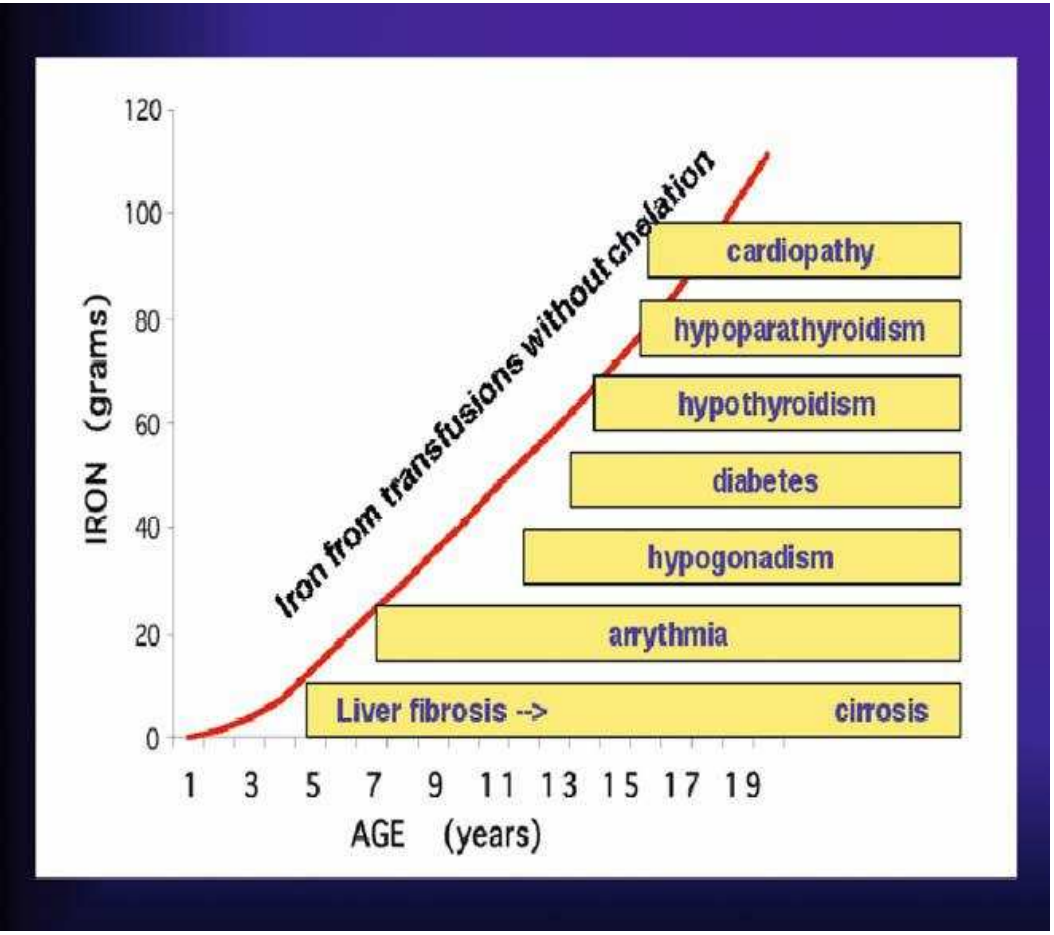
- There is no need to perform post-transfusion Hb

Transfusion Reactions

- **Non – hemolytic febrile reactions**
  - Common in the past decades
  - **Dramatically reduced by leucoreduction, specially pre-storage** which sharply reduces cytokine accumulation and leucocyte alloimmunization
  - Those who get these reactions repeatedly, should be given antipyretics before transfusion

- **Allergic reactions**
  - **Due to plasma proteins**
  - May be mild to severe
  - Occasional reactions may be prevented by antihistaminics (Avil) or steroids before transfusion
  - **For repeated reactions, saline washed RBC should be used**

Iron Overload



Morbidities related to iron overload in relation to age

1 unit of blood = 200 mg of iron

Assessment

- No. of units transfused
- Serum ferritin trend
- Liver biopsy
- SQUID
- MRI T2*
- FibroScan

Agarwal MB Indian J Ped, 76, 2009

Assessment of Iron Overload

- **Serum ferritin**
  - Widely used, most acceptable and feasible
  - Fluctuates with infection and inflammation
  - Following the trend of S. ferritin values is more important than spot value
- **Liver biopsy**
  - Invasive and cannot be repeated frequently
  - Assessment of dry cell mass not available widely
- **SQUID**
  - Measures LIC accurately and correlates highly with results of liver biopsy
  - Very expensive, only 4 machines available

