

TRANSFUSION REGIMENS IN THALASSEMIA INTERMEDIA



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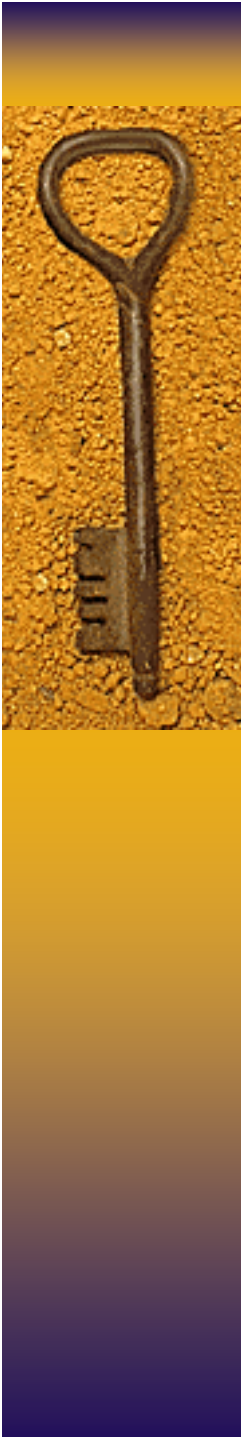
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Outline

- ◆ **Clinical features of the Thalassemia Intermedia (TI)**
- ◆ **Importance of blood transfusions in TI**
- ◆ **Risk/Benefit of blood transfusion in TI**



**‘too haematologically severe to
be called minor,
but too mild to be called
major’**

**TI was first described in 1955 by Rietti-Greppi-
Micheli**



Clinical picture of thalassemia intermedia

*** GREATLY VARIABLE**

*** DEPENDS ON**

Primarily on the underlying molecular defects

(genotype/phenotype correlation)

Several complications

(genetic and nongenetic)

The natural history of thalassemia intermedia

Caterina Borgna-Pignatti, Maria Marsella, and Nicolò Zanforlin

Department of Clinical and Experimental Medicine, Università di Ferrara, Ferrara, Italy

The severity of thalassemia intermedia depends on the degree of imbalance between alpha and non-alpha chains as well as other genetic and environmental factors that modify the natural history of the disease. By definition, the patients spontaneously maintain hemoglobin at or above 7 g/dL, sometimes at the price of intense hyperplasia of the bone marrow that is in turn responsible for bone deformities, osteoporosis, and extramedullary erythropoietic masses that often characterize thalassemia intermedia. Transfusion may become necessary with advancing age, during infection and pregnancy, and when hypersplenism develops. Splenectomy is often needed. Iron overload in nontransfused patients is due to increased gastrointestinal absorption and involves mainly the liver. Complications affecting the lives of patients with thalassemia intermedia include pulmonary hypertension, leg ulcers, pseudoxanthoma elasticum, gallstones, hepatocellular carcinoma, and thromboembolic events.

Keywords: thalassemia intermedia; extramedullary erythropoiesis; pseudoxanthoma elasticum; iron overload; transfusion



Table 1. Genetic mechanisms of thalassemia intermedia: phenotype is correlated to the degree of globin imbalance

<i>Heterogeneous genotypes</i>	
<p>Homozygous or compound heterozygous β-thalassemia</p> <ul style="list-style-type: none">• Presence of mild or silent β-thalassemia alleles• Coinheritance of α-thalassemia• Coinheritance of genetic determinants increasing γ-chain production	<p>Heterozygous β-thalassemia</p> <ul style="list-style-type: none">• Coinheritance of 1 or 2 α-globin chains ($\alpha\alpha/\alpha\alpha$ or $\alpha\alpha\alpha/\alpha\alpha\alpha$)• Heterozygosity for β-thalassemia and structural β-chain variants• Hyperunstable hemoglobins
<p><i>Correspond to heterogeneous phenotypes</i></p>	

The clinical severity of thalassemia intermedia cases are very difficult to predict from their genotypic data.

