Thalassemia intermedia: Revisited

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Abstract

Thalassemia intermedia encompasses a wide clinical spectrum of beta-thalassemia phenotypes. Some thalassemia intermedia patients are asymptomatic until adult life, whereas others are symptomatic from as young as 2 years of age. A number of clinical complications commonly associated with thalassemia intermedia are rarely seen in thalassemia major, including extramedullary hematopoiesis, leg ulcers, gallstones and thrombophilia. Prevention of these complications, possibly with blood transfusion therapy, is ideal since they may be difficult to manage. Currently, many patients with thalassemia intermedia receive only occasional or no transfusions, since they are able to maintain hemoglobin levels between 7–9 g/dl; the risk of iron overload, necessitating adequate chelation therapy, is also a contributing factor. At present, there are no clear guidelines for initiating and maintaining transfusions in thalassemia intermedia for the prevention or treatment of complications. Here, we review the major clinical complications in thalassemia intermedia and suggest some therapeutic strategies based on retrospective clinical observations.

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Introduction

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

Thalassemia intermedia encompasses a wide clinical spectrum. Mildly affected patients are completely asymptomatic until adult life, experiencing only mild anemia and maintaining hemoglobin levels between 7 and 10 g/dl. These patients require only occasional blood transfusions, if any. Patients with more severe thalassemia intermedia 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 thalassemia intermedia indicates the need for an individualized treatment approach. Despite the availability of a number of treatment options, the lack of clear guidelines can present a significant clinical challenge.

Definition and molecular mechanisms of thalassemia intermedia

Clinical definition of thalassemia intermedia

Description of the various thalassemia forms is based on the severity of the condition rather than the underlying genetic abnormality. Although the clinical phenotypes of thalassemia 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 thalassemia intermedia versus thalassemia minor and major can be difficult if based on clinical presentation alone, although certain differentiating parameters...
have been established. In general, thalassemia intermedia is characterized by hemoglobin levels maintained around 7–10 g/dl without the need for regular blood transfusions, by more severe red blood cell abnormalities than thalassemia minor, by a varying degree of spleen enlargement, by increased susceptibility to infections and by skeletal changes such as expansion of the facial bones and obliteration of the maxillary sinuses, which causes protrusion of the upper jaw.

Molecular definition and mechanisms of thalassemia intermedia

The clinical manifestations of thalassemia result from defects in one of two types of polypeptide chains (alpha or beta). For hemoglobin to function properly, the number of alpha-chains must precisely match the number of beta-chains; thalassemia is caused by an imbalance in globin chain synthesis. The beta-thalassemias, including thalassemia intermedia, 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 disease severity. Most thalassemia intermedia patients are homozygotes or compound heterozygotes for beta-thalassemia, 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 thalassemia intermedia compared with thalassemia 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 neutralize the large proportion of unbound alpha-chains.
- Co-inheritance of alpha-thalassemia. This helps to suppress the synthesis of alpha-chains, causing less of an alpha/beta-chain imbalance.

The phenotype of thalassemia intermedia may result from the increased production of alpha-globin chains by triplicated alpha genotype associated to beta-heterozygosity [5,6] and also from the interaction of beta and delta beta thalassemia [7,8].

As illustrated by the above description, defining thalassemia intermedia is not easy and remains a subject of discussion. Therefore, as definitions are intended to label a group with the hope of unifying and facilitating future reference, we propose a clinical ‘decision-to-intervene’-based definition. Here, we categorize a patient as having thalassemia intermedia if they are born with beta-thalassemia that is not transfusion-dependent from infancy, yet during their lifetime anemia-related complications arise that may require therapeutic intervention. In the following sections, the complications where intervention might be necessary will be listed and thus further clarify this definition of thalassemia intermedia.

The thalassemia intermedia phenotype versus genotype

The ability to predict phenotype from genotype has important implications for the screening of beta-thalassemia carriers, for genetic counseling and prenatal diagnosis and for planning the appropriate treatment regimen. Genotype analysis is becoming increasingly important for establishing an early diagnosis of mild beta-thalassemia. Our understanding of the phenotypic diversity of beta-thalassemia has progressed through analysis of the molecular basis of the beta-thalassemia forms, analysis of the genotype/phenotype relationship in thalassemia intermedia and through family studies [9].