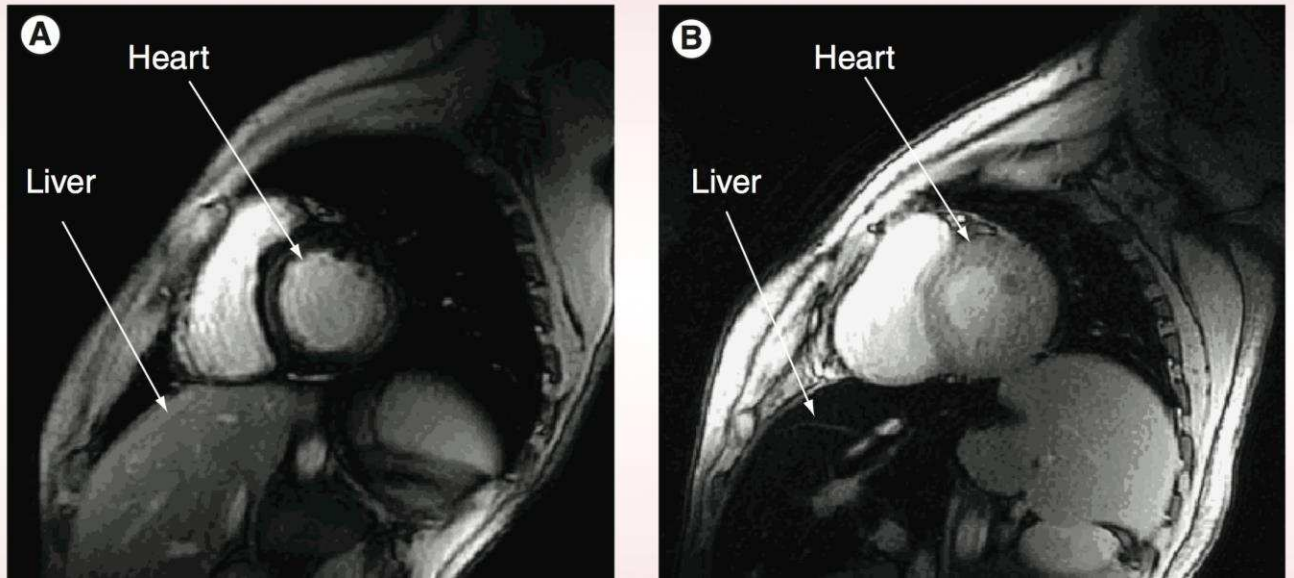
Assessment of Iron Overload

- MRI T2* assessment of cardiac and hepatic iron overload
  - T2* normal values → heart > 20 ms
    → liver > 6.3 ms
  - Useful for monitoring chelation
  - Cardiac iron loading shows no correlation with liver iron

Very low T2* (<6ms)

↓

near 50% risk of developing cardiac failure within one year



FibroScan

- Non-invasive method for early detection of cirrhosis
- Measures tissue stiffness
- Normal upto 7kPa

Advantages

- Short procedure time (<5mins)
- Immediate results
- Can be performed bedside

When to Start Chelation Therapy ?

- S. ferritin > 1000 ng/ml
- After first 15-20 transfusions

Goal – to maintain S. ferritin <1000 ng/ml

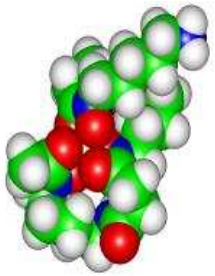
Chelation Therapy in Thalassemia

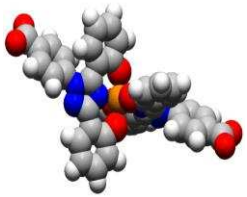
Ideal Iron Chelator

- Selective affinity for iron
- Orally effective
- Long half-life to provide 24 hours chelation coverage
- Good compliance
- Low toxicity
- Low price

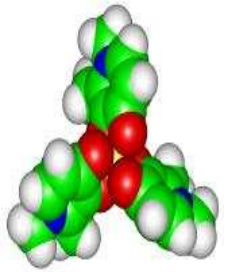
Iron chelators presently available

Desferrioxamine (Desferal, DFO)



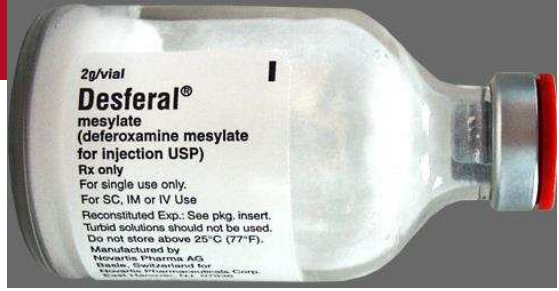


Deferasirox (Asunra, Defrijet, DFX)



Deferiprone (Kelfer, DFP, L1)

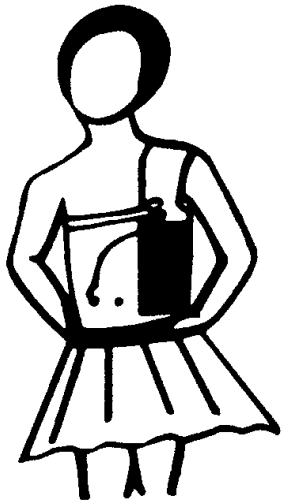
Desferal (DFO)



- First and time-tested iron chelator used worldwide for >35 years, with well established efficacy
- **Not absorbed orally**
- Plasma half-life: 20 min
- **Route of administration: Subcutaneous infusion with pump or intravenous**
- Iron bound DFO excreted in urine and stool (changes urine colour to red)
- Dose : 20-50 mg/kg/day
- **Vit. C increases iron excretion by DFO**
- **Cost : Rs.165 per 500mg vial**

Adverse Effects of DFO

- Low toxicity Overall
- Side effects :
  - Local skin reactions
  - Increased susceptibility to infections like Yersinia
  - Dose related side effects :
    - High frequency hearing loss
    - Visual toxicity
    - Growth retardation
    - Skeletal changes
- Monitoring : audiometry and eye examination annually