Table 2. Mutations external to the globin genes that can modify the phenotype of thalassemia intermedia

Cholelithiasis jaundice	• <u>Gilbert syndrome: homozygosity [(TA)⁷/(TA)⁷]</u> for the mutation of the A(TA) _n TAA motif of the promoter of the bilirubin UDP-glucuronosyltransferase gene
Hypercoagulability	• <u>Factor V Leiden;</u> • Prothrombin mutations; • MTHFR mutations; • <u>Decreased levels of Protein C and S and AT III</u>
Osteoporosis	• Sp1 polymorphism of COL1A1, FokI, and BsmI; polymorphism of the Vit D receptor gene; • Polymorphism of ER α and β genes
Hemochromatosis	• C282Y and H63D alleles

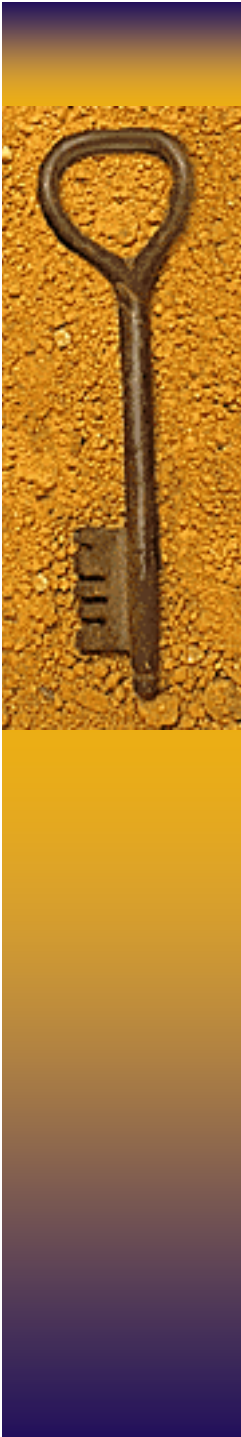
An aggravating effect of splenectomy on hemosiderosis has been suggested

Molecular characterization of β -thalassemia intermedia: a report from Iran

**Aida Arab · Morteza Karimipoor · Ali Rajabi ·
Mohammad Hamid · Sedeigheh Arjmandi ·
Sirous Zeinali**

Published online: 01 December 2010

Three common mechanisms for describing the pathophysiology of TI have been proposed. These include the inheritance of mild β -thalassemia alleles, co-inheritance of α -globin gene mutations and the inheritance of genetic determinants causing high level production of HbF in the absence of high persistence of fetal hemoglobin (HPFH)



Clinical picture of TI

Chronic anemia

Splenomegaly

Growth failure

Ineffective erythropoiesis

Skeletal deformities and Osteopenia

Hepatosplenomegaly

Iron overload

Increased gastrointestinal iron absorption

Non-transfusional iron overload in the liver and less so in the heart

Is Thalassemia Major a life threatening disease?

Previously: YES

Now: NO

**Patients with Thalassemia major are now
`healthy patients`.**

**Is Thalassemia Intermedia a life
threatening disease?**

Previously: NO

Now:

**Patients with thalassemia Intermedia have
poor appearance and quality of life compared to
thalassemia major.**

Quality of Life in Patients with Thalassemia Intermedia Compared to Thalassemia Major

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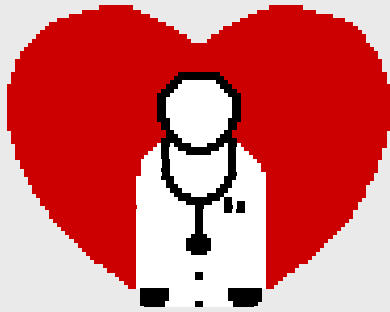
ABSTRACT: The impact of thalassemia major and thalassemia intermedia and their associated complications on quality of life (QOL) is largely unknown. Determining the degree of health impairment as perceived by the patient is essential information needed to recommend suitable therapy. The objective of this study was to evaluate QOL in transfusion-independent patients with thalassemia (non-Tx) compared with that in transfused patients (Tx) and to identify the factors that affect QOL in thalassemia. A convenient sample of 48 thalassemia patients (29 Tx and 19 non-Tx) with mean age of 14.6 years (SD = 7.5 years) were selected during a comprehensive visit to complete a Dartmouth Primary Care Cooperative Information Chart System (COOP) questionnaire. Patients rated QOL from excellent (1) to poor (5) on five dimensions of health status. Scores of 4 or 5 represent major limitations. These results were augmented by a brief medical history and chart review. Forty-one percent of Tx patients and 47% of non-Tx patients reported severe impairments in 1–6 and 1–2 domains, respectively. The most commonly reported affected domains were feelings such as anxiety, depression, and concern of overall health status or indications of recent deterioration in health. In contrast with previous beliefs, transfusion-independent thalassemia patients also suffer serious impairment in QOL. Presented data suggest that all patients with thalassemia undergo QOL assessment so that interventions focused on affected domains can be implemented.

