

* CHAPTER 12

Thalassaemia intermedia

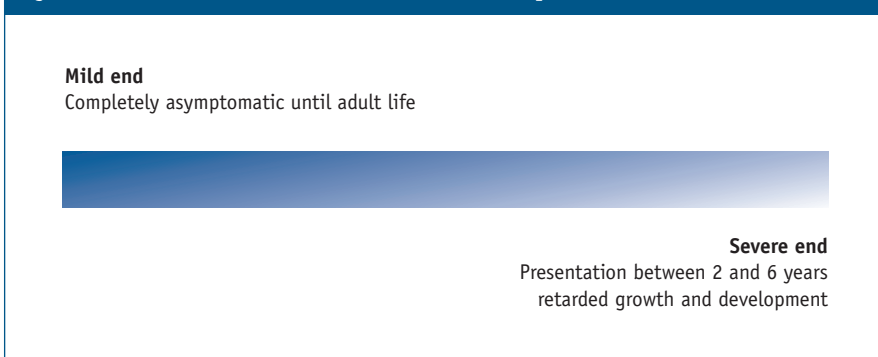
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1. Introduction

The clinical phenotypes of thalassaemia intermedia (TI) lie between those of thalassaemia minor and major, although there is substantial clinical overlap between the three conditions. TI was illustrated in 1955 by Rietti-Greppi-Micheli, who described patients as being “too haematologically severe to be called minor, but too mild to be called major”. Our knowledge of the molecular basis of TI has progressed significantly in the last decade, including an increased understanding of the genetic mutations that lead to the TI phenotypes.

TI encompasses a wide clinical spectrum (Figure 1). Mildly affected patients are completely asymptomatic until adult life, experiencing only mild anaemia and maintaining haemoglobin (Hb) levels between 7–10 g/dL. These patients require only occasional blood transfusions, if any. Patients with more severe TI generally present between the ages of 2 and 6 years, and although they are able to survive without regular transfusion therapy, growth and development can be retarded. The clinical spectrum of TI indicates the need for an individualised treatment approach. Despite the availability of a number of treatment options, the lack of clear guidelines can present a significant clinical challenge.

Figure 1: Thalassaemia intermedia - wide clinical spectrum



2. Definition and molecular mechanisms of thalassaemia intermedia

2.1 Clinical definition of thalassaemia intermedia

Description of the various forms of thalassaemia is based on the severity of the condition rather than the underlying genetic abnormality. Although the clinical phenotypes of thalassaemia minor, intermedia and major differ, there are some similarities. There is an increasing awareness of the need for accurate diagnosis in order to achieve optimal

patient management and to avoid over or under treatment (1, 2). The accurate identification of TI versus thalassaemia minor and major can be difficult if based on clinical presentation alone, although certain differentiating parameters have been established. In general, TI is characterised by Hb levels maintained around 7–10 g/dL without the need for regular blood transfusions, by more severe red blood cell (RBC) abnormalities than thalassaemia minor, by a varying degree of spleen enlargement, and by skeletal changes such as expansion of the facial bones and obliteration of the maxillary sinuses, which causes protrusion of the upper jaw.

Criteria for differentiating thalassaemia major from intermedia at presentation are summarised in [Table 1](#).

Table 1: Criteria to differentiate thalassaemia major from intermedia at presentation

	Thalassaemia major more likely	Thalassaemia intermedia more likely
Clinical		
• Presentation (years)	<2	>2
• Hb levels (g/dL)	6-7	7-10
• Liver/spleen enlargement	Severe	Moderate to severe
Haematological		
• HbF (%)	>50	10-50 (may be up to 100%)
• HbA ₂ (%)	<4	>4
Genetic		
• Parents	Both carriers of high HbA ₂ β-thalassaemia	One or both atypical carriers: - High HbF β-thalassaemia - Borderline HbA ₂
Molecular		
• Type of mutation	Severe	Mild/silent
• Co-inheritance of beta-thalassaemia	No	Yes
• Hereditary persistence of HbF	No	Yes
• δβ-thalassaemia	No	Yes
• $\epsilon\gamma\chi mnI$ polymorphism	No	Yes

2.2 Molecular definition and mechanisms of thalassaemia intermedia

The clinical manifestations of thalassaemia result from defects in one of two types of polypeptide chains (alpha or beta). For Hb to function properly, the number of alpha-chains must precisely match the number of beta-chains; thalassaemia is caused by an imbalance in globin chain synthesis. The beta-thalassaemias, including TI, arise from defective gene function leading to the partial suppression

of beta-globin protein production. The extent of suppression varies from patient to patient and dictates the clinical severity of disease. Most TI patients are homozygotes or compound heterozygotes for beta-thalassaemia, meaning that both beta-globin loci are affected (1). Less commonly, only a single beta-globin locus is affected, the other being completely normal (3). The mild clinical characteristics of TI compared with thalassaemia major result primarily from three different mechanisms (1, 4):

- *Inheritance of a mild or silent beta-chain mutation.* Rather than a complete absence of beta-chain synthesis, the level of synthesis is subnormal. This leads to a smaller imbalance between the number of alpha- and beta-chains compared with an absence of beta-chains.
- *Co-inheritance of determinants associated with increased gamma-chain production.* The increased number of gamma-chains helps to neutralise the large proportion of unbound alpha-chains.
- *Co-inheritance of alpha-thalassaemia.* This helps to suppress the synthesis of alpha-chains, causing less of an alpha/beta-chain imbalance.