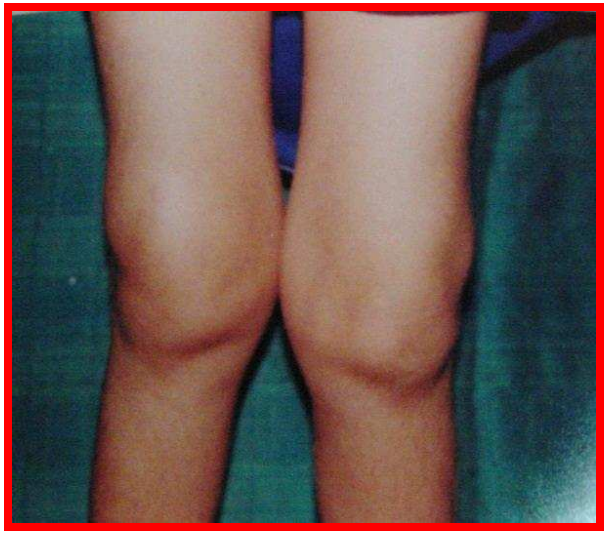


Deferiprone (DFP)

- Oral iron chelator
- Approved in India since 1995
- Half life -135 min
- Compared to DFO:
  - Less effective and more toxic
  - **More cardio-protective**
  - **Cheaper**
- Iron bound DFP excreted in urine (changes its color to red)
- **Can be used in combination with DFO**
- Dose: 75-100mg/kg /day in 2-4 divided doses
- Available as Kelfer 250 and 500mg capsules

Adverse Effects of DFP

- Neutropenia (5%) and agranulocytosis (<1%)
- Arthropathy (10-30%)
- G I symptoms
- Zn deficiency



Monitoring

- CBC every 2-4 weeks and with every febrile episode
- Stop DFP if TLC<3000/mm^3, ANC<1000/mm^3, platelets<1 lakh/mm^3
- Falling WBC or platelet count should be considered a warning

Deferasirox (DFX)

- Approved by FDA in November 2005 and available in India since **April 2008**
- Can be used in children > 2 years
- Half-life : **8-16 hours, once a day dose required**
- **Long half-life provides 24hours protection from NTBI**
- Efficacy similar to DFO
- **Dose : 20-40mg/kg/day**
- **Not recommended to be combined with other chelators yet**
- To be taken empty stomach dispersed in water or juice
- Availability
  Asunra : 400 and 100 mg
  Defrijet : 500 and 250 mg
- Dose can be divided for those who cannot tolerate large quantities at a time

Deferasirox (DFX)

Adverse Effects

Effects	Frequency
Increase in serum creatinine (non-progressive)	**38%**
Gastrointestinal disturbances	**15%**
Skin rashes	**11%**
Elevation of liver enzymes	**0.6% & 15%**

