Thalassaemia and it's Current Status Globally and in Sri Lanka

Prof Sanath P Lamabadusuriya

What is Thalassaemia?

- It is the commonest inherited variety of anaemia
- It is the commonest haemoglobinopathy in Sri Lanka
- Of all the different types, Beta-Thalassaemia major is the commonest type

Global Picture

- Haemoglobin disorders are the commonest clinically serious single gene disorders in the world
- 300,000 – sickle cell disease babies are born each year
- 1.5 % of world population are carriers of β Thalassaemia ie. 80-90 million
- 60,000-70,000 –β Thalassaemia major babies are born each year

Sri Lanka

- Population- 19 million
- Birth rate – 18/1000
- Annual birth cohort: 344,600
- β Thalassaemia carriers 2.2%
- Expected homozygous births/ year 62
- Known homozygotes (patients) 2000

Prevalence of Anaemia in Sri Lankan Children

6 months to 1 year:

<10.5g/dl: 56%

1 year to 5 years:

<11 g/dl: 29.9%

Vast majority is due to Iron deficiency

Clinical Presentation of Thalassaemia

- Anaemia and its manifestations in infancy
- Abdominal distension due to hepatosplenomegaly
- Growth failure

Principles of Management

- Correction of anaemia and maintenance of Hb over 10-12 g/dl
- Chelation of Iron
- Splenectomy-sometimes
- Hormone replacement therapy
- Management of complications

Other Aspects of Management

- Hormone replacement- eg. Oestrogens and Androgens
- Control of diabetes mellitus
- Other hormone replacements
- Folate supplements
- Splenectomy
- Special vaccines- eg. Hib vaccine, Pneumococcal vaccine

Advances in Thalassaemia Management

- **Iron-chelation therapy**
  - No alternatives presently licensed for general use
  - Heightened interest in new agents
- **Augmentation of fetal hemoglobin**
  - Generally less successful than in sickle cell disease
  - No agents yet in routine clinical use
- **Stem cell transplantation**
- **Understanding of thalassemia intermedia, HbE thalassemia**

Strategies for Chelation Therapy

- **Prevention**
  - Prevent tissue damage by early appropriate Rx
  - Maintain hepatic iron <7 mg/gram dw
  - Probably enough to prevent cardiac death (? Other toxicities)
- "**Rescue**"
  - Remove toxic iron: best accomplished with continuous treatment (IV or SC DFO)
  - Remove storage iron

Key to Obtaining Good Outcome

- Expert 'center'
- Expert team
  - Paediatrician/Physician with interest
  - Nurse specialist
  - Clinical psychologist
  - Integrated care with other consultative services
- Continuity of care from childhood to adulthood
- Expectant care

Iron Loading in Transfused Patients

- One unit (420 ml donor blood) = ~200 mg iron
  - 0.47 mg/ml whole blood
  - 1.16 mg/ml 'packed' cells

- Daily loading in splenectomized patients with thalassaemia major, if mean Hb 12 g/dl =
  - Transfusion: 0.4 mg/kg/day
  - Absorption: 1-4 mg/day
  - Total: **~0.5 mg/kg/day**

Goals of Iron-Chelation Therapy

- Clinical cardiac disease – free survival
- Adequate reduction of hepatic iron
- Arrest of hepatic fibrosis
- Adequate growth
- Normal gonadal and endocrine function
- Normal glucose tolerance
- Extended survival

Clinical Complications of Iron Overload

- Cardiac failure, conduction abnormalities
- Hepatic dysfunction
- Infection
- Growth failure
- Abnormal sexual development
- Pancreatic dysfunction
- Thyroid, parathyroid, adrenal insufficiency
- Osteoporosis

Iron Chelating Regimens Under Evaluation

- Deferiprone
- Deferiprone with desferrioxamine ('Combination' therapy)
- Deferasirox(Exjade or Asunra)

Deferasirox (Exjade or Asunra)