The phenotype of TI may result from the increased production of alpha-globin chains by a triplicated or quadruplicated alpha genotype associated with beta-heterozygosity (5-7).

Table 2 shows beta-globin mutations in thalassaemia intermedia and thalassaemia major that have a direct effect on modifying the amount of excess alpha-chains, such as inheritance of abnormal alpha- or gamma-chain genes. Tertiary modifiers are polymorphisms occurring at loci involved in bone, iron and bilirubin metabolism which can affect clinical expression, although these are thought to be of relatively little importance. Recent studies of the JAK2 cytoplasmic tyrosine kinase, which has a vital role in signal transduction from several haemopoietic growth factor receptors, revealed a *V617F* mutation that was implicated in a variety of diseases mainly related to myeloproliferative disorders including polycythaemia vera, essential thrombocythaemia, and idiopathic myelofibrosis. Thalassaemia intermedia patients, however, do not show increased expression of this mutation (8). Environmental factors include social conditions, nutrition and the availability of medical care (9).

A number of studies have attempted to classify patients with TI according to the severity of their condition, although these studies have had only limited success (10, 11). A recent study described the development of a phenotype scoring system that successfully sub-classified TI patients into three separate groups: mild, moderate or severe (12). The severity of TI was graded according to a number of clinical features, such as age at presentation, severity of anaemia, extent of growth retardation and bone marrow hyperplasia, blood transfusion requirements and need

Table 2: Prevalent beta-globin mutations in thalassaemia intermedia and thalassaemia major in patients of Mediterranean origin

Mutations	Thalassaemia intermedia n. (%)	Thalassaemia major n. (%)
cd 39 C→T	72 (24)	136 (53.5)
IVSI-110 G→A	52 (17)	58 (23)
IVSI-6 T→C	94 (31.5)	16 (6.3)
IVSI-1 G→A	8 (2.7)	19 (7.4)
IVSII-1 G→A	14 (4.7)	10 (3.9)
IVSII-745 C→G	11 (3.7)	9 (3.5)
-101 C→T	10 (3.3)	-
cd 6 - A	10 (3.3)	3 (1.2)
-87 C→G	8 (2.7)	-
δβ ^{Siciliana}	13 (4.3)	-
Lepore Boston	2 (0.7)	-
IVSI-5 G→A	-	1 (0.4)
IVSI-5 G→C	1 (0.3)	-
IVSII-844 G→C	1 (0.3)	-
IVSI-2 T→A	1 (0.3)	-
cd 44 - C	-	1 (0.4)
cd 8 - AA	1 (0.3)	1 (0.4)
Total	298 (100)	254 (100)

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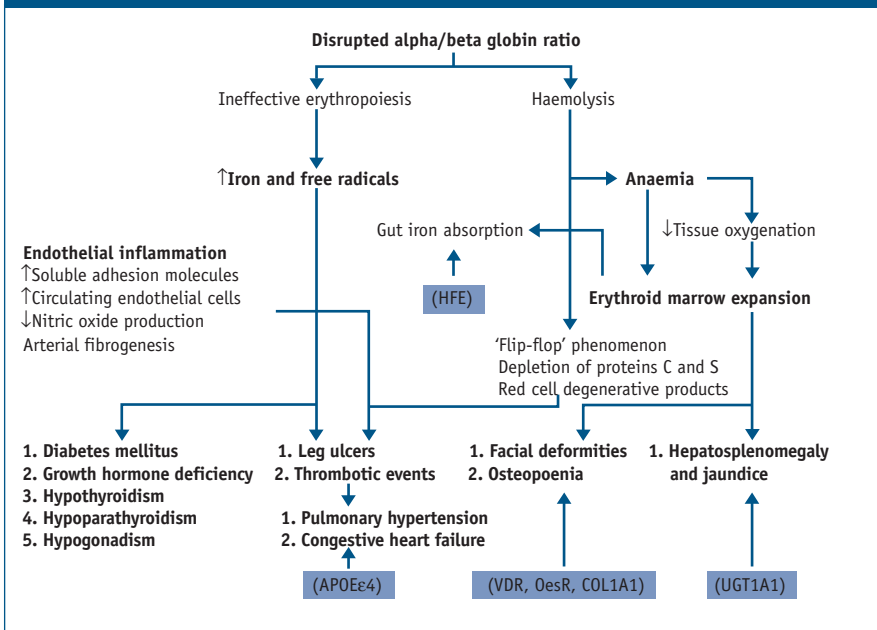
for splenectomy. This classification could prove useful for relating genotype to phenotype and for developing separate treatment guidelines for different disease severities. However, further studies would be required to confirm the reliability and utility of this approach.