THALASSEMIA MAJOR

- **LIFELONG TRANSFUSION
DEPENDENT**

THALASSEMIA INTERMEDIA

- **HETEROGENEOUS DISEASE**
- **LESS SEVERE ANEMIA**
- **SOME ASYMPTOMATIC**
- **OTHERS TRANSFUSION
DEPENDENT**



PRINCIPLES OF TREATMENT IN PATIENTS WITH THALASSEMIA MAJOR / INTERMEDIA

1. BLOOD TRANSFUSION

**2. IRON CHELATION
THERAPY**

**3. SUPPORTIVE
TREATMENT
FOR COMPLICATIONS**

4. SPLENECTOMY

**5. BONE MARROW
TRANSPLANTATION**

1. BLOOD TRANSFUSION

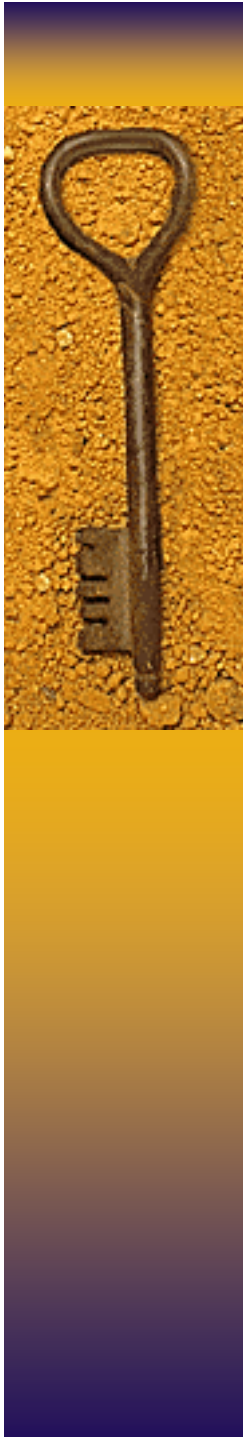
2. SPLENECTOMY

3. IRON CHELATION THERAPY

**4. MODULATION OF FETAL
HEMOGLOBIN PRODUCTION**

**5. SUPPORTIVE TREATMENT
FOR COMPLICATIONS**

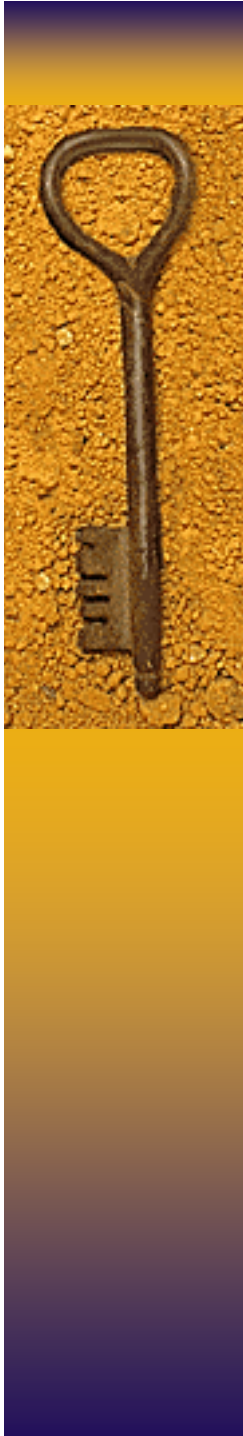
**6. BONE MARROW
TRANSPLANTATION**



**What is the difference between
Thalassemia major and intermedia
treatment?**

TRANSFUSIONS???

