Cross-Talk between Available Guidelines for the Management of Patients with Beta-Thalassemia Major

Khaled M. Musallam a  Michael Angastiniotis b  Androulla Eleftheriou b
John B. Porter c

a Department of Medicine and Medical Specialties, IRCCS Ca’ Granda Foundation Maggiore Policlinico Hospital, University of Milan, Milan, Italy; b Thalassaemia International Federation, Nicosia, Cyprus; c Department of Haematology, University College London, London, UK

Key Words
Iron chelation · Iron overload · Splenectomy · Transfusion

Abstract
Efforts to optimize the management of patients with β-thalassemia major (TM) continue to expand. Evidence from biomedical research evaluating safe and careful processing measures of blood products, the efficacy and safety of oral iron chelators, and noninvasive techniques for the assessment of iron overload are translated into better patient outcomes. The construction of TM management guidelines facilitated the incorporation of such evidence into practice. However, as several aspects of the management of TM remain controversial or governed by resource availability, a concern regarding potential variations in recommendations made by the different guidelines becomes rational, especially for physicians treating TM patients outside countries where the guidelines were constructed. In this work, we overview currently available guidelines for the management of TM and explore apparent similarities and differences between them. The evaluated guidelines included the Thalassaemia International Federation, US, Canadian, UK, Italian and Australian guidelines. We noted a general consensus for most aspects of management, although some guidelines provided more comprehensive and contemporary recommendations than others. We did not identify differences warranting concern, although minor differences in iron overload assessment strategy and more notable variations in the recommendations for iron chelation therapy were observed.

Introduction
As a group, the thalassemias are the most common single gene disorder in the world. They are found at high frequencies in developing regions as well as in large multiethnic Western cities due to an expanding immigrant population [1]. The β-thalassemias are recessively inherited disorders of hemoglobin synthesis resulting from mutations in the β-globin gene and defective β-chain production which lead to an imbalance in α/β-globin chain synthesis, ineffective erythropoiesis, reduced red blood cell survival and subsequent anemia [2]. After genetic confirmation of β-globin gene mutation, the phenotype of β-thalassemia is determined based on clinical observation. Patients whose clinical course is characterized by profound anemia, who present to medical attention in the first 2 years of life and
who subsequently require regular blood transfusions and iron chelation therapy for survival are known to have β-thalassemia major (TM) [3].

Studies evaluating TM cohorts treated in both developed and developing countries continue to show a progressive improvement in life expectancy [4–12]. Alongside increased awareness, education and optimal health care provision efforts, part of this transition in the once fatal disease can surely be attributed to the large body of evidence attained by clinical trials and observational studies conducted in the last 3 decades, which allowed for remarkable advances in diagnostic and therapeutic options. Examples of such advances include introduction of measures for safe and careful processing of blood products, noninvasive techniques for the assessment of iron overload in target organs, oral iron chelators, and prevention/management schemes for specific complications [13].

The need for management guidelines for TM is clearly necessary in such a swiftly evolving field. Throughout the past 4 years, six major TM management guidelines became available for use by thalassemia care takers worldwide: the Thalassaemia International Federation (TIF) [14], US [15], Canadian [16], UK [17], Italian [18] and Australian guidelines [19] (table 1). However, as several aspects of the management of TM remain controversial, a concern regarding potential variations in recommendations made by the different guidelines becomes rational. Also, the availability of diagnostic and treatment modalities may vary by region. Such concerns are largely relevant to physicians treating TM patients outside countries where the guidelines were constructed. This review aims to provide TM health care providers with an overview of currently available guidelines and to explore apparent similarities and differences between them. For each aspect of management, we also indicate whether any novel evidence became available after the publication of the guidelines.