3. Clinical sequelae of thalassaemia intermedia

Three main factors are responsible for the clinical sequelae of TI: ineffective erythropoiesis, chronic anaemia and iron overload. The severity of clinical sequelae primarily depends on the underlying molecular defects. Alpha-chains are highly unstable and precipitate within erythroid precursors in the bone marrow, causing membrane damage and cell death – this is ineffective erythropoiesis (13). Hypertrophy of erythroid marrow in medullary and extramedullary sites, a consequence of severe ineffective erythropoiesis, results in characteristic deformities of the skull and face and may also cause cortical thinning and pathological fractures of long bones (2, 14). The degree of ineffective erythropoiesis is the primary determinant of the development of anaemia, while peripheral haemolysis of mature RBCs and an overall reduction in Hb synthesis are secondary. Chronic anaemia leads to an

increase in gastrointestinal iron absorption, resulting in iron overload which in turn can cause a number of serious complications including cardiac failure and endocrine abnormalities such as diabetes mellitus and hypogonadism (Figure 2).

Figure 2: Pathophysiological sequelae of untreated thalassaemia and corresponding clinical manifestations



APOE 4: apolipoprotein E4; VDR: vitamin D receptor; OesR: oestrogen receptor; COL1A1: collagen type a1; UGT1A1: uridine diphosphate-glucuronyltransferase IA.

4. Complications in thalassaemia intermedia

In addition to the defining symptoms of TI, which are seen to a lesser or greater extent in other forms of thalassaemia, patients with TI experience a number of specific complications that are rare in thalassaemia major (Table 3).

4.1 Splenectomy and cholecystectomy

Splenectomy is now uncommon and is mainly performed late in life. The main indications for splenectomy in TI are a significant enlargement of the spleen and a decrease in mean Hb level in the absence of other transient factors such as infection

Table 3: Prevalence of common complications in thalassaemia intermedia versus major in Italy (15) and Lebanon (16)

Complication (% of patients affected)	TI, Lebanon (n=37)	TI, Italy (n=63)	Thalassaemia major, Lebanon (n=40)	Thalassaemia major, Italy (n=60)
Splenectomy	90	67	95	83
Cholecystectomy	85	68	15	7
Gallstones	55	63	10	23
EMH	20	24	0	0
Leg ulcers	20	33	0	0
Thrombotic events	28	22	0	0
Cardiopathy*	3	5	10	25
PHT	50**	17	10	11
Abnormal liver enzymes	20	22	55	68
Hepatitis C infection	7	33	7	98
Hypogonadism	5	3	80	93
Diabetes mellitus	3	2	12.5	10
Hypothyroidism	3	2	15	11

*Fractional shortening <35%. **PHT was defined as pulmonary artery systolic pressure >30 mmHg. A well enveloped tricuspid regurgitant jet velocity could be detected in only 20 patients, so frequency was assessed in these patients only

(17). Gallstones are much more common in TI than in thalassaemia major because of ineffective erythropoiesis and peripheral haemolysis. Recently, unrelated genetic factors such as uridine 5'-diphospho-alpha-D-glucose (UDPG) deficiency (Gilbert's syndrome) have been reported to increase gallstone formation in patients with thalassaemia (18). For this reason, the gallbladder should be inspected during splenectomy and a cholecystectomy performed if necessary, particularly if the patient is experiencing symptomatic gallstones. This should be undertaken to prevent cholecystitis, which can have serious consequences in splenectomised patients.

4.2 Extramedullary haematopoiesis

Extramedullary haematopoiesis (EMH) is a compensatory mechanism where bone marrow activity increases in an attempt to overcome the chronic anaemia of TI, leading to the formation of erythropoietic tissue masses that primarily affect the spleen, liver and lymph nodes. These masses can be detected by magnetic resonance imaging (MRI). They may cause neurological problems such as spinal cord compression

and paraplegia, and intrathoracic masses (19, 20). Extramedullary haematopoiesis can be managed by radiotherapy (since haematopoietic tissue is highly radiosensitive) (21), transfusion therapy or hydroxyurea (19, 22, 23).