Currently no clear guidelines



Let`s find answers to these questions:

Is transfusion therapy required?


Is transfusion therapy a routine treatment approach for patients with thalassaemia intermedia?

What are the risks/benefits of transfusion therapy?

Which regimens of Transfusion therapy ?

(Tailored or Regular)

Patients with non-Transfusion dependent Thalassemia Intermedia



Patients	
no	21
Age	10-53
Age of diagnosis	2-14
< 18 y	7
> 18 y	14
Female	12
Male	9

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Amount of Transfusion in Patients with Non-Transfusion dependent Thalassemia Intermedia

Transfusion number	n	Age
None	4	10, 12, 25, 44
< 10	3	23, 28, 33
10-20	6	14, 15, 19, 24, 32, 40
20-30	3	12, 15, 35
30-50	2	36, 38
>50	3	16, 51, 53
Total	21	10-53

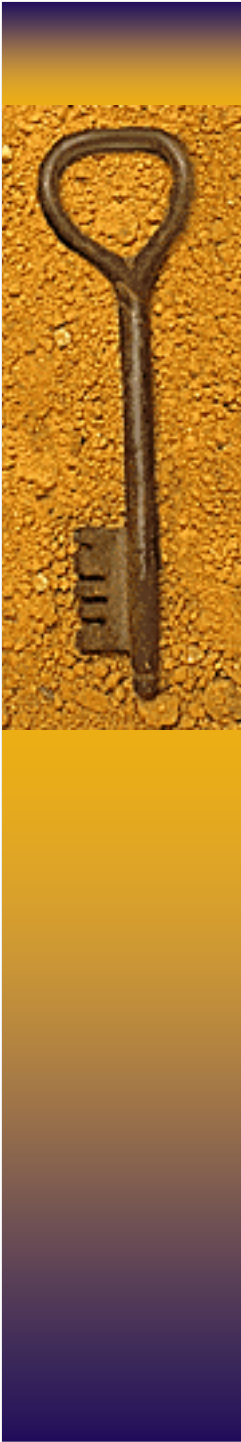
Patients with Non-Transfusion dependent Thalassemia Intermedia

	n	%
Splenomegaly	11	52
Massive splenomegaly	3	14
Splenectomy	7	33
Gall stones	6	27
Cholecystectomy	4	18

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Patients with Non-Transfusion dependent Thalassemia Intermedia



Complications	n	%
Osteoporosis	11	52
Growth failure ($< 3.$ persantil, childhood)	4/7	57
Short stature (adult)	2/11	18
Extrameduller hematopoiesis (spinal cord)	3	14
Bone pain (severe)	3	14
Gout, Infection	2	10
Syncop, hypothyroidy epistaxis, hair loss, pins and needles	1	5
Thrombosis	1	5

**<10 years
childhood**

- Autoimmune hemolytic anemia
- Thalassemic physical appearance
- Hypersplenism

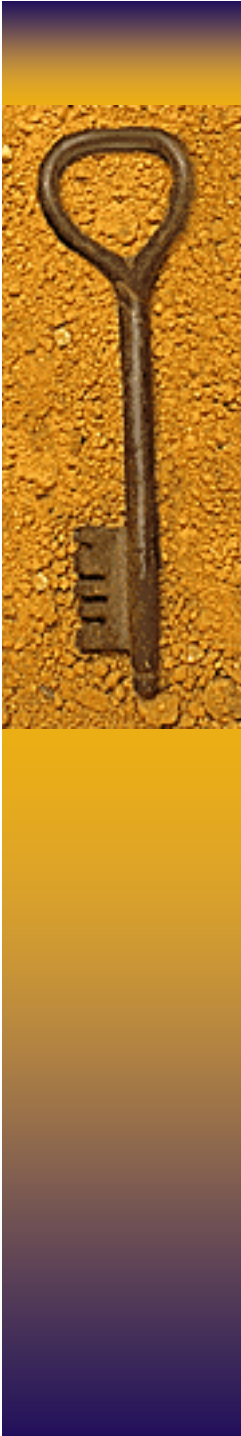
**10-50 years
adult**

- Iron overload
 - Heart disease
 - Thromboembolism
 - Extramedullary erythropoiesis
- Endocrinopathies
Cholelithiasis
Leg ulcers