- Regimen 10-30 mg/kg 30 min before breakfast
- 100 mg tablet Rs 80/=
- 400 mg tablet Rs 200/=
- Expenditure – 50% of desferrioxamine

Deferiprone Toxicity

• Agranulocytosis	0.6-4%
• Neutropaenia	“5.4/100pt-years”
• Zinc deficiency	14%
• Nausea	10-20%
• Accelerated hepatic fibrosis	0-37%
• Fluctuating LFTs	44%
• Arthropathy	6-50%
• Dropouts(Unexplained)	20-55%

Expenditure For Chelation

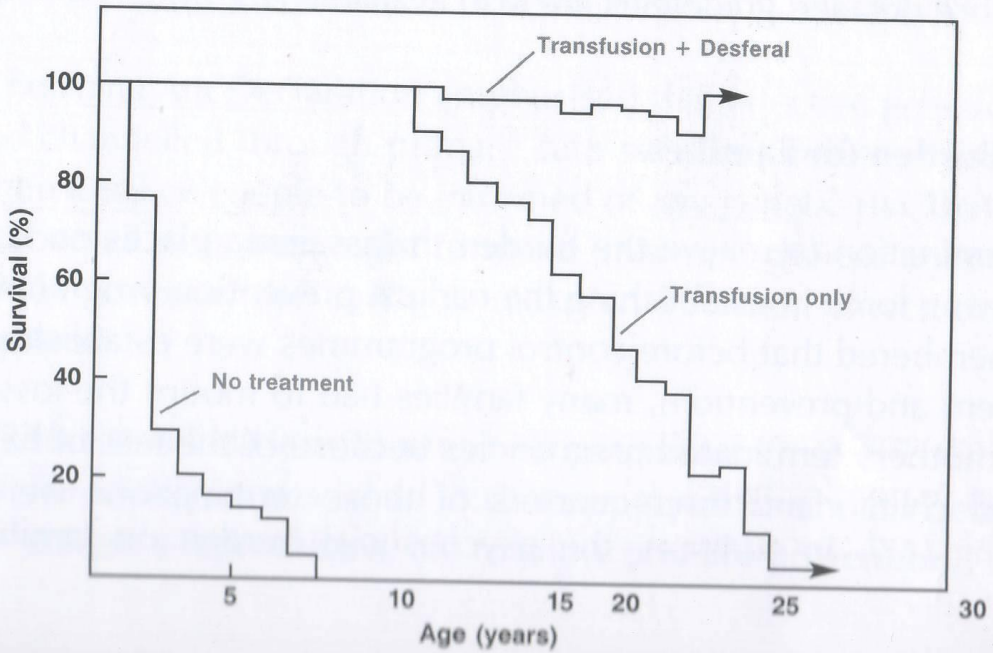
Name	Year	Quantity	Value in Rs.
Desferrioxamine injection 500mg	2002	130,556	48,375,256.00
	2003	162,114	61,760,471.00
	2004	131,745	70,673,059.00
	2005	214,600	71,624,050.00
	2006	299,924	103,669,059.00
	2007		98,950,000.00
	2008		141,780,000.00
Deferiprone capsule 250mg	2002	97,400	2,301,812.00
	2003	127,500	2,855,325.00
	2004	.....	.....
	2005	16,600	251,088.00
	2006	35,400	433,812.00
	2007		730,000.00
	2008		860,000.00
Deferiprone capsule 500mg	2002	74,200	2,854,474.00
	2003	25,700	988,679.00
	2004	55,900	1,631,266.00
	2005	35,100	867,465.00
	2006	47,900	1,358,105.00
	2007		1,350,000.00
	2008		1,730,000.00