4.3 Leg ulcers

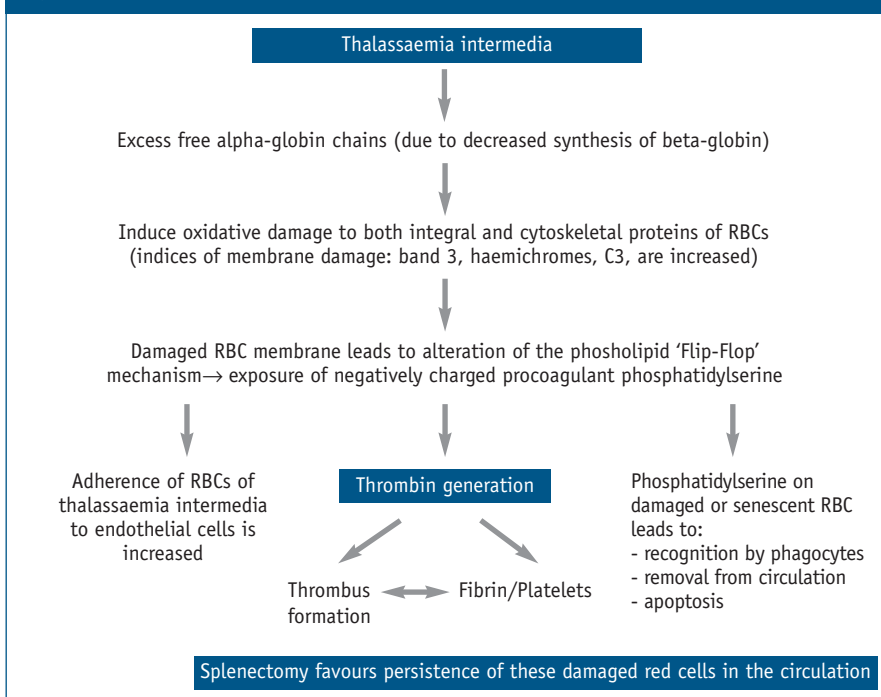
Leg ulcers are more common in older than in younger patients with TI. It is unclear why ulcers develop in some patients who are maintained at relatively low Hb levels and have the same amount of foetal Hb (HbF) as others in whom ulcers do not develop. The skin at the extremities of elderly TI patients can be thin due to reduced tissue oxygenation, and this makes the subcutaneous tissue fragile and increases the risk of lesions from minimal trauma. Once an ulcer has started to develop it is very painful and difficult to cure, although regular blood transfusions may provide some relief in persistent cases. Simple measures may be beneficial, such as keeping the patient's legs and feet raised above the level of the heart for 1–2 hours during the day or sleeping with the end of the bed raised. Zinc supplementation (24) and pentoxifylline, which alters the rheological properties of the RBCs (25), can help accelerate the healing of ulcers. Hydroxyurea also has some benefit, either alone or in combination with erythropoietin (26). In addition, the use of an oxygen chamber can provide moderate relief since tissue hypoxia may be an underlying cause of the ulceration (27).

4.4 Thrombophilia

Patients with TI have an increased risk of thrombosis compared with a normal age and sex-matched population and with thalassaemia major patients. This was evident in a recent epidemiological study where 3.9% of 2,190 patients with TI and 0.9% of 6,670 patients with thalassaemia major experienced a thrombotic event (28). In TI patients, these events primarily occurred in the venous system and comprised deep vein thrombosis (DVT) (40%), portal vein thrombosis (19%), stroke (9%), pulmonary embolism (12%) and others (20%). Moreover, splenectomised patients were shown to have a higher risk of thrombosis than non-splenectomised patients. Non-transfused patients and patients with a low haemoglobin level (<9g/dL) were also shown to have a higher occurrence of thrombotic events. There are several possible reasons for this, including the procoagulant activity of damaged circulating RBCs, as it is thought that RBC remnants expose negatively charged phosphatidyl-serine residues through the 'Flip-Flop' phenomenon and subsequently initiate thrombosis (29). Other possible mechanisms include activation of platelets, endothelial cells and monocytes, depletion of antithrombotic factors (proteins C and S), and concomitant cardiac, endocrine or hepatic dysfunction (30). Risk factors for developing thrombosis in patients with TI are age (>20 years), previous thromboembolic events, splenectomy and family history.

Deep vein thrombosis, pulmonary thromboembolism and recurrent arterial occlusion have been described in patients with TI, mostly occurring without any other risk factors (31). Cappellini and colleagues reported that around 30% of patients with TI who had been followed for 10 years experienced venous thromboembolic events (32), suggesting the presence of a chronic hypercoagulable state (32, 33). It is important to be aware of these complications since thromboembolism plays an important role in cardiac failure. Recommended treatment options include platelet anti-aggregation agents such as aspirin in patients with thrombocytosis, or anticoagulant agents such as low molecular weight heparin in patients with documented thrombosis or those undergoing surgery. Blood transfusions might be considered in order to reduce damaged circulating RBCs exposing phosphatidyl-serine. Establishing a risk-assessment model may aid in stratifying patients according to low- and high-risk groups, according to intrinsic (number of circulating RBCs, procoagulant mutations) and extrinsic (infection, surgery, pregnancy, splenectomy) risk factors, to help implement an appropriate prophylactic plan (Figure 3).

Figure 3: Thrombotic mechanism in thalassaemia intermedia



4.5 Pulmonary hypertension and congestive heart failure

Pulmonary hypertension (PHT) is prevalent in patients with TI (59.1%) (34), and is thought to be the primary cause of congestive heart failure (CHF) in this patient population. The mechanism underlying PHT in TI is unclear, although evidence indicates a local pathophysiological response in the pulmonary vascular bed that is independent of thromboembolism due to DVT. Suggested mechanisms include endothelial dysfunction with increased inflammation and apoptosis, decreased nitric oxide and nitric oxide synthase production, pulmonary haemosiderosis and local thrombosis (Figure 4). A retrospective analysis showed that splenectomised females with significant anaemia, thrombocytosis and elevated ferritin levels, were at greatest risk for developing PHT (35). Preliminary results have demonstrated that PHT is reversible by blood transfusion and treatment with aspirin and warfarin. Several echocardiographic studies have confirmed that cardiac ejection fraction is rarely affected in TI (36). Nevertheless, patients with TI often have an increased cardiac output, and left ventricular wall dimensions proportional to the dilutional volume overload secondary to chronic anaemia (37).