However, predicting phenotype from genotype in thalassemia intermedia is still difficult due to genetic and environmental modifying factors [10]. The primary genetic modifiers are the numerous different alleles at the beta-chain locus that can cause either complete or marked reduction in beta-chain synthesis. Secondary genetic modifiers are those 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 that can affect clinical expression. Environmental factors include social conditions, nutrition and the availability of medical care [9,11].

A number of studies have attempted to classify patients with thalassemia intermedia according to the severity of their condition, although these studies have had only limited success [12,13]. A recent study described the development of a phenotype scoring system that successfully sub-classified thalassemia intermedia patients into three separate groups: mild, moderate or severe [14]. The severity of thalassemia intermedia was graded according to a number of clinical features, such as age at presentation, severity of anemia, extent of growth retardation and bone marrow hyperplasia, blood transfusion requirements and need for splenectomy. This classification could prove useful for genotype/phenotype relation 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.

Clinical sequelae of thalassemia intermedia

Three main factors are responsible for the clinical sequelae of thalassemia intermedia: ineffective erythropoiesis, chronic anemia and iron overload. The severity of clinical sequelae primarily depends on the underlying molecular defects. Alpha-chains are highly unstable and precipitate into erythroid precursors in the bone marrow, causing membrane damage and cell death — this is ineffective erythropoiesis [15]. Hyper trophy 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 [2,16]. The degree of ineffective erythropoiesis is the primary...
determinant of the development of anemia, while peripheral hemolysis of mature red blood cells and an overall reduction in hemoglobin synthesis are secondary. Chronic anemia leads to an increase in gastrointestinal iron absorption, resulting in iron overload that can cause a number of serious complications including cardiac failure and endocrine abnormalities such as diabetes mellitus and hypogonadism (Fig. 1).

Complications in thalassemia intermedia and their treatment

In addition to the defining symptoms of thalassemia intermedia, which are seen to a lesser or greater extent in other forms of thalassemia, patients with thalassemia intermedia experience a number of specific complications that are rare in thalassemia major (Table 1 [17]).

Splenectomy and cholecystectomy

Splenectomy is now uncommon and is mainly performed late in life. The main indications for splenectomy in thalassemia intermedia are a significant enlargement of the spleen and a decrease in mean hemoglobin level in the absence of other transient factors such as infection. Gallstones are much more common in thalassemia intermedia than in thalassemia major because of ineffective erythropoiesis and peripheral hemolysis. Recently, tertiary genetic factors such as uridine-diphospho-glucuronyl-transferase deficiency (Gilbert’s syndrome) have been reported to increase gallstone formation in patients with thalassemia [18–20]. 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 splenectomized patients.

Table 1
Prevalence of common complications in thalassemia intermedia versus major in Italy [17] and Lebanon (unpublished data)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Thalassemia intermedia, Lebanon (n = 37)</th>
<th>Thalassemia intermedia, Italy (n = 63)</th>
<th>Thalassemia major, Lebanon (n = 40)</th>
<th>Thalassemia major, Italy (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>90</td>
<td>67</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>85</td>
<td>68</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Gallstones</td>
<td>55</td>
<td>63</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Extramedullary hematopoiesis</td>
<td>20</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>20</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>28</td>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiopathy*</td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>50</td>
<td>17</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Abnormal liver enzymes</td>
<td>20</td>
<td>22</td>
<td>55</td>
<td>68</td>
</tr>
<tr>
<td>Hepatitis C infection</td>
<td>7</td>
<td>33</td>
<td>7</td>
<td>98</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>5</td>
<td>3</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>2</td>
<td>12.5</td>
<td>10</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3</td>
<td>2</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

* Fractional shortening <35%.

b Pulmonary hypertension was defined as Pulmonary Artery Systolic Pressure >30 mm Hg. A well-enveloped tricuspid regurgitant jet velocity could be detected in only 20 patients, so frequency was assessed in these patients only.
**Extramedullary hematopoiesis**

Extramedullary hematopoiesis is a compensatory mechanism where bone marrow activity increases in an attempt to overcome the chronic anemia of thalassemia intermedia, 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. They may cause neurological problems such as spinal cord compression and paraplegia and intrathoracic masses [21–25]. Extramedullary hematopoiesis can be managed by radiotherapy, since hematopoietic tissue is highly radiosensitive [26], as well as transfusion therapy and hydroxyurea [21,27–30].