Summary of Expenditure

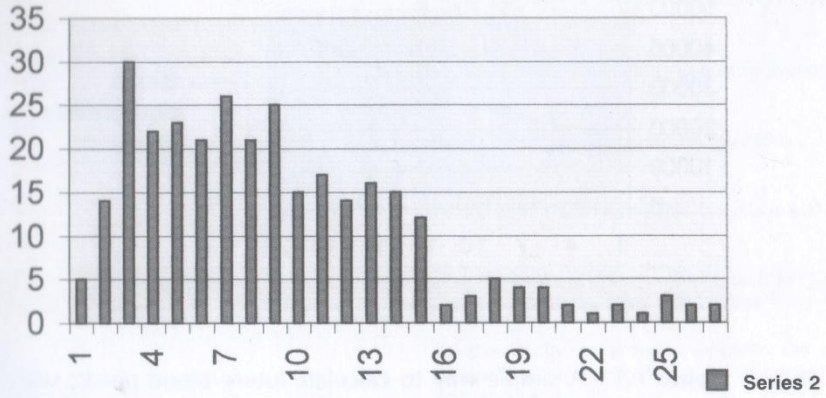
	Desferrioxamine	Deferiprone	Total
2002	48,375,256.00	5,156,286.00	53,531,542.00
2003	61,760,471.00	3,844,004.00	65,604,475.00
2004	70,673,059.00	1,631,266.00	72,304,325.00
2005	71,624,050.00	1,118,553.00	72,742,603.00
2006	103,669,059.00	1,791,917.00	105,460,976.00
2007	98,950,000.00	2,080,000.00	101,030,000.00
2008	141,780,000.00	2,590,000.00	144,370,000.00

Survival curve

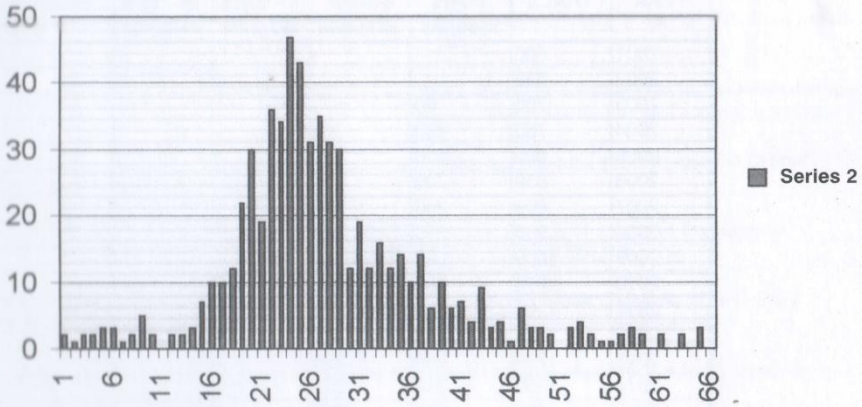
Figure 1.2 - Survival Curve *(reproduced from Modell et al, 1992)*



Age distribution of thalassaemics in a country with no prevention



Age distribution in a country with full treatment and prevention



In the first graph, we see that patients are mostly infants (non-prevention) and children (early deaths).
In the second graph, we see the gap in the early years, with patients mostly in their mid-twenties.

Why is prevention important?

- Disease burden- 2000 patients with beta thalassemia major
  1000 patients with HbE/Thalassemia
  60 new cases per year

- Expenditure-Chelation
  Blood transfusions
  Infusion pumps
  Hidden expenditure

Palestine

- Population 3 million
- Screening with MCV if <79 fL
- Hb electrophoresis > 3.5% A_2 -β thal carrier
- 2001 -2004
  - 57,242 screened
  - 49,900 received thalassaemia free certificate
  - 3,352 (5.8%) had low MCV and 852 (1.54%) were carriers

Palestine (contd.)

