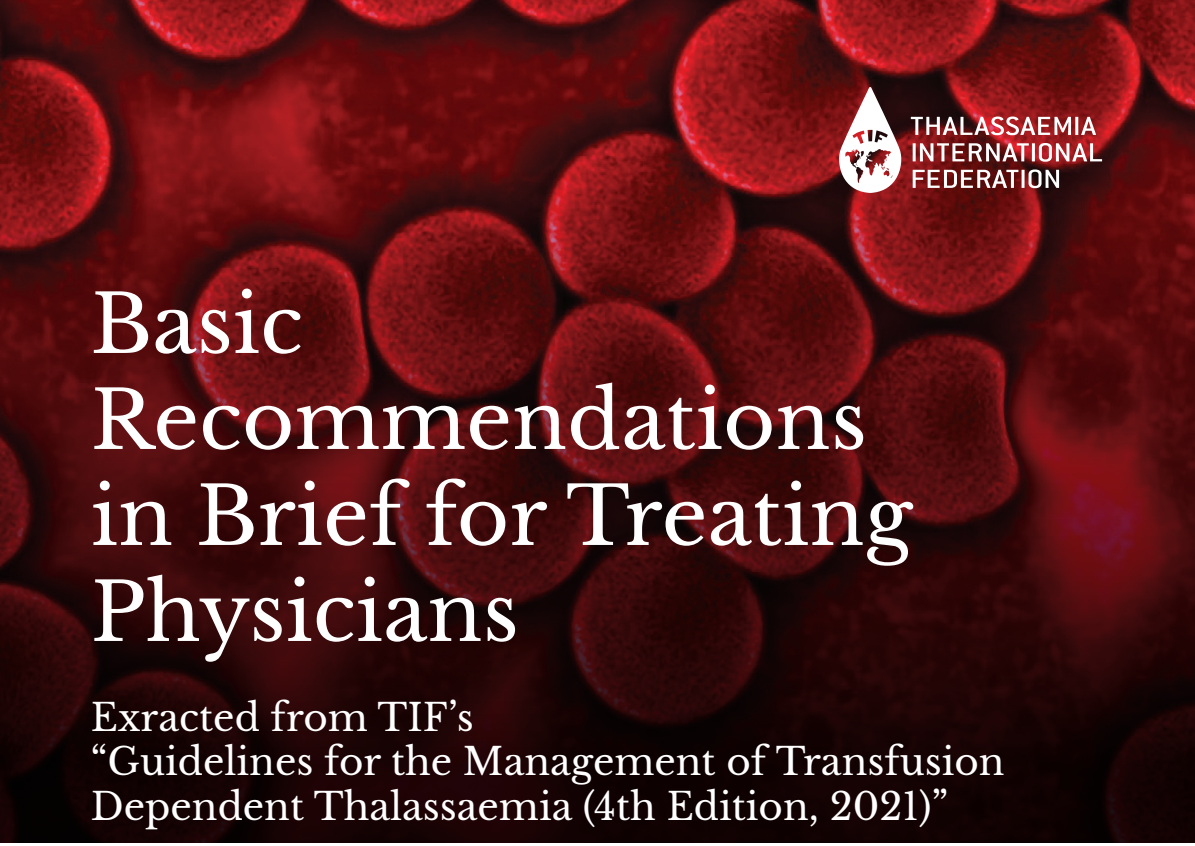

THALASSAEMIA INTERNATIONAL FEDERATION

Basic Recommendations in Brief for Treating Physicians

Exracted from TIF's "Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

Contents

About the Thalassaemia International Federation (TIF):

THALASSAEMIA INTERNATIONAL FEDERATION, a non-governmental, patient driven umbrella organisation, established in 1986, supports today, the rights of patients for access to quality health, social and other care through its work with over 200 national thalassaemia associations in 62 countries across the world. It was founded by a small group of doctors and patients/parents who represented National Patient Associations, mainly from Cyprus, Greece, Italy, UK and USA i.e. Countries where thalassaemia had been recognized early as a genetic, hereditary disorder with huge medical, public health, social and economic repercussions if left unaddressed in terms of both effective prevention and management. Thus, these were the countries where strong research activity was initiated and the first control programmes were implemented in the early 1980s, with measurable success. The rationale of these founding members lay on the establishment of an international umbrella organisation to build on the accumulated experience and the knowledge gained, aiming to support the efforts of other countries since by the mid-1980s the worldwide prevalence of the disease had been well verified.