**Leg ulcers**

Leg ulcers are more common in older than in younger patients with thalassemia intermedia. It is unclear why ulcers develop in some patients who are maintained at relatively low hemoglobin levels and have the same amount of fetal hemoglobin as others in whom ulcers do not develop. The skin at the extremities of elderly thalassemia intermedia 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 h during the day or sleeping with the end of the bed raised. Zinc supplementation [31] and pentoxifylline, which alters the rheological properties of the red blood cells [32], can help accelerate the healing of ulcers. Hydroxyurea also has some benefit, either alone or in combination with erythropoietin [33]. In addition, the use of an oxygen chamber can provide moderate relief since tissue hypoxia may be an underlying cause of the ulceration [34].

**Thrombophilia**

Patients with thalassemia intermedia have an increased risk of thrombosis compared with a normal age- and sex-matched population and with thalassemia major patients. This was evidenced in a recent epidemiological study where 4% of 2190 patients with thalassemia intermedia and 0.9% of 6670 patients with thalassemia major experienced a thrombotic event [35]. In thalassemia intermedia patients, these events primarily occurred in the venous system and comprised deep vein thrombosis (40%), portal vein thrombosis (19%), stroke (9%), pulmonary embolism (12%) and others (20%). Moreover, splenectomized patients were shown to have a higher risk of thrombosis than non-splenectomized patients. There are several possible reasons for this, including the procoagulant activity of damaged circulating red blood cells, as it is thought that red blood cell remnants expose negatively charged phosphatidyl-serine through the ‘Flip-Flop’ phenomenon and subsequently initiate thrombosis [36]. Other possible mechanisms include coinheritance of coagulation defects [37], depletion of antithrombotic factors (proteins C and S), endothelial inflammation and stressful conditions that increase thrombotic burden. Risk factors for developing thrombosis in patients with thalassemia intermedia 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 thalassemia intermedia, mostly occurring without any other risk factors [36,38]. Cappellini and colleagues reported that around 30% of patients with thalassemia intermedia who had been followed for 10 years experienced venous thromboembolic events [37], suggesting the presence of a chronic hypercoagulable state [36,39]. It is important to be aware of these complications since thromboembolism plays an important role in cardiac failure. Recommended treatment options, which are reasonable although not supported by compelling evidence from the literature, include platelet anti-aggregation agents such as aspirin [40] in patients with thrombocytosis or anti-coagulant 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 red blood cells exposing phosphatidyl-serine.

**Pulmonary hypertension and congestive heart failure**

Pulmonary hypertension is prevalent in patients with thalassemia intermedia (59.1%) [41] and is thought to be the primary cause of congestive heart failure in this patient population. Pulmonary hypertension as a complication of thalassemia was first noted in 1990 by hematologists from Thailand, who described pulmonary hypertension in patients who had been splenectomized for thalassemia. The mechanism underlying pulmonary hypertension in thalassemia intermedia is unclear, although evidence indicates a local pathophysiological response in the pulmonary vascular bed that is independent of thromboembolism due to deep vein thrombosis. Suggested mechanisms include endothelial dysfunction with increased inflammation and apoptosis, decreased nitric oxide and nitric oxide synthase production, pulmonary hemosiderosis and local thrombosis. A retrospective analysis showed that splenectomized females with significant anemia, thrombocytosis and elevated ferritin levels, were at greatest risk for developing pulmonary hypertension [42]. Preliminary results from Thailand have demonstrated that pulmonary hypertension is reversible by blood transfusion and treatment with aspirin and warfarin [43]. Several echocardiographic studies have confirmed that cardiac ejection fraction is rarely affected in thalassemia intermedia [44]. Nevertheless, patients with thalassemia intermedia often have an increased cardiac output and left ventricular wall dimensions proportional to the dilutional volume overload secondary to chronic anemia [45].