As anaemia and iron overload are uncommon in well-transfused and chelated thalassaemia major patients, they are likely to be at the heart of the pathophysiology of PHT. A recent study demonstrated a significant correlation between iron overloading in the liver and pulmonary artery systolic pressure independent of left ventricular filling pressures (38). Regular transfusion and iron chelation therapy is therefore indicated in TI patients who are well-stratified according to the early detection of PHT indices. Sildenafil has also been successfully used to treat PHT (39), although data from large patient numbers are lacking in TI.

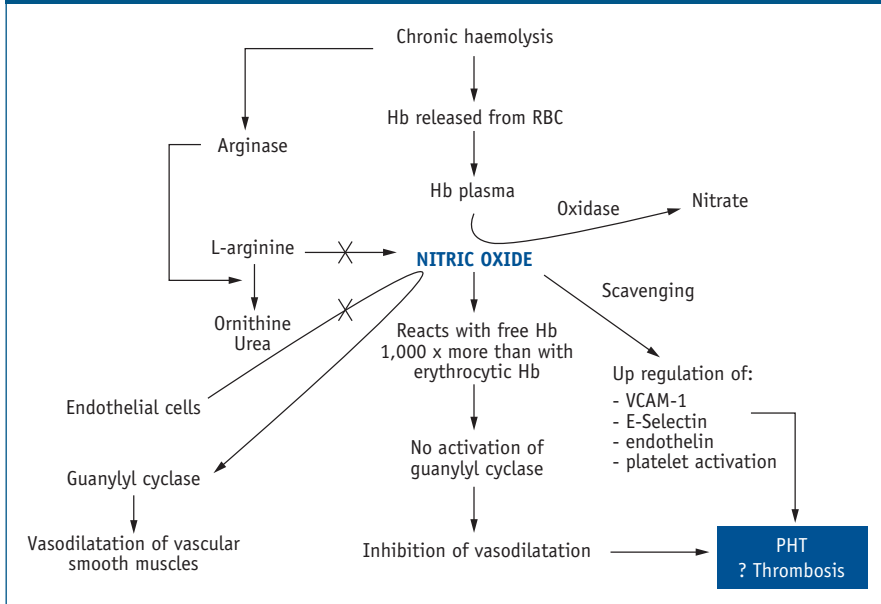
4.6 Hepatitis

Hepatitis due to viral (B and C) infections is less frequent in TI than in patients with thalassaemia major, since blood transfusions are much less common in TI. Abnormal liver enzymes (e.g. increased alanine and aspartate aminotransferase) are frequently observed in TI patients, primarily due to hepatocyte damage resulting from iron overload. Normalisation of liver enzyme levels is often observed during appropriate chelation therapy.

4.7 Endocrine function

Hypogonadism, hypothyroidism and diabetes mellitus are quite rare in TI. Although patients with TI generally experience puberty late, they have normal sexual development and are usually fertile. Hypothyroidism is sometimes observed late in life.

Figure 4: Pathophysiology of pulmonary hypertension in thalassaemia intermedia



4.8 Pregnancy and infertility

Women with TI may have spontaneous successful pregnancies although complications during pregnancy may occur (40). The chronic anaemia of TI can cause an increase in spontaneous abortions, pre-term labour and intrauterine growth retardation, while endocrine complications due to haemosiderosis are common (41). The course and outcome of 19 pregnancies was assessed in 16 women with thalassaemia, including four with TI (42). All pregnancies were uneventful and elective Caesarean section was performed in each case. The mean birth weight of the babies was 3000 g and all were normal except for one case of omphalocele. The largest study to date assessed 44 TI women who had 83 pregnancies, all spontaneous, 30 from Lebanon and 53 from Italy (43). These pregnancies resulted in 20.5% abortions, 77.1% live-births and 2 intrauterine foetal deaths at 26 and 36 weeks' gestation. The mean gestational age (GA) at delivery was 36.5 weeks and birthweight was 2551 g. In pregnancies progressing >20 weeks' gestation, pre-term delivery and intrauterine growth restriction (IUGR) were noted in 31.8% and 24.2% respectively. In those complicated by IUGR, Caesarean delivery (CS) rate was 87.5%. Two women (Italy) developed severe alloimmune haemolytic anaemia. One progressed to cardiac failure at 35 weeks'

gestation and had CS. The other underwent CS for IUGR and non-reassuring foetal heart monitoring and was scheduled for a splenectomy postpartum. Worsening alloimmune anaemia also developed in 2 women from Lebanon who required splenectomy within eight weeks postpartum. Transfusion was required in 35/44 women during pregnancy (79.5%), with 27.3% requiring transfusion during pregnancy for the first time. The lowest mean Hb level was 6.7 ± 2.0 vs. 8.3 ± 1.2 g/dL in Lebanon and Italy respectively. The average ferritin level before pregnancy was 885.2 ± 658.9 vs. 1232.8 ± 902.9 $\mu\text{g/L}$ after pregnancy. In total, CS was performed in 48 pregnancies (72.7%), the indications being elective (41.7%), repeat (31.2%) and obstetrical (27.1%). Pregnancy outcome was similar between Lebanon and Italy with the exception of a significantly higher rate of livebirths in Italy.