OUR MISSION: The prioritisation of thalassaemia on national health agendas and the development and implementation of effective disease – specific control (prevention and clinical management) programmes within national healthcare systems based on universal coverage.

OUR VISION: To support the provision of equal access of every patient with thalassaemia to high quality health, social and other care in a truly patient-centred healthcare setting.

OUR VALUES: Transparency, reliability, ethos, accountability, independence and patient-centredness.

OUR WORK:

• Education • Advocacy • Collaborations/ Networking • Research • Raising Awareness

OUR PARTNERS:

- World Health Organisation: in official relations since 1996
- United Nations: in special consultative status with the United Nations Economic and Social Council (ECOSOC) since 2017
- Council of Europe: Participatory status in the Conference of International NGOs since 2019
- European Union: Official partners of the European Commission in the field of Health since 2018

Our Motto: Unity & Knowledge constitute our Strength!

THALASSAEMIA INTERNATIONAL FEDERATION

Blood Transfusion in Thalasseamia

Exracted from TIF's
"Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

An effective transfusion regimen will result in:

- Correction of anaemia.
- Good growth and development.
- Good energy levels.
- Sufficient suppression of intra and extramedullary haematopoiesis.

To safeguard the health of patients with thalassaemia, blood should be obtained from carefully selected, regular, voluntary, non-remunerated donors and should be collected, processed, stored and distributed by dedicated, quality assured blood transfusion centres.

Criteria for initiating transfusion therapy:

For deciding whom to transfuse, the following should be included in the investigations:

Laboratory criteria:

- Confirmed diagnosis of thalassaemia.
  - Haemoglobin level (Hb) <70 g/l on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections) AND/OR
- Clinical criteria irrespective of haemoglobin level: Hb > 70 g/l with any of the following:
  i. Significant symptoms of anaemia
  ii. Poor growth / failure to thrive
  iii. Complications from excessive intramedullary haematopoiesis (bone marrow expansion) such as pathological fractures and facial changes
  iv. Clinically significant extramedullary haematopoiesis

Transfusion Programmes

Target	*Rationale*
To maintain the pre-transfusion haemoglobin level 95-105 g/L.	Promotes normal growth, allows normal physical activities, adequately suppresses bone marrow activity in most patients, and minimizes transfusional iron accumulation.
Pre-transfusion Hb level of 110-120 g/l	For patients with heart disease, clinically significant extramedullary haematopoeisis or other medical conditions.
Younger children may require a fraction of a unit	Desired – actual Hb g/l) x weight x 0.3/haematocrit of transfused unit = ml to be transfused
A careful record of transfused blood should be maintained for each patient	Volume or weight of the blood units, the hct of the units or the average hct of units with similar anticoagulant-preservative solutions, and the patient's weight

Calculate the annual blood requirements as volume of transfused blood or pure red cells (haematocrit 100%) per kg of body weight.

Pure red cells per kg of body weight) when multiplied by 1.08, gives the estimated amount of iron per ml of RBC.

EXAMPLE

Patient weight: 40 kg
Transfusion amount and schedule: 600 ml every 4 weeks
Average haematocrit of transfused red cells: 60%

Annual blood requirement: 13 transfusions x 600 ml/40 kg =195/kg
Annual pure red cell requirements: 195 ml/kg/yr x 60%
(average haematocrit) = 117 ml/kg/yr

Annual transfusional iron loading:
117 ml/kg/yr of pure red cells x 1.08 mg iron per ml pure red cells = 126 mg iron
Daily transfusional iron loading: 126 mg iron/yr/365 days = 0.34 mg/kg

If the annual transfusion requirements rise above 200 ml/kg/year of pure red cells, splenectomy may be considered.