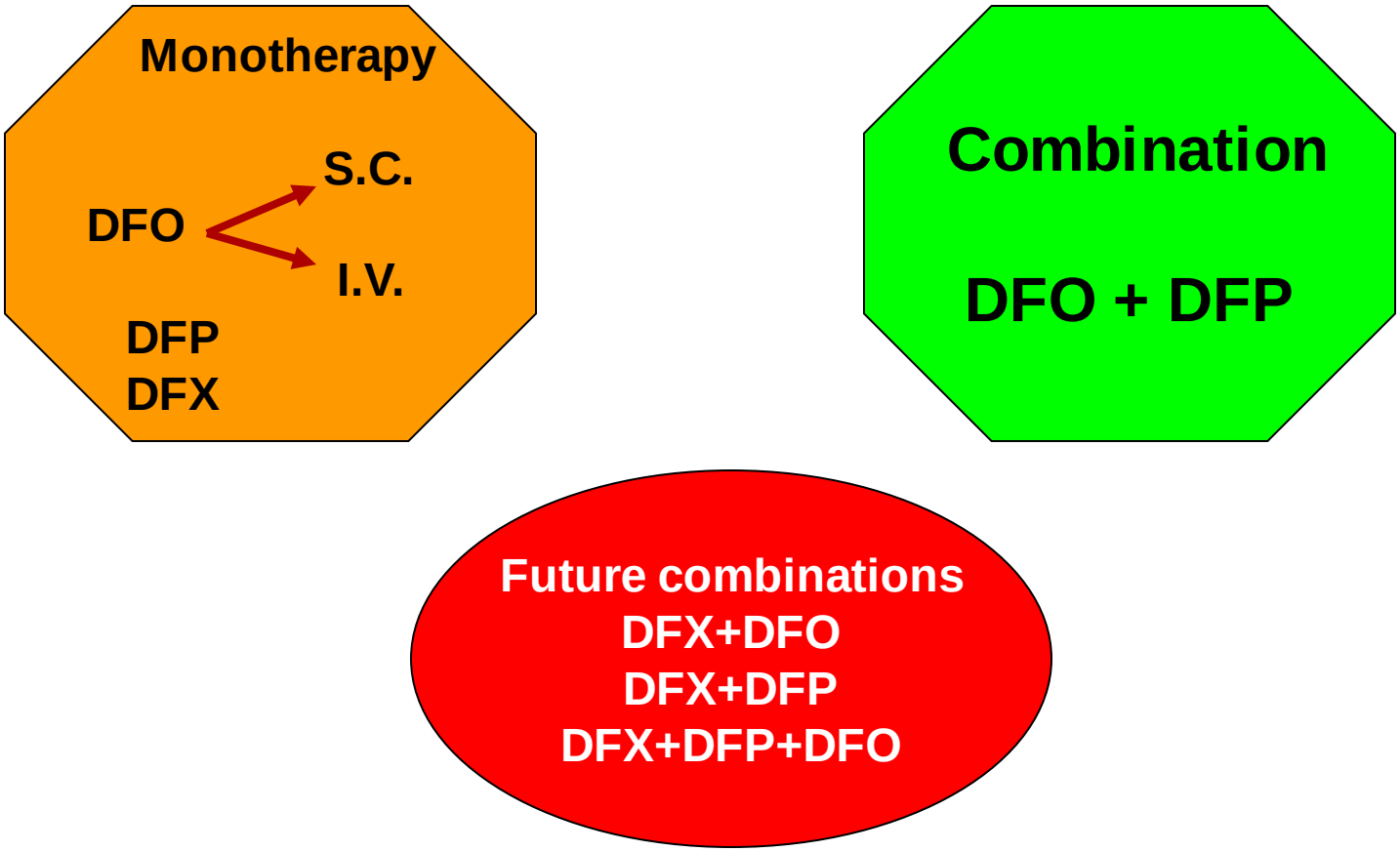
Monitoring Guidelines

Test	Frequency
Serum ferritin	Monthly
Serum creatinine*	2x prior to therapy and monthly thereafter
Proteinuria	Monthly
Liver function	Monthly
Auditory and ophthalmic	Prior to therapy and yearly thereafter
Pediatric growth	Yearly

Oleptiss

- Deferasirox : 90mg, 180mg and 360mg film coated tablets
- **May be taken on an empty stomach or with a light meal**
- **Tablet can be swallowed whole with water or crushed and taken by sprinkling onto soft food (yoghurt etc.)**
- Dose: 7-28mg/kg/day
- **Cost : Rs.173 for 360mg tab**
- Monitoring : same as Asunra/Defrijet

Potential Regimens of Chelation



Adjustment of dose and use of combination should be under direct supervision of doctor

Combination Chelation: When is it required?

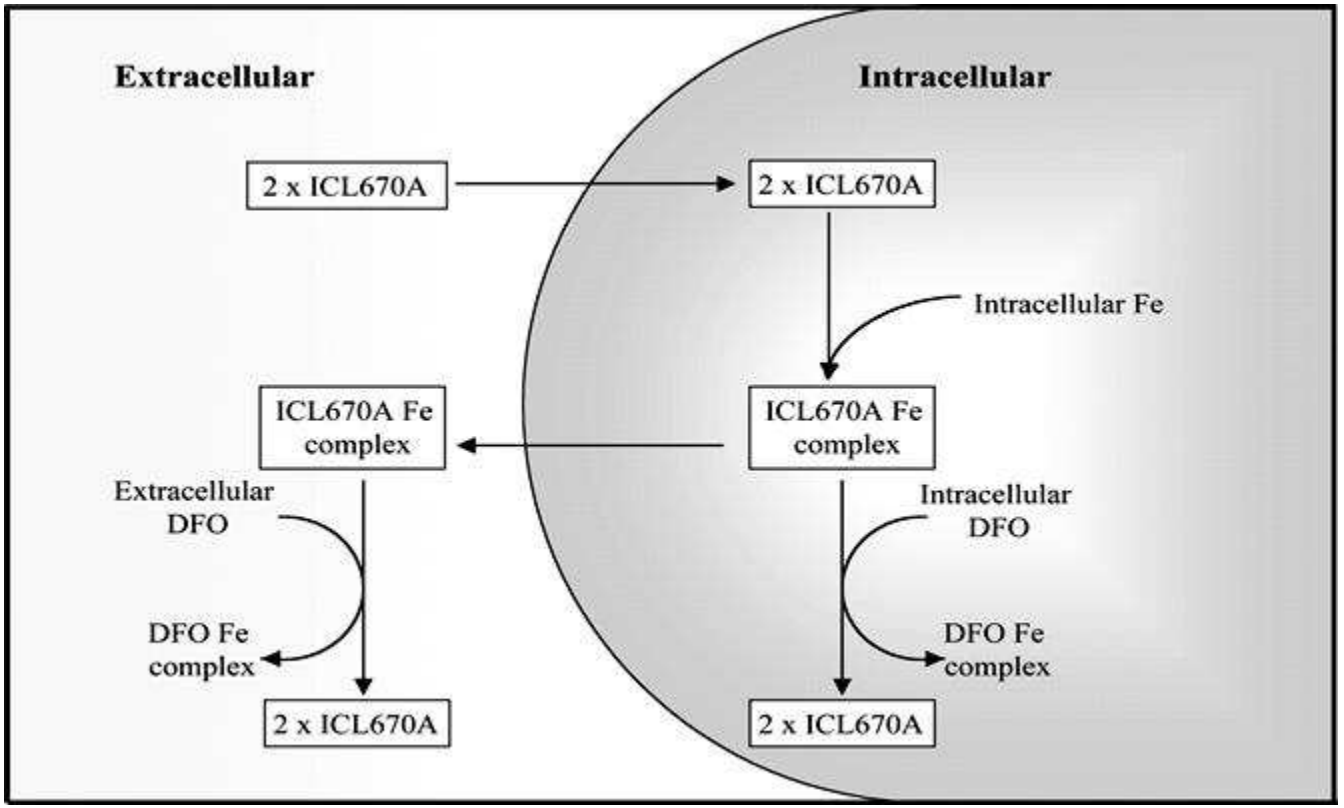
- **Poor response to chelation monotherapy**
- Intolerance to adverse effects
- Poor compliance:
  - Route of administration
  - Cost
- **Heavily iron overloaded patients**
- In cases of cardiac and other organ dysfunction
- **When a rapid fall of S. ferritin is required:**
  - Before BMT
  - Before planning pregnancy