### Transfusion Therapy

The TIF, US, Canadian and UK guidelines provide recommendations on transfusion therapy (table 2). There is a general agreement between the four guidelines, although some provide more comprehensive recommendations than others. After a confirmed genetic diagnosis of thalassemia, clinical assessment of the necessity for regular transfusion therapy should ensue. All guidelines agree that the decision to initiate regular transfusion therapy should not be exclusively based on anemia. Monitoring patients over a period of time and careful observation of measures indicative of the severity of ineffective erythropoiesis, growth and development, quality of life, as well as of coexisting clinical complications is recommended. Anemia requiring intervention in this setting is defined by a hemoglobin threshold of <7 g/dl, not measured during a period of acute infection. However, a single threshold for all patients irrespective of the underlying genotype may be overly prescriptive, as for example in the severe forms of hemoglobin E/β-thalassemia, where greater adaptation to low hemoglobin values exists due to a right-shifted oxygen dissociation curve [20].

---

Table 1. Overview of guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year of publication</th>
<th>Source</th>
<th>Coverage</th>
<th>Resources</th>
<th>Industry funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIF</td>
<td>2008</td>
<td>TIF</td>
<td>All aspects of management</td>
<td>Biomedical literature Expert panel</td>
<td>None disclosed</td>
</tr>
<tr>
<td>US</td>
<td>2009</td>
<td>Children’s Hospital and Research Center Oakland</td>
<td>All aspects of management</td>
<td>Biomedical literature Expert panel</td>
<td>None disclosed</td>
</tr>
<tr>
<td>Canadian</td>
<td>2009</td>
<td>Anemia Institute for Research and Education Thalassemia Foundation of Canada</td>
<td>All aspects of management</td>
<td>Biomedical literature Expert panel</td>
<td>None disclosed</td>
</tr>
<tr>
<td>UK</td>
<td>2008</td>
<td>United Kingdom Thalassaemia Society</td>
<td>All aspects of management</td>
<td>Biomedical literature Expert panel</td>
<td>None disclosed</td>
</tr>
<tr>
<td>Italian</td>
<td>2008</td>
<td>Italian Society of Hematology</td>
<td>Iron overload and chelation therapy</td>
<td>Biomedical literature Expert panel</td>
<td>None disclosed</td>
</tr>
<tr>
<td>Australian</td>
<td>2011</td>
<td>Independent Australian hematologists and pediatricians</td>
<td>Iron overload and chelation therapy</td>
<td>Biomedical literature Expert panel</td>
<td>Novartis Australia</td>
</tr>
</tbody>
</table>
The use of leukoreduced blood, stored for less than 2 weeks and matched for the patient’s ABO and Rh(D) antigen profile is recommended. Matching for other antigens [Rh(C, c, E, e) and Kell] is preferred by the TIF guidelines although it is more strongly recommended in the other three guidelines. The recommended target pretransfusion hemoglobin level ranges between 9 and 10.5 g/dl, with minor differences. The US and TIF guidelines further recommend a higher pretransfusion target (10 or 11–12 g/dl, respectively) for patients with cardiac dysfunction. They also recommend a posttransfusion threshold for a hemoglobin level of ≤14 g/dl with a mean hemoglobin level of 12 g/dl.

**Iron Overload Assessment and Chelation Therapy**

All evaluated guidelines provide recommendations on iron overload assessment and chelation therapy.

**Iron Overload Assessment: Method of Choice**

All guidelines caution that serum ferritin levels fluctuate in response to inflammation, abnormal liver function and metabolic deficiencies. Moreover, all guidelines agree that spot measurements of serum ferritin levels may provide unreliable estimates of the iron overload status, relying on data from cross-sectional studies reporting correlation coefficients between serum ferritin levels and other iron overload indices. However, serum ferritin level assessment is economically favorable and may be the only iron overload measure available in some countries. Thus, the guidelines provide various approaches to interpreting serum ferritin levels to guide initiation or monitoring of iron chelation therapy. All guidelines recommend serial measurement of serum ferritin levels. This would not only help observe trends of iron overload or depletion but would also enable consideration of an absolute iron status value with higher cer-
tainty (e.g., considering the average of two values retrieved 1–2 months apart). Of note, the Italian guidelines indicate that serum ferritin level measurement may be more reliable if restricted to the early transfusional period (low iron burden) in patients with a known iron intake history. The Canadian guidelines also mention that the uncertainty in serum ferritin level may be overcome through local calibration against liver iron concentration (LIC) values.