Recommendations:

Transfuse every 2-5 weeks, maintaining pre-transfusion haemoglobin above 95-105 g/ l or up to 110-120 g/l for patients with cardiac complications.

Keep a record of red cell antibodies, transfusion reactions and annual transfusion requirements for each patient.

Keep the post-transfusion haemoglobin below 130-150 g/l.

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Ensuring Safe Blood Transfusion in Transfusion Dependent Patients (TDP)

Exracted from TIF's
"Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

The aim of blood transfusion in thalassaemia is to deliver a safe and effective transfusion regimen whilst minimising the burden of transfusion therapy on everyday life.

Use a product that is ctollected, tested, processed and administered following faithfully established quality and safety regulations and administered by staff well trained in blood transfusion therapy and performed in a system with a good haemovigilance structure:

adverse events reporting is key to the safety of blood transfusion.

To safeguard the health of patients with thalassaemia or other patients needing regular blood transfusions, blood should be obtained from carefully selected donors based on voluntary non-remunerated practices, processed, stored appropriately and distributed by dedicated, quality assured blood transfusion centres. Such centres should adhere to the directives of regional and international bodies such as European Union (EU), the World Health Organisation (WHO) or the American Association of Blood Banks (AABB), with additional consideration of national needs, resources and prevalence of infectious agents.

Target	*Rationale*
Screening for infectious agents	Hepatitis B, hepatitis C, HIV, syphilis and, in some countries additional infectious agents including newly emergent infections.
Careful donor selection	Use accepted questionnaire to screen donors. Favour voluntary, regular and non-remunerated blood donors.
Extended RBC antigen typing pf patients (before first transfusion)	At least D, C, c, E, e, Kell If available full RBC pheno/genotyping panel.
Compatible blood at each transfusion	ABO, Rh(D) compatible blood. Choosing units compatible for ABO, C, c, E, e and Kell antigens is highly recommended.
Screening for new antibodies before each transfusion	An IAT cross-match or perform an electronic cross-match where allowed.
Use of leucodepleted packed red cells	Pre-storage filtration is strongly recommended, but blood bank pre-transfusion filtration is acceptable. Bedside filtration is only acceptable if there is no capacity for pre-storage filtration or blood bank pre-transfusion filtration. Reduction to 1 x 10^6/L or less leucocytes per unit is considered the critical threshold for eliminating adverse reactions attributed to contaminating white cells.
Washed red cells	Only for patients who have severe allergic reactions.
Cryopreserved (frozen) red cells	For patients who have unusual red cell antibodies or who are missing common red cell antigens.
Storage of packed red cells	Red cells stored in CPD-A use within one week of collection. Red cells stored in additive solutions for less than two weeks of collection where available.

Adverse Reactions

- Non-haemolytic febrile transfusion (NHFTR) dramatically decreased by leukoreduction.
- Allergic reactions are usually due to plasma proteins. Mild allergic reactions can be prevented with the use of antihistamines or corticosteroids before transfusion. Recurrent allergic reactions can be reduced by washing the red cells to remove the plasma. Patients with IgA deficiency and severe allergic reactions may require blood from IgA-deficient donors.
- Acute haemolytic reactions (HTR), due to errors in patient identification or blood typing and compatibility testing: begin within minutes or sometimes hours after a transfusion. The transfusion should be stopped immediately and IV fluids should be administered to maintain intravascular volume. Disseminated intravascular coagulation may require the use of heparin. The identification of the patient and the donor unit should be re-checked. The blood bank should also be alerted to the possibility of an undetected alloantibody.
- Alloimmunization occurs in 10-20% of patients with thalassaemia and is more common in children who begin transfusion therapy after 1-3 years of age. The use of extended antigen matched donor blood is effective in reducing the rate of alloimmunization.
- Delayed transfusion reactions usually occur within 5-14 days of transfusion and are characterized by unexpected levels of anaemia, usually caused by an alloantibody. A sample should be sent to the blood bank to investigate the presence of a new antibody and to repeat cross-matching of the last administered units.
- Autoimmune haemolytic anaemia: a serious complication usually but not always occurs in patients with alloantibodies. Steroids, immunosuppressive drugs, intravenous immunoglobulin and rituximab are used for the clinical management of autoimmune haemolytic anaemia.
- Transfusion-related acute lung injury (TRALI) is caused by specific anti-neutrophil or anti-HLA antibodies. Dyspnoea, tachycardia, fever and hypotension during or within six hours of transfusion, hypoxemia with bilateral infiltrates typical of pulmonary oedema. Management includes oxygen, steroids, diuretics and, when needed, assisted ventilation.
- Transfusion-associated graft versus host disease (TA-GVHD) is caused by viable lymphocytes in donor red cell units and is often fatal. It occurs within 1-4 weeks of transfusion with fever, rash, liver dysfunction, diarrhoea and pancytopenia due to bone marrow failure. To reduce the risk, donated blood from a family member should be avoided or, if used, should always be irradiated before transfusion.
- Transfusion-associated circulatory overload (TACO) can occur in the presence of cardiac dysfunction, or when the rate of transfusion is inappropriately fast.