**> 50 years
adult**

- Pseudoxanthoma Elasticum
- Pulmonary Hypertension

Transfusion	Mutations	Complications
None (n:4)	IVS II-I/IVS 1-6 CD 8/ alfa triplication 2 NA	4 splenomegaly 1 osteoporosis
< 10 (n:3)	-30/-30 2 NA	3 splenomegaly (1 massive) 1 osteoporosis 1 splenectomy 1 cholecistectomy
10-20 (n:6)	2 IVS 1-6/IVS 1-6 CD 39/IVS I-6 CD 39/CD 39 -30/-30 NA	2 massive splenomegaly, 4 gall stones, 3 osteoporosis, 3 splenectomy , 2 growth failure, 2 EMH, 9 others
20-30 (n:3)	IVS II-I/IVS II-I NA (n:2)	1 joint ache, 2 splenectomy , 1 splenomegaly, 1 infection, 1 gall stones, 1 osteoporosis, 1 splenectomy, 1 growth failure, 3 others
30-50 (n:2)	IVS I-6/Codon 8 NA	2 splenomegaly, 1 cholecistectomy, 1 bone deformities, 1 gall stones
>50 (n:3)	-30/-30 2 NA	2 splenomegaly, 1 splenectomy , 1 cholecistectomy, 2 osteoporosis, 1 short stature, 1 EMH, 1 hypotiroidi, 1 amenore,



Is the transfusion received after the complications are developed?

Do transfusions prevent complications?

Do the complications increased by transfusions?

Answers to these questions are not clear yet.



When did the patients receive transfusion? (in patients with non-transfusion dependent Thalassemia Intermedia)

Transfusion number	5-7 g/dL	7-9 g/dL	9-10 g/dL	>10 g/dL
None	-	-	2	2
< 10	-	2	1	
10-20	1	4	1	-
20-30	1	1	1	-
30-50	-	2	-	-
> 50	-	2	1	-
Total	2	11	6	2

Decision of transfusion is not difficult in mild or severe forms of thalassemia intermedia.

Individual treatment modality is required in the moderate form of disease.



Transfusion indications in patients with non-transfusion dependent Thalassemia Intermedia

Indication of transfusion	Patients n
Infection	13
Hipersplenism	9
Operation	9
Growth failure	8
Extrameduller hematopoiesis	3
Pregnancy	2

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THALASSEMIA INTERMEDIA

No adequate clinical definition

Broad clinical spectrum:

1. Hb level persistently between 90–100 g/l with splenomegaly

(Mild TI)

2. Hb levels in the 50–60 g/l range present relatively late, with growth failure, gross skeletal deformities (severe TI).

These children should be transfused to avoid these complications (treated as having TM)