Proportion of body iron available for chelation at any moment of time is limited.

Iron excretion is dose dependent with wide subject-to-subject variation.

Combination Chelation

- **Concerns:**
  - Will the efficacy increase?
  - Will there be additional side effects?
- **Shuttle effect:**



Combination of DFO and DFP

- **One of the most studied and effective means of decreasing iron overload**
- **Reverses cardiac and early endocrine dysfunction**
- **No additional adverse effects**

- In patients with well established cardiac disease, therapy with DFO and DFP is superior to DFO monotherapy
- Intensive combined chelation normalized iron load as assessed by cardiac T2* MRI, S ferritin and LIC. Also reversed cardiac and multiple endocrine complications
- Statistical higher total iron excretion by DFO + DFP combination as compared to monotherapy with DFO or DFP

Farmaki K et al. Br J Haematol 2010;2011:451-58

Lai ME et al. Blood Cells Mol Dis 2010;45:136-39

Aydinok Y et al. Hematological 2007;92:1599-1606

Splenectomy

- With current transfusion and chelation protocols very few splenectomies are required as compared to those in earlier years
- Splenomegaly due to under-transfusion may be reversible. Patient should receive adequate transfusions
- After splenectomy there is an increased risk of venous thrombosis, silent brain infarcts, pulmonary hypertension and severe infection
- It should be restricted to certain indications only such as :
  - Increased blood requirement (200-220ml/kg/yr of 75% hematocrit)
  - Cytopenia (low WBC and / or platelets)
  - Massive splenomegaly

Splenectomy

- Following vaccines should be given at least 2 weeks before splenectomy:
  - Pneumococcal
  - HiB
  - Meningococcal
  - Typhoid
- Chemoprophylaxis : oral penicillin for whole life
- Careful monitoring
- Early reporting in case of fever

Routine Health Care

- **Vaccination**
  - All routine vaccines required for children
  - Additionally, thalassemics should receive Hep A, chickenpox, pneumococcal and typhoid vaccination
  - **Splenectomized patients:** revaccination with meningococcal and typhoid vaccine after 3 years and pneumococcal vaccine after 5 years

Diet for Thalassemics

- **In well-transfused thalassemia majors (pre-transfusion Hb> 9 g/dl), intestinal absorption of iron is suppressed. Dietary restriction is therefore, not warranted**
  - Foods rich in iron (liver, iron-fortified breakfast cereals, health drinks) should be avoided
  - Dietary restriction of iron-rich food is more important for under-transfused and non-transfused

- Drinking tea with meals reduces iron absorption

Education and Employment

- Children should be enrolled at normal schools and colleges
- Well-managed patients generally do not face difficulties in performing work

SGRH, Delhi

Total no. of cases	**187**
> 20 yrs of age	85
Occupation: • Teacher/ lecturer • Job • Business	 8 23 22
Total	**53 (62%) working**

Gabriel Theophanous (33/M)
Virgin London Marathon
42 km
2006 – 5h 55min
2013 – 5h 29min

Walk to the Base Camp of K2 2001

Walk to the Base Camp of Nanga Parbat 2002

Walk to Base Camp to K2 (K2 Quest) 2004

Walk to the Base Camp of Masherbrum 2003

Clinical and Laboratory Evaluation Checklist

- **Monthly**

CBC

- **Every 3-6 months**

Anthropometry and complete GPE
S.ferritin
BUN / S Cr. (monthly for pts. on DFX)
SGOT/SGPT (monthly for pts. on DFX)
For more than 5 year age
Calcium / Phosphorus / Alk PO_4
Fasting blood sugar
For more than 10 year age
Uric acid

Modified from guidelines for the management of TDT, TIF publication, 2014

Clinical and Laboratory Evaluation Checklist

- **Yearly**

Anti Hbs
Anti HCV
HIV
25 (OH) Vit. D
Audiological and ophthalmological exam (for patients on DFO and DFX)
For more than 5 year age
T3 T4 TSH
For more than 8 year age
MRI T2* for heart and liver iron overload
For more than 10 year age
Endocrine evaluation, GTT
DEXA scan
Ultrasound abdomen for gallstones

Clinical and Laboratory Evaluation Checklist

- Tests to be performed if indicated

24 hr. Holter monitoring
Cardiac stress test
Hepatitis C panel
Hepatitis B panel
Special endocrine tests