THALASSAEMIA INTERNATIONAL FEDERATION

Iron Overload: Assessment and Monitoring

Exracted from TIF's
"Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

Iron overload occurs when iron intake is increased over a sustained period of time as a result of:

- red blood cell transfusions (mainly in Transfusion Dependent Thalassaemia [TDT]) and
- increased absorption of iron through the gastrointestinal (GI) tract in both TDT but mainly in Non-Transfusion Dependent Thalassaemia [NTDT]).

Iron that is not bound to naturally occurring molecules such as **transferrin**, or **ferritin** or to **therapeutic iron chelators,** generates a variety of reactive oxygen species (ROS), most notably hydroxyl radicals. These generate lipid peroxidation that results in organelle and DNA damage and cause **apoptotic cell death, increasing the risk of vital organs' damage including neoplasia such as hepatoma**.

Iron accumulation is **toxic** to many tissues, causing **heart failure, cirrhosis, liver cancer, growth retardation and multiple endocrine abnormalities.**

Diagnosis and Monitoring of Iron

Method	*Ranges*	*Frequency of measurement*	*Useful Comments*
Serum ferritin (SF)	Target value is currently between 500-1000 µg/l.	Measured at least every 3 months (1-3 months).	SF may not reflect total body iron levels or organ specific levels. It fluctuates in response to inflammation, abnormal liver function and metabolic deficiencies
Estimation of annual blood usage	Pure red cells per kg of body weight) x 1.08, gives the estimated amount of iron per ml of RBC	Annual	Annual record of blood usage (ml/kg packed red cells) and daily iron loading (mg/kg/day) / patient
Liver iron concentration (LIC)	• Stable levels in the range 3-7 mg/g dw	• Yearly / Every other year	Measured by MRI-based methods. Sequential MRI LIC estimations in an individual patient should be by the same standardized and regularly calibrated methodology. Liver biopsy may be used very rarely and mainly for liver morphology assessment. This has been largely replaced by MRI based methods.
	• Levels 7-15 mg/g dw	• At least yearly	
	• Levels > 15 or levels falling rapidly	• 6 - 12 monthly	
Myocardial iron	• No cardiac iron, low risk of heart failure HF ≥ 20 ms	• 1-2 years	Assessed by T2* cardiac MRI using an externally validated protocol and software
	• Mild to moderate cardiac iron, low risk of HF 10–19 ms	• Yearly	
	• High cardiac iron, m toderate risk of HF 6–9 ms	• 6 monthly	
	• High cardiac iron, high risk of HF <6 ms	• 6 monthly	
24h urinary iron estimation	-	Not widely used	Useful if using deferoxamine or deferiprone, but inherent variability in iron excretion
NTBI* & LPI**	Of possible value as a guide to routine treatment or prognosis	Personalized needs	But value in routine monitoring not yet established
Organ function as an indicator of iron induced damage	Include biochemistry, echocardiography, LFTs, hormone levels etc	-	Aspects of multidisciplinary management

*NTBI: Non Transferrin Bound Iron
**LPI: Labile Plasma Iron

How is iron measured?