Folic acid deficiency is common in TI and occurs due to poor absorption, low dietary intake, or, most significantly, an increased demand for folic acid from active bone marrow. This is a particular concern in pregnancy since deficiency can cause neural tube defects, such as spina bifida, in the growing foetus. During pregnancy, women with TI should therefore be given oral folic acid supplementation (around 1 mg/day), and should be carefully monitored in order to assess the need for transfusion therapy and to avoid haemodynamic compromises. The major fear of initiating transfusions during pregnancy is the development of alloantibodies. These can aggravate anaemia and progress into severe haemolytic anaemia refractory to transfusions and thus increase the complication rate. Caesarean section may be required in TI patients due to the associated cephalopelvic disproportion secondary to skeletal deformity and short stature, especially in non-transfused women. Splenectomy is usually performed in TI women for decreased levels of haemoglobin, hyperactivity of the spleen, leukopenia and symptomatic thrombocytopenia.

4.9 Iron overload

Non-transfused TI patients can still be at risk of the clinical sequelae of iron overload (as commonly seen in regularly transfused thalassaemia major patients) due to increased intestinal iron absorption triggered by chronic anaemia, ineffective erythropoiesis and, possibly, decreased serum hepcidin (44). The principal methods of determining body iron levels are measurement of serum ferritin levels and assessment of liver iron concentration (LIC) from biopsy tissue. Many patients with TI have serum ferritin and LIC levels above the recommended threshold levels identified in patients with thalassaemia major, indicating a risk of significant morbidity and mortality. Serum ferritin levels were seen to increase with age, reflecting increased iron accumulation over time, even in the absence of transfusion therapy (45).

A significant correlation between serum ferritin and LIC has been established in regularly transfused patients with thalassaemia major. However, recent studies on TI patients reported a different observation (44, 46). In these studies, serum ferritin levels were seen to be significantly lower in patients with TI than in those with thalassaemia major, despite comparable LIC. This highlights the variability in iron loading in patients with TI and the need for a more accurate assessment of iron burden in these patients.

Non-invasive approaches for determining liver iron concentration are increasingly used as an alternative to biopsy, although R2 MRI is currently the only validated approach. A significant positive correlation between mean serum ferritin and LIC values was observed even in splenectomised TI patients (45). Again, serum ferritin levels were significantly lower than in comparable thalassaemia major patients, while both groups had similar LIC on R2 MRI (45). Therefore, evaluation of serum ferritin levels appears to underestimate the extent of iron overload in the thalassaemia intermedia population. It has been suggested that, in transfused patients, iron is preferentially distributed to the reticuloendothelial system and that ferritin synthesis and release is responsible for higher serum ferritin levels. In contrast, in non-transfused patients, iron accumulated as a result of hyperabsorption is accumulated in hepatocytes and, therefore, lower serum ferritin levels are seen (46). Where serum ferritin levels provide the only available indication of iron levels, we would suggest that levels below 1,000 ng/mL should not be used as a negative predictor of significant iron overload in patients with TI, and iron chelation therapy may hence be mandated.

Significant correlations were recently observed between non-transferrin-bound iron (NTBI) and both serum ferritin and LIC, confirming the value of this method for assessing iron overload in TI (47). Splenectomised patients had higher serum NTBI levels than non-splenectomised patients, which could be attributed to the function of the spleen in scavenging iron free radicals, including NTBI. In the future, it is likely that measurement of NTBI levels will be a useful element of patient management for assessing the iron status of patients with TI receiving iron chelation therapy. The results of a recent study on TI patients showed that these patients do not have cardiac iron overload as measured by cardiac T2* MRI (48). This is consistent with previous data showing that patients with thalassaemia intermedia are generally less prone to cardiac iron overload associated with morbidity/mortality when compared with patients with thalassaemia major. Nonetheless, continued transfusions may eventually lead to cardiac iron overload.

4.10 Summary of thalassaemia intermedia complications

Unfortunately, it is not always possible to successfully manage the numerous

complications associated with TI, so prevention is the preferable option. This may be achieved through regular and effective transfusion therapy, assessment of baseline iron burden, low-dose aspirin and anticoagulant treatment, preferably with low molecular weight heparin to prevent DVT.

5. Management of thalassaemia intermedia

There are a number of options currently available for managing patients with TI, including transfusion therapy, modulation of HbF production and haematopoietic stem cell transplantation.

5.1 Transfusion therapy and iron chelation

Although transfusion therapy is not currently a routine treatment approach for patients with TI, it can afford significant benefits. The decision to initiate therapy should be based on the presence and severity of signs and symptoms of anaemia, including the failure of growth and development (13). As the rate of iron loading is variable in TI, an assessment of LIC is advisable before initiating transfusion therapy. Patients with TI may benefit from an individually tailored transfusion regimen, compared with the regular transfusion regimens implemented in thalassaemia major, to help prevent transfusion-dependency. Alloimmunisation is a relatively common observation in TI, although the risk is decreased if transfusion therapy is initiated before the age of 12 months (49); Kell and Rhesus phenotyping prior to transfusion therapy is also recommended (50). Some physicians advocate the concomitant administration of steroids for 3–5 days, although this approach is not used by all physicians and its effectiveness remains unproven.