As anemia and iron overload are uncommon in well-transfused and chelated thalassemia major patients, they are likely to be at the heart of the pathophysiology of pulmonary hypertension. Regular transfusion and iron chelation therapy are, therefore, indicated in thalassemia intermedia patients who are well stratified according to the early detection of pulmonary
hypertension indices. Sildenafil has also been successfully used to treat pulmonary hypertension [46], although data from large patient numbers are lacking in thalassemia intermedia.

Hepatitis

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

Endocrine function

Hypogonadism, hypothyroidism and diabetes mellitus are quite rare in thalassemia intermedia. Although patients with thalassemia intermedia generally experience puberty late [47], they have normal sexual development and are usually fertile. Hypothyroidism is sometimes observed late in life.

Pregnancy and infertility

Women with thalassemia intermedia may have spontaneous successful pregnancies although complications during pregnancy may occur [48]. The chronic anemia of thalassemia intermedia can cause an increase in spontaneous abortions, pre-term labor and intrauterine growth retardation, while endocrine complications due to hemosiderosis are common [49]. The course and outcome of 19 pregnancies was assessed in 16 women with thalassemia intermedia, including four with thalassemia intermedia [50]. All pregnancies were uneventful, and elective Cesarean section was performed in each case. The mean birthweight of the babies was 3000 g, and all were normal except for one case of omphalocele. However, a separate study following nine pregnancies in four thalassemia intermedia patients made rather different observations [51]. Intrauterine growth restriction (<10th percentile) was a reported complication in 57.1% (4/7) of cases. Transfusion therapy was required for most patients, even in those who were non-transfusion-dependent. Patients who received transfusions for the first time during pregnancy developed antibodies that contributed to worsening anemia. Pregnancy did not cause cardiac or endocrine problems in any thalassemia intermedia patients in either of these two reported studies. In unpublished observations from Italy, 17 pregnancies occurred spontaneously among 40 patients with thalassemia intermedia who had a mean age of 38.7 ± 10 years. During pregnancy, all the patients were regularly transfused so maintained pre-transfusional hemoglobin levels of 9.0 ± 0.5 g/dl. Although the pregnancies reached full term, an elective cesarean section was performed in 50% of the cases. In one case of twin pregnancy, a cesarean section was performed at 32 weeks gestation. There were no observed complications for either the patients or the babies.

Folic acid deficiency is common in thalassemia intermedia 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 fetus. During pregnancy, women with thalassemia intermedia 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 hemodynamic compromises.

Prevention of thalassemia intermedia complications

Unfortunately, it is not always possible to successfully manage the numerous complications associated with thalassemia intermedia, so prevention is the preferable option. This may be achieved through regular and effective transfusion therapy, low-dose aspirin and anticoagulant treatment, preferably with low molecular weight heparin to prevent deep vein thrombosis.

Management of thalassemia intermedia

There are a number of options currently available for managing patients with thalassemia intermedia including transfusion therapy, modulation of fetal hemoglobin production and bone marrow transplantation.

Transfusion therapy and iron chelation

Although transfusion therapy is not currently a routine treatment approach for patients with thalassemia intermedia, it can afford significant benefits. The decision to initiate therapy should be based on the presence and severity of signs and symptoms of anemia, including the failure of growth and development [15]. As the rate of iron loading is variable in thalassemia intermedia, an assessment of liver iron concentration is advisable before initiating transfusion therapy. Patients with thalassemia intermedia may benefit from an individually tailored transfusion regimen, compared with the regular transfusion regimens implemented in thalassemia major, to help prevent transfusion dependency. Alloimmunization is a relatively common observation in thalassemia intermedia, although the risk is decreased if transfusion therapy is initiated before the age of 12 months [52]; Kell and Rhesus phenotyping prior to transfusion therapy is also recommended [53]. 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.