THALASSEMIA INTERMEDIA

3. Hb values between 60 and 90 g/l, growth and development reasonably well (moderate TI).

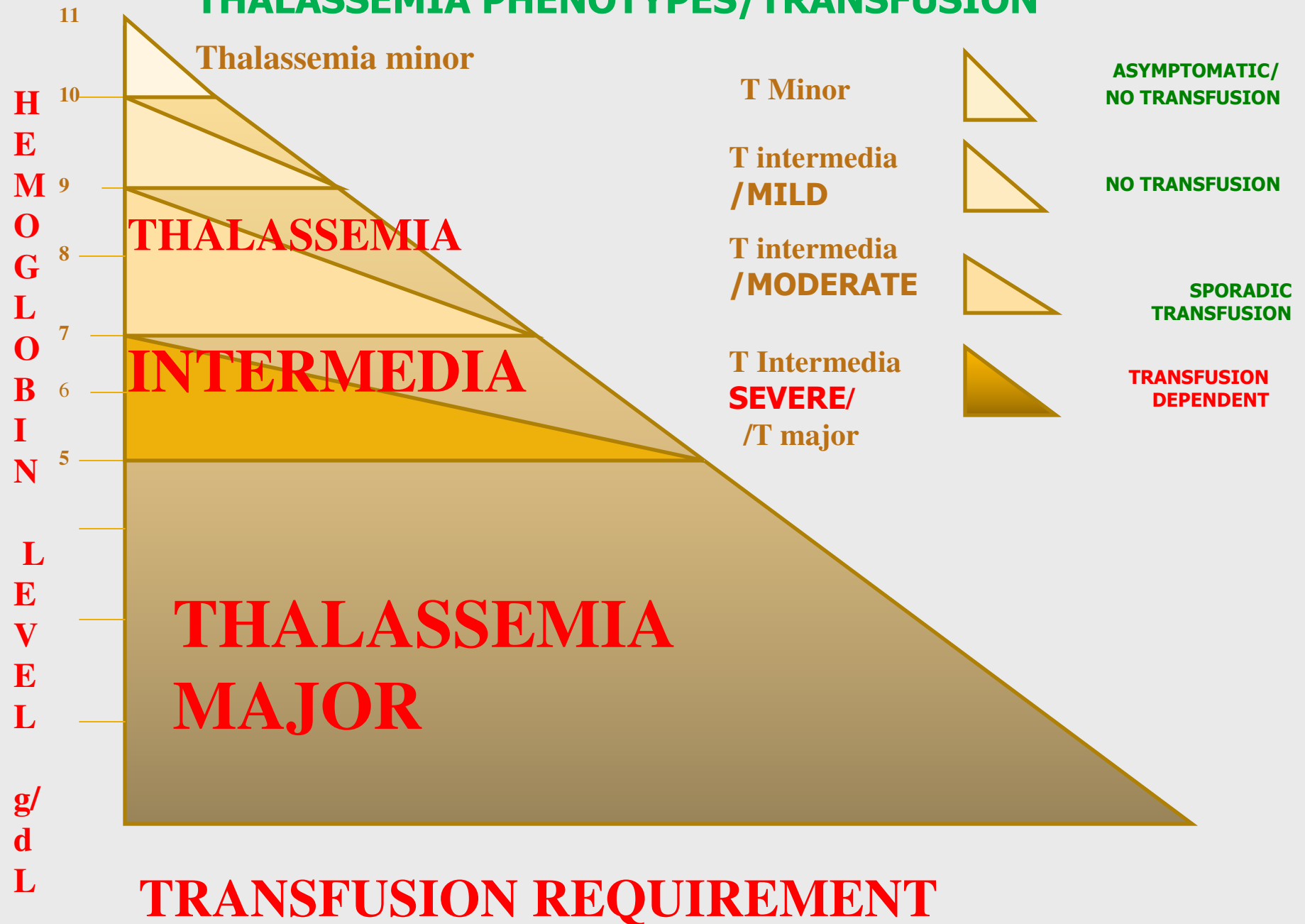
The decision to transfuse is difficult.

Transfusions may require if complications develop.

Transfusion may become necessary with advancing age, during infection and pregnancy, and when hypersplenism develops.

Diagnosis can be made after an observation and often requires revision (Steinberg et al 2009).

THALASSEMIA PHENOTYPES/TRANSFUSION



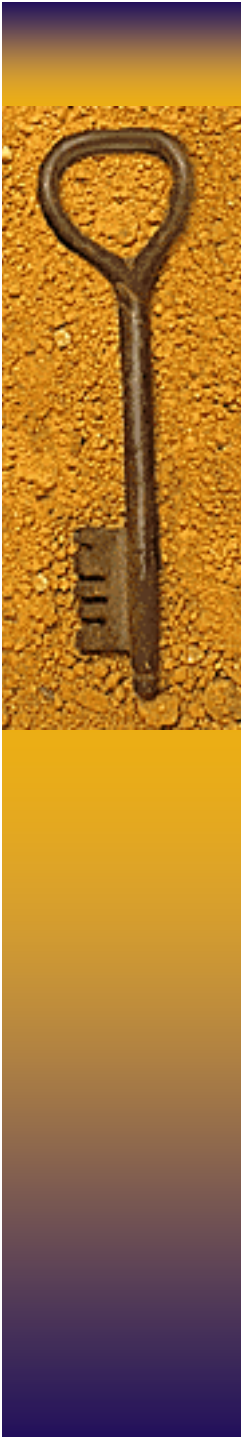


TRANSFUSION THERAPY/ THALASSEMIA INTERMEDIA

Not a routine treatment approach, can afford significant benefits.