Alternate Approaches

Augmenting synthesis of fetal hemoglobin

- Role of hydroxyurea (HU)
  - HU causes proliferation and differentiation of erythroid precursors which maintain γ gene chain synthesis programme
  - Well documented benefit in sickle cell disease
  - Inconsistent results in thalassemia major
  - Results better in Xmn1 polymorphism

Response to HU According to Xmn1 Polymorphism (SGRH)

Xmn1	Total	Complete	Partial	Nr/ne
+/+	41	21	08	12
+/-	26	03	07	16
-/-	03	01	00	02

($p<0.02$)

Termination of Transfusion by HU

- R.A.
- DOB 29-03-1989
- Xmn1 +/+
- Age at diagnosis & first BT 1yr 2 mths
- Received regular BT till July 1999
- Started on hydroxyurea 375mg/day in July 1999
- Received blood transfusions from Feb 2004-Jan 2005 as he developed hypersplenism & underwent splenectomy in Dec 2004
- No BT after Jan 2005

Month	Hb (in gms)
March '99	9.2
July '99	7.2
November '99	7.6
March '00	8.2
July ' 00	8.3
November '00	8.5
March ' 01	8.4
July '01	8.5
November '01	8.7
March ' 02	8.6
July ' 02	8.6
November '02	8.9
March ' 03	9.2
July '03	9.3
November '03	9.6

Started on HU

Hydroxyurea was stopped in December 2003.

Started with transfusions from February 2004.

Spleen and Gall Bladder were removed in December 2004.

Transfusion after surgery given in Janunary 2005.

Hydroxyurea was started again.

Month	Hb(in gms)
March '05	8.3
July '05	8.5
November '05	8.6
March '06	8.8
July '06	8.8
November '06	8.2
March '07	8.6
July '07	8.9
November '07	9.2
March '08	9.3
July '08	9.5
November '08	9.4
March ' 09	8.9
July '09	9.2
November '09	9.3
March '10	9.5
July '10	9.6
November '10	9.4
March '11	9.6
July '11	9.2

New Drugs on the Horizon

- Sotatercept and Luspatercept
- Correction of ineffective erthyropoiesis
- Initial findings show Hb increased of more than 1.5g/dl in NTDT and decreased transfusion requirement in thal major of upto 50%

.Porter, J B Abstract book 6th Intl Conference of Thalassemia 2016

Bone Marrow Transplantation

- Offers cure for thalassemia

Gene Therapy

- **Introduction of a normal copy of the gene in a cell which is defective**
- Viral microorganisms (lentiviral vector) have been used with promising results
- 6 thalassemia patients treated worldwide till 2013, including 3 with HbE/β-thal in France and 3 with β-thal major in the USA
- Multicentric ongoing clinical trial in the USA, France, Australia and Thailand has observed a rapid decrease in transfusional requirement or even transfusional independence in some cases of thalassemia major
- Still considered experimental

Take Home Message

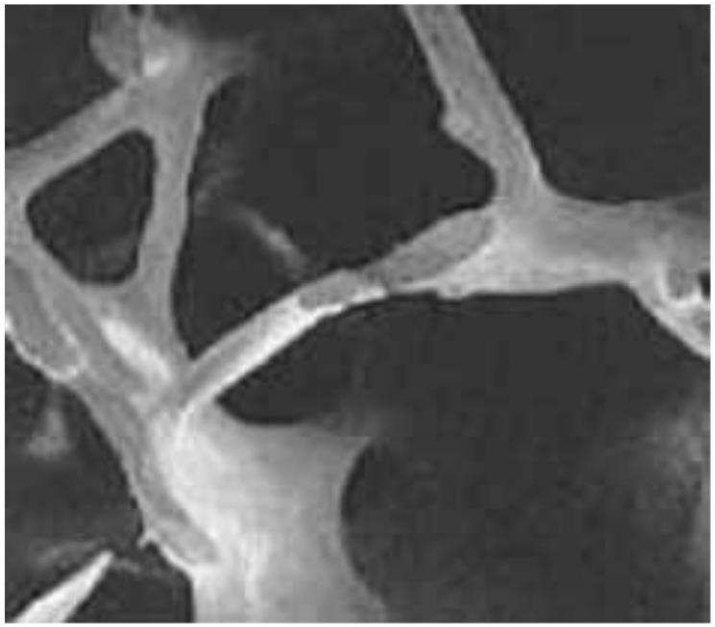
- Thalassemia is a treatable disorder that can be managed well with transfusion and chelation therapy

- Treatment based only on standard guidelines and recommendation should be followed

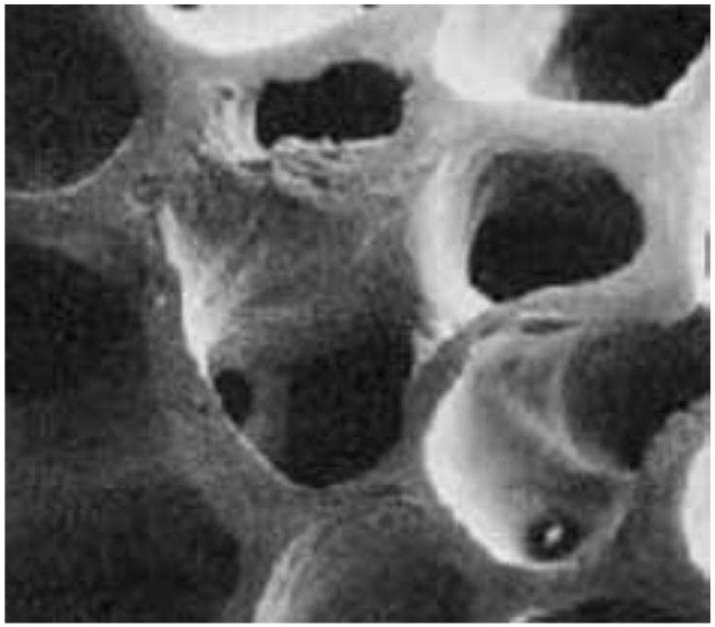
- If the disease is managed by optimal treatment, thalassemics can enjoy a near-normal lifestyle and experience regular physical and emotional development from childhood to adulthood including parenthood