- 105 cases- both partners were carriers and their marriages were cancelled voluntarily or by order of QQ (Qudi Qudah) legitimate courts
- Before screening 33-21 cases / year
- After screening 7 / year
  - 2 marriages abroad
  - 5 misdiagnosed

Iran

- Population: 70 million
- Estimate: 3 million carriers 20,000 patients
- Main stratergies
  - Screening of couples who decide to marry
  - 650,000 screened
  - 1000 accepted counsellors' recommendations
  - 210 cases prevented
  - USD 20 million saved


Thank you

Where in Sri Lanka ?

- North Central Province
- North Western Province
- Uva
- Central Province
- Western Province

Monitoring System (1)

- An identity card
  - Thalassaemia patients
  - Carriers
- Notification of patients and carriers to central registry
- Cascade screening
  - Total number in cascade
  - Total number screened
  - Total number of carriers
  - Cascade extending from carriers
- Voluntary screening
  - Total number screened
  - Total number of carriers

Monitoring System (2)

- Percentage coverage of screening of eligible youths and adolescents
- Incidence of unsafe marriages
- Incidence of high risk pregnancies
- Incidence of thalassaemia (new cases)

β Thalassaemia major

Why is Prevention Important?

- High frequency of the condition
- To avoid fatalities from untreated β Thalassaemia
- The expense and difficulty of providing optimum treatment for patients, which creates a burden on patients, families and national health service.
- Prevention is good public health practice for a genetically determined disease.
- Cost effectiveness
- Relieves burden on families.

Service Indicators for Prevention

- Number of births per year
- Number of pregnancies per year
- Annual births of carriers and pregnant carriers per year
- Annual number of at risk couples and at risk pregnancies
- Annual number of prenatal diagnoses

Health Education

- Professional education
- Informing the public
  - School curriculum and other programmes
  - Mass media
- Informing policy makers
- Form patient-parent associations

Public Education Programmes

- Media
  - Print
  - Electronic: radio, TV
- Posters
- Leaflets
- Lectures
  - Schools
  - Places of work

General Demographic Data

- Population size
- Population characteristics
- Crude birth rate
- Infant mortality rate
- Financial factors such as GDP, GNP
- Consanguinity rate

Training Programme- workshops

- Thalassaemia Medical Officers- 5 days
- Other Medical Officers- 1 day
- Nurses – 1 day
- Public Health Midwives – 1 day
- Registrars of marriages, Marriage brokers- ½ day
- School teachers and students – ½ day

Screening

- Basic data
- Haematology
- Hb electrophoresis
- Identification card for carriers and patients

Basic Data

- Full name
- Date of birth (DOB)
- Sample date (should not be transfused during previous 4 months)

Haematology (Coulter Counter)
CBC/ FBC

Hb, RBC, MCH, MCV, RDW

- MCV < 78 fL
- MCH < 27 pg

(test within 24 hours; otherwise falsely elevated MCV)

Hb Electrophoresis

Methods?

1. At pH 8.6 using cellulose acetate
2. At pH 6.0 using acid agarose or citrate
3. Isoelectric focusing
4. HPLC High Performance Liquid Chromatography

$Hb\ A_2 > 3.5\%$

Causes of reduced red cell indices & normal Hb electrophoresis

- Iron deficiency
- Heterozygous α- thalassaemia
- Heterozygous for mild β thalassaemia mutation
- Co- inheritance of heterozygous δ with β thalassaemia
- Heterozygous γ δ β thalassaemia

Other Screening Methods

- Osmotic fragility of RBC
- Fetal sampling

Osmotic fragility of RBC

NESTROFT

(Naked eye single tube red cell osmotic fragility test)

- Blood in EDTA
- 0.36 % buffered saline

- Text- clearly visible: Negative
- Text-not visible because of turbidity: Positive
- False positives in: Iron deficiency
- Positive in both β and α thalassaemia carriers

Laboratory Equipment Required

- Coulter Counters for CBC/ FBC (at District level)
- HPLC machines: 5
  - Ragama**
  - Kurunegala*
  - Anuradhapura*
  - Badulla*
  - Trincomalee or Batticaloa
  - Hambantota