The decision to initiate transfusion therapy should be based on not only the Hb level* but also;

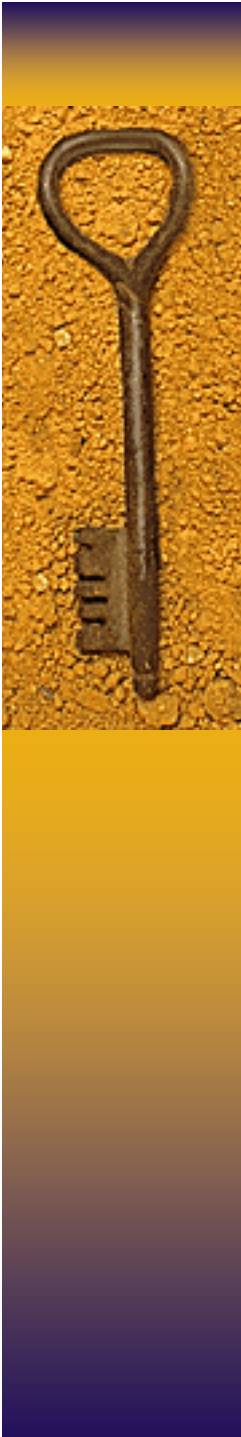
**Signs and symptoms of anaemia,
The patient's well being, particularly with respect to
Activity,
Failure of growth and development,
and the early appearance of skeletal changes or
other disease-complications**



The prevailing approach

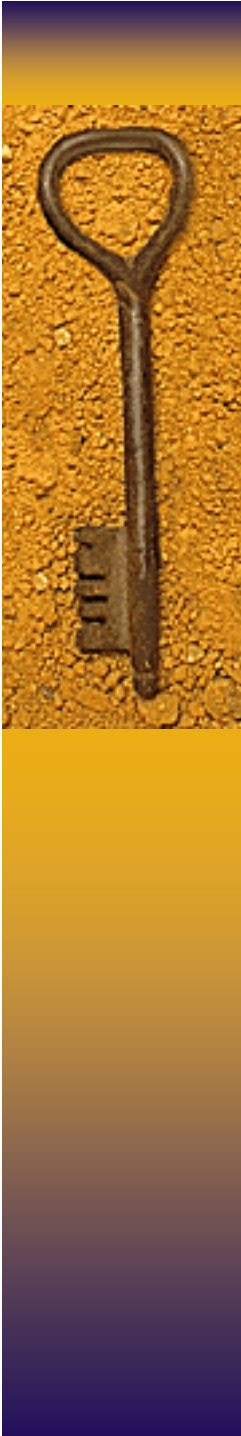
- **Avoidance of early blood transfusions and**
- **Concomitant requirement for chelation therapy,**
- **Reserving the transfusion until later in the disease course when complications manifest.**

Guidelines for the clinical management of the thalassemia 2007



Indications to transfuse regularly in Thalassemia Intermedia

- **Chronic anemia (Hb < 7 g%)**
- **Bone deformities**
- **Failure to grow**
- **Extramedullary erythropoiesis**
- **Heart failure**
- **Pregnancy**



Patients with thalassaemia intermedia may benefit from an **individually tailored transfusion regimen, compared with the regular transfusion regimens implemented in thalassaemia major, to help prevent transfusion-dependency.**



Optimal management of β thalassaemia intermedia

Ali T. Taher,¹ Khaled M. Musallam,¹ Maria Domenica Cappellini² and David J. Weatherall³