Excess iron in TI patients can be an intrinsic problem; the risk of iron overload is further increased with transfusion therapy. Although the clinical consequences are ultimately the same, iron overload in non-transfused patients with TI develops more slowly than transfusional iron overload (51). It has been estimated that the rate of iron loading in non-transfused patients is 2–5 g/year (52) compared with 7.5–15.1 g/year in transfused patients (17). As a result, the decision to transfuse in TI is often delayed and may never actually be made. Iron overload can, however, be readily controlled with chelation therapy. The current reference therapy is deferoxamine, which has demonstrated significant morbidity and mortality benefits in iron overloaded patients (53, 54). However, the demanding regimen of frequent and prolonged subcutaneous infusion can impact on patient compliance and quality of life (55–57). The availability of an oral iron chelator that is effective and well tolerated could allow more patients to benefit from transfusion therapy in the knowledge that consequential iron overload can be effectively treated.

The initiation of iron chelation therapy in patients with TI depends not only on the amount of excess iron, but also on the rate of iron accumulation, the duration of exposure to excess iron and various other factors in individual patients (58). A direct assessment of LIC is recommended, either by biopsy or by a non-invasive method such as R2 MRI. Chelation therapy should generally be initiated if LIC exceeds 7 mg/g dry weight of liver tissue (59), however lower levels of LIC for initiation of chelation therapy must be considered (60) particularly now with the availability of oral iron chelators (60).

5.2 Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (HSCT), where the marrow of an affected patient is replaced from the stem cells of an unaffected donor, is an established treatment for beta-thalassaemia. Although successful HSCT can offer a cure, it can be unsuccessful (e.g. if the thalassaemia returns), may lead to complications (e.g. graft-versus-host disease, growth impairment, neurological complications), and can even result in death (61-63); the risk for a failed transplantation depends primarily on the health and age of the patient. The decision as to which patients are eligible for transplantation is complex and is related to both the quality of life and expected survival-time of the transplanted patient, when compared with supportive care only. This is particularly relevant in patients with TI, especially in those who are only mildly affected. Due to the risks involved, transplantation is considered appropriate only for patients with a human leukocyte antigen (HLA)-matched donor, which comprises only 30-40% of all beta-thalassaemia patients, at most (65). As HLA type is genetically determined, there is a 25% chance that any two siblings will be a match.

5.3 Modulation of foetal haemoglobin production

Increasing the synthesis of HbF can help to alleviate anaemia and therefore improve the clinical status of patients with TI (66). Production of HbF is reactivated during recovery from marrow suppression after treatment with cytotoxic drugs, therefore it is postulated that these agents may alter the pattern of erythropoiesis and increase the expression of gamma-chain genes. Several cytotoxic agents with this effect have been identified, including cytosine arabinoside and hydroxyurea (67-69). Recently published results from Iran, evaluating six years of hydroxyurea therapy in transfusion dependent patients with TI, are encouraging. A significant decrease in the need for blood transfusions was observed in many patients; the need was completely obviated in some patients (70). Erythropoietin has also been shown to increase HbF levels in some patients with TI (66). Preliminary trials with intravenous and oral butyric acid derivatives have shown increases in foetal and total Hb levels in

patients with TI (71-74), and the acceptable safety profile of these agents makes them promising therapeutic targets. It is unclear how butyrates stimulate gamma-globin production or why some patients respond to treatment while others do not. However, the overall trial results with HbF-stimulating agents are somewhat disappointing. Studies using combined treatments have shown greater promise than the individual agents alone (75). Further clinical evaluation is required to clarify the value of this approach, especially in view of the reduced oxygen delivery capacity of HbF, as this might favour the implementation of a target Hb level higher than 10 g/dL in response to increased need (e.g. PHT, coronary heart disease and chronic obstructive pulmonary disease [COPD]) and an increased ratio of HbF/HbA.

6. Recommendations for the management of thalassaemia intermedia

Despite a number of available treatment options, there are currently no clear guidelines for managing TI. There is, therefore, a clear need for more studies evaluating potential therapeutic options. Until that time we recommend the use of a system-centred risk stratification model in order to individualise patient treatment for each complication.

1. **Growth and development:** follow up with anthropometric measurements.
2. **Extramedullary haematopoiesis:** particularly those causing abnormal facies and symptoms such as neural encroachment.
3. **Endocrine abnormalities:** emphasis on osteopenia, bone fractures and pain, and infertility.
4. **Cardio-pulmonary assessment:** use echocardiography for increased cardiac index as an early sign of cardiac decompensation, and tricuspid regurgitation jet velocity plus spirometry and a 6 minute walk-test for early detection of PHT.
5. **Hypercoagulability-associated states:** including stroke, DVT, pulmonary embolus, superficial thrombophlebitis, pregnancy, sepsis, long-distance travel, COPD, CHF, factor deficiencies, surgery and malignancies, and leg ulcers.
6. **Significant anaemia:** with limitation of exercise tolerance, or in association with stressful conditions that increase oxygen demand, such as infection, asthma, COPD and coronary heart disease.
7. **Psychological challenges:** such as depression or poor performance at school.
8. **Intrinsic iron overload:** as assessed by liver biopsy, R2 MRI, or NTBI may be mandated to indicate baseline iron burden before initiating transfusion therapy.