The increased intestinal iron absorption that is characteristic of anemia means that excess iron is 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 thalassemia intermedia develops more slowly than transfusional iron overload [54]. As a result, the decision to transfuse in thalassemia intermedia 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 [55,56]. However, the demanding regimen of frequent and prolonged subcutaneous infusion can impact on patient compliance and quality of life [57–59]. Recent data with deferiprone, an oral iron chelator, have suggested superiority over deferoxamine for removing cardiac iron [60,61], and even higher efficiency when combined with deferoxamine leading to reversal of congestive heart failure among patients with thalassemia major [62]. This has been attributed to a ‘shuttle-effect’, where deferiprone, which has better cardiomyocyte permeability, delivers iron to the circulation to be picked up by deferoxamine [63]. A clinical trial assessing the superiority of combination therapy over subcutaneous deferoxamine is ongoing, the results of which will form a strong evidence-based platform for adoption of this protocol. Certain reservations concerning the widespread use of deferiprone were raised by reports of less effectiveness in removing iron from the liver and, more importantly, a continuous need for monitoring leukocyte count while on therapy due to the risk of leucopenia and subsequently fatal infections [64–66]. An oral, once-daily iron chelator, deferasirox, has recently been approved for use in the USA and other countries where the latter complications are not present [67]. The most common reported adverse events with deferasirox include mild-moderate, transient gastrointestinal disturbances, rash, and mild, non-progressive increases in serum creatinine [68]. The initiation of iron chelation therapy in patients with thalassemia intermedia 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 [69]. Studies in thalassemia intermedia have observed liver biopsy patterns similar to those in thalassemia major as well as increased levels of liver iron concentration in parallel with small increases in serum ferritin [70,71], suggesting that the determination of body iron is indicated in any patient with elevated ferritin levels. A direct assessment of liver iron concentration is recommended, either by biopsy or by a non-invasive method such as magnetic resonance imaging, since this provides a more reliable assessment of body iron levels than both transferrin saturation and measurement of serum ferritin [72]. Chelation therapy should generally be initiated if liver iron concentration exceeds 7 mg/g dry weight of liver tissue [73]. Lower levels of liver iron concentration for initiation of chelation therapy can be considered now with the use of oral chelation therapy [74].

Bone marrow transplantation

Bone marrow transplantation, where the marrow of an affected patient is replaced with that of an unaffected donor, is an established treatment for beta-thalassemia. Although successful marrow transplantation can afford a cure, it can be unsuccessful (e.g., if the thalassemia returns), may lead to complications (e.g., graft-versus-host disease, growth impairment, neurological complications), and can even result in death [75–78]; the risk of 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 thalassemia intermedia, 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-matched donor, which comprises only 30–40% of all beta-thalassemia patients, at most [79]. As human leukocyte antigen type is genetically determined, there is a 25% chance that two siblings will be a match.

Modulation of fetal hemoglobin production

Increasing the synthesis of fetal hemoglobin can help to alleviate anemia and, therefore, improve the clinical status of patients with thalassemia intermedia [80]. Production of fetal hemoglobin 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 [81–83]. Recently published results from Iran, evaluating 6 years of hydroxyurea therapy in transfusion-dependent patients with thalassemia intermedia, are encouraging. A significant decrease in the need for blood transfusions was observed in many patients; the need was completely obviated in some patients [30]. Erythropoietin has also been shown to increase fetal hemoglobin levels in some patients with thalassemia intermedia [80]. Preliminary trials with intravenous and oral butyric acid derivatives have shown increases in fetal and total hemoglobin levels in patients with thalassemia intermedia [84–87], 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 fetal hemoglobin-stimulating agents are somewhat disappointing. Studies using combined treatments have shown greater promise than the individual agents alone [88]. Further clinical evaluation is required to clarify the value of this approach, especially in view of the reduced oxygen delivery capacity of fetal hemoglobin, as this might favor the implementation of a target hemoglobin level higher than 10 g/dl in response to increased need (e.g., pulmonary hypertension, coronary heart disease and chronic obstructive pulmonary disease) and an increased ratio of fetal hemoglobin/adult hemoglobin.