2011 Blackwell Publishing Ltd, *British Journal of Haematology*, **152**, 512–523

Although the term TI lacks specific molecular correlates, and the diagnosis remains largely clinical, a genotype/phenotype association has been observed (Galanello & Cao, 1998). The β thalassaemias, including TI, arise from defective gene function leading to the partial suppression of β globin protein production. Most TI patients are homozygotes or compound heterozygotes for β thalassaemia, meaning that both β globin loci are affected

Current indications for transfusion therapy in TI

Haemoglobin level < 50 g/l

Declining haemoglobin level in parallel with profound enlargement of the spleen (at a rate exceeding 3 cm/year)*

Growth failure (height is more indicative of growth pattern than weight) or poor performance at school

Diminished exercise tolerance

Failure of secondary sexual development in parallel with bone age

Severe bony changes

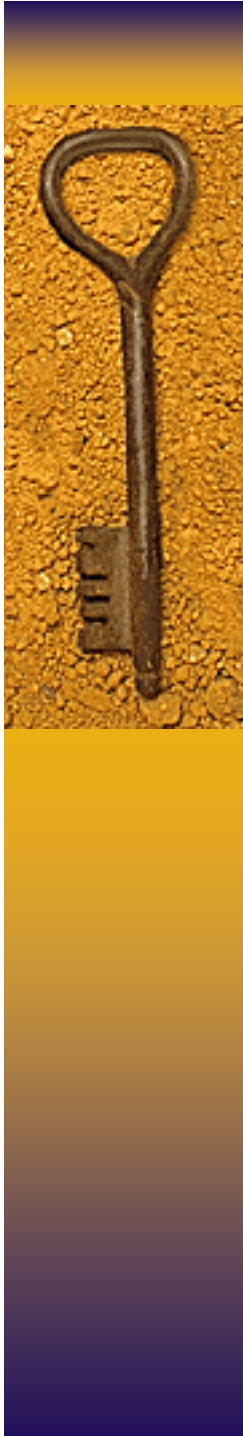
Pregnancy

Infection

Other specific complications (e.g. Heart failure, pulmonary hypertension, thromboembolic disease, leg ulcers, priapism)

*At least in periods of maximal growth and development.

Ali T. Taher, Khaled M. Musallam, Maria Domenica Cappellini and David J. Weatherall. Optimal management of b thalassaemia intermedia British Journal of Haematology, 152, 512–523, 2011



Until solid evidence-based guidelines are available, individualised treatment should be entertained.



OPTIMAL CARE study

Patients who received intermittent or regular transfusion regimens suffered fewer complications:

**Chronic anaemia,
Ineffective erythropoiesis, and
Haemolysis (mainly EMH, PHT, and thrombosis);**

while suffering from a higher rate of iron overload related endocrinopathy (Taher et al, 2010).

Transfused TI patients:

fewer thromboembolic events, PHT, and silent brain infarcts as compared to transfusion naive patients (Taher et al, 2006, 2010; Aessopos et al, 2007). (Taher et al, 2008).

Blood transfusion in patients with TI will require closer monitoring and should be individually tailored to meet patient needs.

Alloimmunization is a relatively common observation in TI, and the risk is decreased if transfusion therapy is initiated before the age of 12 months

REGULAR TRANSFUSION / BENEFITS	REGULAR TRANSFUSION /RISKS	TAILORED TRANSFUSION
Bone deformities	Transfusion dependency	Childhood
Growth failure	Transfusion transmitted infections	Bone deformities
Autoimmune Hemolytic Anemia	Transfusion reactions	Growth failure
Extramedullary erythropoiesis	Iron overload	School performance
Hypersplenism	Heart disease	Adulthood
Hyperuricuria and Gout	Osteoporosis	Pregnancy
Pseudoxantoma Elasticum	Growth failure	Work performance
Thrombo-embolism	Delayed puberty	All
Pulmonary Hypertension	Diabetes Mellitus	Infections
Heart Disease from hypoxia	Hypothyroidy	Hypersplenism
Increased iron absorption	Hypoparathyroidy	Symtomatic anemia
Cholelithiasis	Cost (Need of chelation)	Transfusion independency
Infections	Hospital dependency	Psychologic effects
Leg ulcers	Psychologic effects	