Osteoporosis

A



B



Osteoprotic (A) and Normal (B) bone.

- Seen in upto 70-80% of adult TM pts
- Prominent cause of morbidity leading to bone pain and risk of fractures
- Assessed by **DEXA scan**

Osteoporosis

Prevention

- Adequate intake of calcium and Vit D
- Regular exercise
- Avoid smoking, nicotine, pan masala and alcohol

Management

- Calcium and Vit D
- Bisphosphonates
- Sex hormone replacement

Causes
↑ed osteoclast activity
Marrow expansion
Anemia
Hemosiderosis
Delayed puberty & hypogonadism
↓ed vit D level
Endocrinopathies
DFO
Lack of physical activity

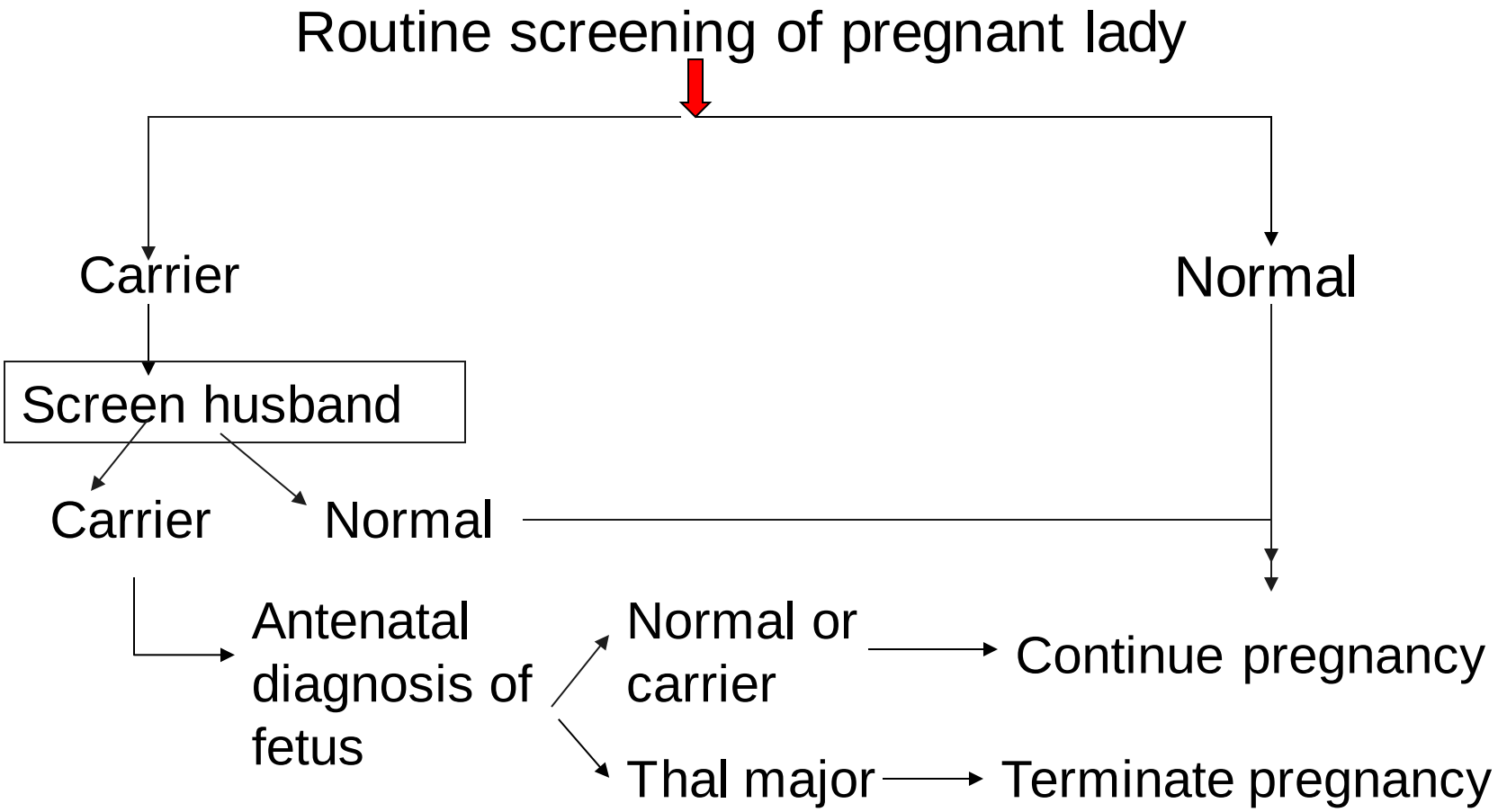
Growth in Thalassemia

- Prevention and treatment of growth abnormalities include :
  - Proper blood transfusion to maintain pre-transfusion Hb >9g/dL
  - Proper chelation to attain S.ferritin <1000ng/ml
  - Correction of nutritional deficiencies (protein – calorie, folate, Vit. D, zinc) when suspected
  - Correction of hypersplenism
  - To rule out gluten enteropathy
  - Early diagnosis and management of delayed puberty, hypothyroidism, growth hormone deficiency and impaired glucose tolerance and diabetic mellitus