There is some variation between the guidelines as to the recommended method of LIC measurement. Despite being the only direct measure (gold standard) of LIC, all guidelines highlight the limitation of liver biopsy considering the invasiveness of the procedure. Among alternative noninvasive techniques, the use of a superconducting quantum interference device is presented as an option, when available, by the TIF, US and Canadian but not by the UK or Australian guidelines. The Italian guidelines recommended that the superconducting quantum interference device should be reserved for experimental use since there is no calibration homogeneity and LIC could be underestimated. With regard to magnetic resonance imaging (MRI), the TIF, Italian and Australian guidelines recommend the use of the R2 hepatic MRI while the Canadian and UK guidelines present both the R2 and T2* hepatic MRI as an option. The T2* MRI was originally developed to estimate myocardial iron but the first description of the method also demonstrated a clear relationship between liver T2* and LIC measured by biopsy [21]. However, it was later evident that the original T2* method underestimated LIC by a factor of about 2-fold, and a new calibration showing acceptable linearity and reproducibility over an LIC range up to 30 mg/g dry weight (dw) was demonstrated [22]. Moreover, recent work shows that T2* measurement of LIC has international reproducibility [23]. T2* MRI may become more commonly recommended particularly when it offers evaluation of both cardiac and hepatic iron overload at the same time.

All guidelines recommend cardiac siderosis assessment by cardiac T2* MRI, considering its poor association with other iron overload indices in transfusion-dependent patients on chelation therapy, and its good association with cardiac outcomes. Good correlation between different centers and machines was demonstrated in recent studies [23], and the technique is now validated as a true measure of cardiac iron, correlating with chemical measurement on postmortem cardiac biopsies [24].

---

**Iron Overload Assessment: Frequency of Monitoring**

The recommended frequency by most guidelines for serial serum ferritin level measurement is every 3 months (some guidelines did not indicate a specific frequency). There are differences with regard to recommendations on the frequency of LIC and cardiac T2* assessment. The Italian guidelines recommended annual LIC and cardiac T2* measurement intervals. However, the TIF, US, Canadian, UK and Australian guidelines recommend more frequent assessment in patients who show values indicative of considerable iron loading (table 3). Although the latter approach is rational for LIC measurement, the value of frequent assessment of cardiac T2* over short (<1 year) time intervals is questionable in the light of recent evidence revealing the slow kinetics of loading and unloading of cardiac iron with respect to liver iron [25]. Moreover, the Italian guidelines only recommend cardiac T2* assessment in patients with non-optimal control of LIC. However, recent data also show that TM patients may still have a cardiac T2* <20 ms with LIC concentrations in the range of 1.2–9.0 mg/g dw [25]. Thus, cardiac T2* measurement may be needed in all TM patients irrespective of their LIC, particularly if it has not been performed before. However, if a patient has stable control of LIC and ferritin and has normal recent cardiac T2*, yearly cardiac T2* assessment may not always be necessary.

**Eligibility for Iron Chelation Therapy**

All guidelines recommend initiating iron chelation therapy after patients have received 10 or more transfusions or after reaching a serum ferritin level >1,000 ng/ml (table 3). The US, Canadian and Italian guidelines also provide an alternative LIC threshold reflecting the need for iron chelation therapy. Although the US and Italian guidelines recommend chelation therapy when patients show LIC levels beyond the upper normal level in healthy volunteers (>3 mg/g dw), the Canadian guidelines use a more conservative threshold of 7 mg/g dw. The objective in all guidelines is to prevent liver damage and to prevent the spread of iron outside the liver to the endocrine system and heart. Historically, ferritin values of 1,000 ng/l equivalent to LIC values of about 7 mg/g dw were used as triggers for starting chelation with desferrioxamine (DFO). This is because with DFO, the risk of side effects from overchelation increases below serum ferritin values of 1,000 ng/l. With oral chelators, there is some evidence that lower levels of iron overload may be better tolerated but this has not yet been incorporated into most guidelines.
Table 3. Recommendations for iron chelation therapy