1. Serum Ferritin - A laboratory based biochemical test.
2. MRI - Magnetic Resonance based methods standardized and regularly calibrated to measure specifically ron load e.g. T, T2* or R, R2, for cardiac (usually T2*) and for LIC (usually R2 or R2*).

Notes:

- For MRI examinations children may need to be sedated
- Patients with pacemakers or metal implants cannot use MRI
- Trends in the SF level over time can predict changes in total body iron

Main recommendations:

1. Uncontrolled transfusional iron overload increases the risks of heart failure, endocrine damage, liver cirrhosis and hepatocellular carcinoma.
2. Liver iron concentration can be used to calculate total body iron, and serum ferritin is an approximate marker of LIC.
3. Routine tests are essential to control iron chelation therapy

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Iron Chelation: The Management of Iron Overload

Exracted from TIF's
"Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

Iron chelation therapy:

- **Prevention therapy:** to maintain safe levels of body iron at all times, by balancing iron intake from blood transfusion with iron excretion by chelation (iron balance). Preferred method.
- **Rescue therapy:** to remove excess iron stored or accumulated over time in the body.
- **Emergency therapy:** to urgently intensify iron chelation in case of iron-induced heart failure.
- **Dose adjustment of therapy:** to adjust dosing and treatment regimens to changing circumstances identified by careful monitoring of body iron and its distribution; monitoring is important to avoid:
  i. under-chelation with increased iron toxicity; or
  ii. over-chelation and increased chelator toxicity.
- **Intermittent high-dose chelation** used usually in patients facing challenges (mainly adherence) to address iron overload can induce negative iron balance but this method does not provide continuous protection from labile iron and also may be associated with increased risks of toxicity from the iron chelator.

Iron chelators - Three iron chelators are licensed to date for clinical use:

Category	*DFO (Deferoxamine)*	*DFX (Deferasirox)*
Children age 2-6 years	First line for TM	First line in USA Under European Licensing (EMA) Exjade is a medicine used to treat chronic iron overload (an excess of iron in the body) in: • children aged 2 to 5 years with beta thalassaemia major who receive frequent blood transfusions, when deferoxamine (another medicine used to treat iron overload) cannot be used or is inadequate; • patients from 2 years of age with beta thalassaemia major who receive infrequent blood transfusions, when deferoxamine cannot be used or is inadequate;
Children age 6 - 10-years and adults	Fist line TM	First line for TM and first line for NTDT Under FDA and European Licensing (EMA) • patients from 6 years of age who have beta thalassaemia major (an inherited blood disorder in which patients do not have enough normal haemoglobin in the blood) and who receive frequent blood transfusions; • patients from 10 years of age with non-transfusion-dependent thalassaemia syndromes, when deferoxamine cannot be used or is inadequate
Route	s.c./i.m./ i.v injection	Oral, dispersed tablet.
Dosage and frequency	20-60 mg/kg 5-7 x /week, 50 mg/kg in EU Children's dose up to 40 mg/kg	14-28 mg/kg/day once daily for film coated tablet. Lower doses in NTDT.
Contra-indications	Pregnancy (but has been used in 3rd trimester) Hypersensitivity	Pregnancy. Hypersensitivity. Estimated creatinine clearance <60 ml/min. Hepatic impairment or renal failure.
Precautions	Monitor ferritin; if it falls to <1000 µg/l , reduce dose (so mean daily dose/ferritin remains <0.025). Monitor audiometry regularly, particularly as ferritin falls Monitor eyes regularly including electroretinography if on high doses. Fever suggestive of septicaemia with organisms that used ferrioxaine (Yersinia, Klebsiela) Renal failure or diminishng renal function with other comorbidities.	Monitor creatinine trends for 1st 4 weeks after starting or after dose escalation, then monthly. If rapid fall in serum ferritin to <1000 µg/l, dose reduce. If ferritin 500 µg/l consider very low doses. Proteinuria may occur, occasionally with renal tubular acidosis. Monitor urine protein regularly. Prescribing to the elderly; non-fatal G/I bleeding, ulceration, may occur; caution with drugs of known ulcerogenic or haemorrhagic potential, (e.g. NSAIDs,corticosteroids, oral bisphosphonates, and anticoagulants). Hypersensitivity reactions. Monitor liver function regularly.
Potential drug interactions	Co-administration with prochlorperazine: may lead to temporary impairment of consciousness. Gallium-67: Imaging results may be distorted by rapid urinary excretion of DFO-bound gallium-67. Discontinuation 48 hours prior to scintigraphy is advisable.	Theoretical interactions with drugs metabolized by CYP3A4 e.g. midazolam. Theoretical interactions with drugs metabolized by CYP1A2: e.g. theophylline. Gallium-67 as with DFO. Oral preparations containing polyvalent cations as with DFP.