Prevention of Thalassemia

- Awareness
- Carrier screening
  - **Family centered approach -** *"cascade" screening*
  - **Population screening**
    - Institutional
    - Premarital
    - **Antenatal**
- Genetic counseling
- Antenatal diagnosis
  - CVS: 10-12weeks

Prevention of Thalassemia

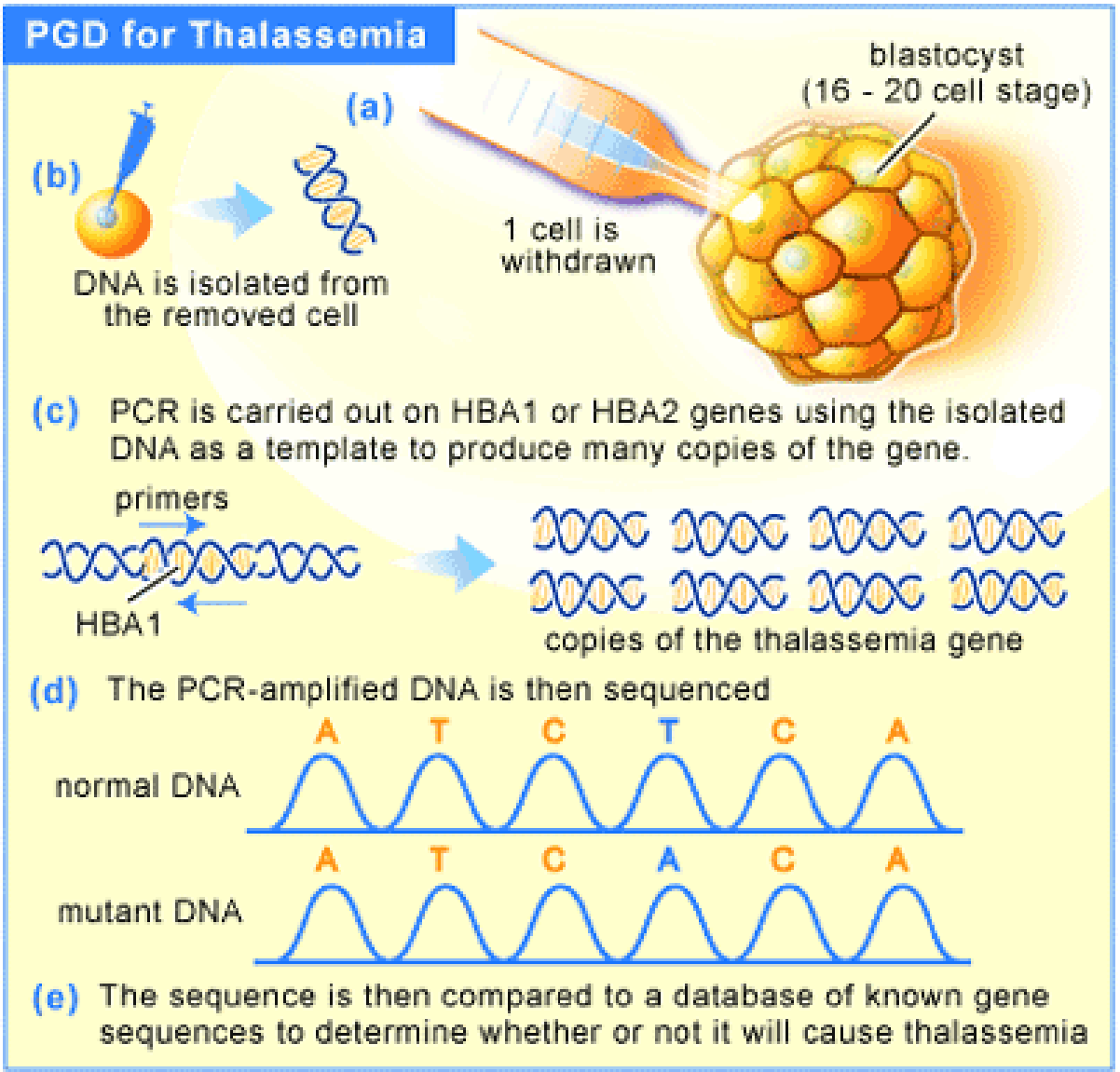


Prenatal Diagnosis – Newer Developments

Fetal DNA in maternal blood:

- Fetal DNA can be detected in maternal blood by 5 weeks of gestation
- Fetal DNA is smaller than maternal DNA
- Prenatal diagnosis is possible by studying mutations in fetal DNA

Pre-implantation Genetic Diagnosis (PGD)



Has been extended to HLA typing for embryo selection so as to serve as a stem cell donor for a previously affected child within the same family

Thalassemia is preventable