<table>
<thead>
<tr>
<th>TIF</th>
<th>US</th>
<th>Canada</th>
<th>UK</th>
<th>Italy</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility for chelation</strong></td>
<td>10–20 units of pRBC, or SF &gt;1,000 ng/ml</td>
<td>10–20 units of pRBC, or SF &gt;1,000 ng/ml, or LIC &gt;3 mg/g dw</td>
<td>10–12 units of pRBC, or SF &gt;1,000 ng/ml</td>
<td>&gt;10 units of pRBC, or SF &gt;1,000 ng/ml, or LIC &gt;ULN (if unknown transfusion history or inappropriate prior chelation)</td>
<td>10–20 units of pRBC, or SF &gt;1,000 ng/ml</td>
</tr>
</tbody>
</table>

| **Monitoring iron overload** | | | | | |
| Serial SF | LIC (preferable) | Cardiac T2* | Serial SF Q3 mo | LIC Q1 y | Serial SF Q3 mo |
| - Well chelated: Q 1 y | - LIC >Q 3 mo | - Cardiac T2* | - Q 1–2 y if >20 ms | Cardiac T2* | - Q 1 y if >20 ms |
| - Abnormal values: Q 3–6 mo | - SF >7 mg/g dw and LIC >15 mg/g dw | - Q 6 mo if <20 ms | - Q 3 mo if <10 ms or cardiac dysfuncion | - Q 6 mo if <10 ms |
| - Cardiac disease: as indicated | - SF >1,000–2,500 ng/ml or LIC >7 mg/g dw | | | - Q 6 mo if <10 ms or cardiac dysfunction |

| **Chelation regimen** | Initiation | | | | |
| DFO or | DFO, or | DFO, or | DFO or | DFO or | DFO or |
| - DXF in <2 y (US) or >6 y (EU) | - DFX in patients with ineffective, intolerance or noncompliance to DFO | - DFO (gold standard) | - DFX in patients with intolerance or noncompliance to DFO | - DFX in patients with intolerance or noncompliance to DFO | - DFX in patients with intolerance or noncompliance to DFO |
| - DFP in >10 y (second line) | - DFP in patients resistant or intolerant to DFX | - DFX (gold standard) | - DFX in patients nonadherent to DFO | - DFX in patients nonadherent to DFO |
| Responsive to monotherapy or significant cardiac siderosis/disease | | | | | |
| - Intensive 24 h DFO | | | | | |
| - DFO+DFP | Persistently high SF or LIC >15 mg/g dw and cardiac T2* <10 ms | | | | |
| - Intensive 24 h DFO | | | | | |
| (50–60 mg/kg/d) | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
Choice of Chelator

Differences are noted with regard to recommendations on the type of chelation therapy to be used for selected patient groups (table 3). It should be noted that at the time the guidelines were prepared, deferiprone was approved in Europe for second-line therapy in TM patients resistant to DFO, but it had not yet received approval in the US. However, the Food and Drug Administration recently approved deferiprone in this setting. Deferasirox was approved as a first-line therapy in TM patients ≥2 years of age in the US, while in Europe, it was approved as first-line therapy for patients ≥6 years of age and as second-line therapy in children 2 to <6 years of age who are resistant to DFO. Despite variations in the presentation of recommendations and in the thresholds for iron indices used to flag moderate and severe iron overload between the six guidelines, we herein compare the recommendations according to relevant clinical settings.

Starting Chelation Therapy in a Newly Diagnosed Child with TM Who Became Eligible for Chelation Therap...
and bone formation [26]. However, data on the efficacy and safety of deferasirox in children <10 years of age is limited. In one recent study recruiting 91 TM children <10 years of age, an oral formulation of deferasirox showed an efficacy and safety profile similar to that reported in earlier studies with deferiprone tablets in older children and adults [27]. Although deferasirox is approved for first-line therapy in TM children ≥2 years old in the US, in Europe, it is only approved as a second-line therapy for extremely young children between 2 to <6 years of age. This is attributed to the small number of patients aged 2–6 years in the 1-year, phase 3, randomized trial showing noninferiority of deferasirox to DFO [28]. However, recent data confirm the long-term efficacy and safety of deferasirox in this subset of patients followed for a period of 5 years [29]. Moreover, a recent observational study compared 111 transfusion-dependent children (aged ≤5 years) who had been prescribed either first-line deferasirox or DFO for at least 12 months and concluded that deferasirox has noninferior efficacy compared with DFO and an acceptable safety profile including effects on growth parameters [30].