Recommendations for the management of thalassemia intermedia

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

1. **Growth and development**: follow up with anthropometric measurements.

2. **Extramedullary hematopoiesis**: particularly those causing abnormal facies and symptoms such as neural encroachment.

3. **Endocrine abnormalities**: emphasis on osteopenia, bone fractures and pain, and infertility.

4. **Cardiopulmonary assessment**: use echocardiography for increased cardiac index as an early sign of cardiac decompensation, and tricuspid regurgitation jet velocity plus spirometry and a 6-min walk test for early detection of pulmonary hypertension.

5. **Hypercoaguability-associated states**: including stroke, deep vein thrombosis, pulmonary embolus, superficial thrombophlebitis, pregnancy, sepsis, long-distance travel, chronic obstructive pulmonary disease, congestive heart failure, factor deficiencies, surgery and malignancies and leg ulcers.

6. **Significant anemia**: with limitation of exercise tolerance, or in association with stressful conditions that increase oxygen demand, such as infection, asthma, chronic obstructive pulmonary disease and coronary heart disease.

7. **Psychological challenges**: such as depression or poor performance at school.

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 alloimmunization with delayed initiation of transfusion, clinicians should consider regular or more frequent transfusions and iron chelation therapy for patients with thalassemia intermedia.
- Table 2 details our recommendations of which patients with thalassemia intermedia should be transfused and splenectomized.

In addition, based on observational data showing folic acid deficiency in thalassemia intermedia and since folic acid supplementation is harmless, inexpensive and of potential benefit, we feel it is imperative that all thalassemia intermedia patients be prescribed continuous folic acid supplementation despite a lack of compelling evidence. Based on the same reasoning, antiplatelet medication such as aspirin should also be given early in the disease course, particularly in splenectomized patients. However, this medication should be given with caution due to the risk of bleeding in patients with pseudoxanthoma elasticum that is, although rare, a coexisting problem in patients with thalassemia. Finally, women with thalassemia intermedia 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.

**Future perspectives for the management of thalassemia intermedia**

There are currently two major issues regarding the management of thalassemia intermedia. The first is how to approach and manage complications in adult thalassemia intermedia 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 thalassemia intermedia result from chronic anemia, iron overload and a hypercoaguable state.

Each post-adolescent thalassemia intermedia 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). Concomitant steroids should also be given for protection from alloimmunization, aspirin for stroke prevention and life-long low molecular weight heparin in patients with a history of thrombotic events or transient heparin in those with a short period of increased thrombotic burden. Finally, magnetic resonance imaging assessment of liver iron concentration should be performed to monitor body iron levels; liver biopsy can be used if magnetic resonance imaging is unavailable.

For adolescent thalassemia intermedia patients, deciding upon the correct treatment modality is difficult. However, we recommend the following:

1. A guarded approach to the need for splenectomy and delay in initiating transfusion unless considered necessary based on the above mentioned indications.

2. 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.

3. Regular follow-up with echocardiography for cardiac complications and initiation of therapy at earlier disease onset to prevent progression.

4. Regular follow up of liver iron concentration with magnetic resonance imaging or liver biopsy.

5. Avoid smoking, prolonged immobilization and use of oral contraceptives or an intrauterine device.

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**Table 2**

<table>
<thead>
<tr>
<th>Indications for transfusion</th>
<th>Indications for splenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth failure or poor performance at school</td>
<td>Growth retardation or poor health</td>
</tr>
<tr>
<td>Transient stressful conditions (e.g., pregnancy, infection)</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>Symptomatic anemia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Congestive heart failure ± pulmonary hypertension</td>
<td>Increased transfusion demand</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>Symptomatic splenomegaly</td>
</tr>
</tbody>
</table>
Discussion

Thalassemia intermedia 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 thalassemia intermedia 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 thalassemia intermedia, 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 thalassemia intermedia, in this paper, we present some recommendations based on a system-centered risk stratification model to help individualize patient treatment.

References