Other considerations include:

- Review of splenectomy as a procedure of choice, especially with its potential role in increasing thrombotic burden and the associated risk of sepsis;

- Due to the increased risk of alloimmunisation with delayed initiation of transfusion, clinicians should consider regular or more frequent transfusions and iron chelation therapy for patients with TI;
- **Table 4** details our recommendations as to which patients with TI should be transfused and splenectomised.

Table 4: Indications for transfusion and splenectomy in thalassaemia intermedia

Indications for transfusion	Indications for splenectomy
Growth failure or poor performance at school	Growth retardation or poor health
Transient stressful conditions (e.g. pregnancy, infection)	Leukopenia
Symptomatic anaemia	Thrombocytopenia
CHF ± PHT	Increased transfusion demand
Leg ulcers	Symptomatic splenomegaly

In addition, we feel it is imperative that all TI patients be prescribed continuous folic acid supplementation. Anti-platelet medication such as aspirin should also be given early in the disease course, particularly in splenectomised patients. However, this medication should be given with caution due to the risk of bleeding in patients with pseudoxanthoma elasticum that, although rare, can be a coexisting problem in patients with thalassaemia. Finally, women with TI should avoid the use of oral contraceptive pills and intrauterine devices due to the risk of thrombotic events and infection; barrier contraception is recommended as an alternative.

6.1 Future perspectives for the management of thalassaemia intermedia

There are currently two major issues regarding the management of TI. The first is how to approach and manage complications in elderly TI patients and the second is what should be done to prevent the development of these complications in younger patients. There is no compelling evidence to support any of the approaches described previously, although it is logical to conclude that most complications in TI result from chronic anaemia, iron overload and a hypercoagulable state.

Each elderly TI patient should be reviewed separately and stratified by risk in accordance with the previously described system-based model. Hydroxyurea may be a suitable initial approach, followed by transfusion and iron chelation therapy with deferoxamine subcutaneous infusion (three times weekly). Aspirin should be given for stroke prevention, and life-long low molecular weight heparin for patients with a history of thrombotic events, or transient heparin for those with a short period

of increased thrombotic burden. Finally, R2 MRI assessment of LIC should be performed to monitor body iron levels; liver biopsy can be used if MRI is unavailable. The use of NTBI is to be further evaluated.

For younger TI patients, deciding upon the correct treatment modality is difficult. However, we recommend the following:

- A guarded approach to the need for splenectomy and delay in initiating unless considered necessary based on the above mentioned indications;
- Early initiation of transfusion and iron chelation therapy if there is evidence of growth abnormalities, poor performance at school or a psychological impact secondary to facial deformities;
- Regular follow-up with echocardi-doppler for cardiac complications and initiation of therapy at earlier disease onset to prevent progression;
- Regular follow up of LIC with MRI, liver biopsy or potentially NTBI;
- Avoid smoking, prolonged immobilisation and use of oral contraceptives or an intrauterine device.

7. Conclusions

TI has a wide clinical spectrum, as some patients are completely asymptomatic until adult life whereas others present with the condition at 2 years of age and experience retarded growth and development. Many patients with TI do not currently undergo transfusion therapy due to difficulties in deciding when to initiate therapy as well as the lack of a convenient and effective iron chelator. However, the availability of such a therapy may increase the use of transfusions in patients with TI, allowing them to benefit from this therapeutic approach and avoid any subsequent clinical complications. As there are currently no clear guidelines for the management of TI, we have presented some recommendations based on a system-centred risk stratification model to help individualise patient treatment.

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Multiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/iron-handbook2009answers.htm>

- 1. The mild clinical characteristics of thalassaemia intermedia compared with thalassaemia major result primarily from:**

- a) Inheritance of a mild beta-chain mutation
- b) Co-inheritance of determinants associated with increased gamma-chain production
- c) Co-inheritance of alpha-thalassaemia
- d) All of the above

2. All of the following complications are more frequent in thalassaemia intermedia compared to thalassaemia major except one:

- a) Leg ulcers
- b) Gallstones
- c) Hypogonadism
- d) Pulmonary hypertension

3. The increased incidence of thrombotic complications in thalassaemia intermedia is mainly associated with:

- a) Splenomegaly
- b) Transfusion independence
- c) Atherosclerosis
- d) Prothrombotic mutations

4. Which one of the following statements is true concerning iron-overload indices in thalassaemia intermedia:

- a) Non-transfused patient with thalassaemia intermedia do not exhibit iron overload
- b) Serum ferritin levels were shown to decrease with age
- c) Thalassaemia intermedia patients are generally highly prone to cardiac iron overload
- d) Serum ferritin levels are lower in thalassaemia intermedia than corresponding thalassaemia major patients with similar liver iron concentration

5. All of these agents have been investigated for modulation of foetal haemoglobin production in thalassaemia intermedia except:

- a) Hydroxyurea

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- b) Erythropoietin
- c) Folic acid
- d) Butyric acid derivatives