Continuation/Modification of Chelation Therapy

In patients with moderate iron overload and no cardiac iron (a cardiac T2* >20 ms), the Canadian, UK and Italian guidelines recommend DFO as a first-line therapy. Deferasirox is recommended for patients resistant, intolerant or noncompliant to DFO, while deferiprone is recommended for patients resistant or intolerant to deferasirox. However, the Australian guidelines recommend deferasirox or DFO + deferiprone in the first-line setting. The remaining guidelines provide no specific recommendations in this setting assuming these would be extrapolated from recommendations regarding initiation of chelation therapy in children. In patients with a cardiac T2* <20 ms, the Canadian guidelines recommend deferasirox (for patients with a cardiac T2* of 10–20 ms) while the UK guidelines recommend deferiprone monotherapy.

In patients with severe iron overload (indicated with serum ferritin >2,500 ng/ml or LIC >15 mg Fe/g dw in most guidelines) and no cardiac iron (a cardiac T2* >20 ms), all guidelines recommend intensive DFO therapy. The Canadian and Italian guidelines provide DFO + deferiprone as an alternative while the US and Australian guidelines recommend deferasirox as an alternative. The UK guidelines recommend optimizing dosing and compliance or switching the existing chelator. In patients with a cardiac T2* <20 ms, all guidelines recommend intensive DFO or DFO + deferiprone therapy. The US and Australian guidelines further recommend deferasirox in the subset of patients with a cardiac T2* value of 10–20 ms.

In patients with cardiac dysfunction, all guidelines recommend intensive DFO or DFO + deferiprone therapy in this setting.

The guideline recommendations are primarily based on drug approval status at the time in respective countries, evidence from clinical trials and observational studies, or expert opinion of the writing panel. Any of these factors could explain the observed differences between guidelines in certain scenarios. Since the guidelines were published, two major advances occurred. First, deferiprone was approved in the US for the treatment of iron overload in TM patients who are resistant to DFO. Second, data from several new clinical trials as well as from extended follow-up of previous trials evaluating the efficacy of oral chelators became available. Deferiprone monotherapy and the combination of DFO + deferiprone were shown to be superior to DFO monotherapy for the outcomes of improvement in right ventricular ejection fraction [31, 32], and more importantly, cardiac mortality [33, 34]. Moreover, long-term follow-up of patients recruited in the initial deferasirox trials confirmed its efficacy and safety over a period of 5 years [29]. Deferasirox therapy was also associated with improved hepatic outcomes in TM patients [35]. The efficacy of deferasirox to chelate cardiac iron in patients with cardiac T2* <20 ms and no cardiac dysfunction was also demonstrated in a trial lasting for 3 years [36], although another trial showed that the benefit is less favorable in patients with elevated LIC [37]. These data, alongside several other ongoing trials, will help answer persisting gaps in knowledge and guide the establishment of future guidelines. Of particular importance is the paucity of data comparing the oral chelators head to head or their combination, as such evidence is currently restricted to small pilot studies or retrospective observational cohorts [38–43]. Evaluation of the efficacy and safety of new oral chelators is ongoing [44].

Dosing Considerations

We assessed whether the following important dosing considerations were mentioned in the guidelines.

The TIF, US, Canadian and UK guidelines cautioned that the DFO dose should be lower (<40 mg/kg/day) in growing children than in adults due to adverse effects on bone development and growth. Otherwise, the mention of standard dosing of the three chelators of all guidelines followed the prescribing information of the drugs. However, only the TIF and UK guidelines mentioned that dose selection is important to the response rate for DFO and deferasirox therapy. Evidence has shown that the effective
dose of DFO or deferasirox is affected by the rate of transfusional iron loading allowing a rational basis for dose selection [45]. Dosing also primarily relies on whether the main goal is treatment or prevention of iron overload. The maximum deferasirox dose recommended in most guidelines was 30 mg/kg/day (except in the US and Australian guidelines which allowed higher doses). However, evidence that may have emerged after publication of the remaining guidelines confirmed the efficacy and safety of deferasirox at doses of >30 mg/kg/day [46], and such doses may be needed in patients with severe iron overload unresponsive to lower doses. As patients reach serum ferritin values of <1,000 ng/ml, dose reduction in DFO is recommend by most guidelines due to a high toxicity risk. Although data confirm the safety of deferasirox therapy at such low levels [47], dose reduction is still recommended until more evidence becomes available.

Safety Monitoring

All guidelines provide detailed information regarding the adverse events associated with the use of the chelators, and some provide recommendations for safety monitoring (table 3). These generally follow standards and recommendations provided by the manufacturers.

Recently, and based on data primarily retrieved from case reports, a boxed warning was added to the US deferasirox prescription information, although this amendment has not been adopted by the European Health Authority or applied globally. The warning indicates that it may cause renal and hepatic impairment, including failure and gastrointestinal hemorrhage. In some reported cases, these reactions were fatal. However, these reactions were observed in patients with advanced age, high-risk myelodysplastic syndromes, underlying renal or hepatic impairment, or low platelet counts. It should also be noted that many of the reported cases lacked apparent evidence of causality [48]. Safety data with deferasirox in TM children and adults are now available for up to 5 years of treatment and confirm an absence of progressive increases in serum creatinine over longer-term treatment, even in heavily iron-loaded patients who require dose escalation to >30 mg/kg/day [29, 46].

Splenectomy

The TIF, US, Canadian and UK guidelines provide recommendations regarding splenectomy in patients with TM. All guidelines agree that physicians should adopt a guarded approach and restrict splenectomy to certain indications, in view of the observation of an increased risk of venous thrombosis and pulmonary hypertension, alongside overwhelming infections after splenectomy. More recent studies continue to confirm such associated adverse events [49]. The TIF and US guidelines further recommended that splenectomy should be avoided in children <5 years of age because of a considerably greater risk of fulminant postsplenectomy sepsis.

The recommended indications for splenectomy include the following. (1) Increased blood requirement that prevents adequate control with iron chelation therapy. In this setting, alloimmunization, concurrent infections or suboptimal transfusion therapy should be ruled out. There are slight differences in the recommended threshold of annual transfusion volume (75% hematocrit) to be used to flag an increased blood requirement: TIF, 200–220 ml/kg/year; US, 225–250 ml/kg/year; Canada, 250–275 ml/kg/year; UK, 200–220 ml/kg/year. (2) Hypersplenism leading to cytopenias. (3) Symptomatic splenomegaly.

All guidelines recommend thromboprophylaxis perioperatively in patients with thrombocytosis. There is also a consensus regarding preoperative immunization against Streptococcus pneumoniae, Haemophilus influenzae type B and Neisseria meningitides, as well as postoperative oral antibiotic prophylaxis. The TIF and Canadian guidelines reflect upon the duration of postsplenectomy antibiotic prophylaxis: it should be continued until 5 years of age, although beyond this age, the duration remains controversial. The TIF and US guidelines also recommend annual influenza virus vaccination.

Management of Specific Complications

Only the TIF, US, Canadian and UK guidelines provide information on the management of specific complications in TM, and these are summarized in online supplement 1 (www.karger.com/doi/10.1159/000345734).

Conclusion

There was a general consensus between available guidelines for the management of patients with TM, although some guidelines provided more comprehensive and contemporary recommendations than others. We did not identify differences warranting concern, although minor differences in iron overload assessment strategy and more notable variations in the recommendations for iron chelation therapy were observed. However, with ongoing ad-
vances in the field and continued efforts to answer remaining gaps in knowledge, these differences are expected to be reduced. Establishment of local guidelines in resource-poor countries is encouraged, especially in that the availability and cost of novel diagnostic techniques and interventions present an important limitation.

References


Disclosure Statement

K.M.M.: honoraria, Novartis Pharmaceuticals. J.B.P.: honoraria and research grant funding, Novartis Pharmaceuticals. The remaining authors have no conflicts of interest to disclose.
Revisiting TM Management Guidelines