Iron chelators (contd.)- Three iron chelators are licensed to date for clinical use:

Category	*DFP (Deferiprone)*
Children age 2-6 years	Under European licensing, there are limited data available on the use of deferiprone in children under six years. Under USA licensing, Ferriprox® (deferiprone) Oral Solution is an iron chelator indicated for the treatment of transfusional iron overload in adult and paediatric patients 3 years of age and older with thalassemia syndromes, sickle cell disease and other anemias.
Children age >6 years and adults	Approved if other chelator or DFO are not tolerated or inadequate (European Medicines Agency (EMA), Summary of Product Characteristics, Update 15/03/21,Paediatric population). Under USA licensing, Ferriprox® Tablets are an iron chelator indicated for the treatment of transfusional iron overload in adult and paediatric patients aged 6 years[1] and older with thalassemia syndromes, sickle cell disease and other anemias.
Route	• Oral, tablet or liquid
Dosage and frequency	1. 75 -100 mg/kg/day in 3 divided doses daily 2. 75-99t mg/kg/dg Oral Twice-A-Day (TAD) Formulation Ferriprox® (FDA approved)
Contra-indications	• Pregnancy • History of neutropenia or condition with underlying risk of cytopenia • Hypersensitivity including Henoch Schönlein purpura: urticaria and periorbital oedema with skin rash
Precautions	– Measure neutrophil count (ANC) before starting and monitor ANC weekly **EMA licensing:** the absolute neutrophil count (ANC) monitored every week during the first year of therapy. For patients whose DFP has not been interrupted during the first year of therapy due to any decrease in the neutrophil count, the frequency of ANC monitoring may be extended to the patient's blood transfusion interval (every 2-4 weeks) **FDA licensing:** Due to the risk of agranulocytosis, monitor ANC before and during therapy: • First 6 months of therapy: Monitor ANC weekly; • Next 6 months of therapy: Monitor ANC once every two weeks; • After one year of therapy: Monitor ANC every two to four weeks (or at the patient's blood transfusion interval in patients. – For neutropenia : ANC < 1.5 x 109/ l) interrupt treatment – For agranulocytosis (ANC < 0.5 x109/ l), consider hospitalisation – Advise patients to report immediately symptoms of infection; interrupt if fever develops – Monitor for symptoms of arthropathy – Monitor liver function regularly – No guidance on dose adjustment at low ferritin
Potential drug interactions	– Theoretical interactions with UGT1A6 inhibitors (e.g. diclofenac, probenecid or silymarin (milk thistle) – Avoid concomitant use with drugs associated with neutropenia – Gallium-67 as with DFO – Oral preparations containing polyvalent cations (e.g., aluminium containing antacids, and zinc) allow at least a 4-hour interval

Summary Recommendations

1. Uncontrolled transfusional iron overload increases the risks of heart failure, endocrine damage, liver cirrhosis and hepatocellular carcinoma.
2. Liver iron concentration can be used to calculate total body iron
3. Serum ferritin is an approximate marker of LIC, but real trends in body iron may be missed, particularly at high levels of iron overload
4. Chelation therapy is an effective treatment modality in improving survival, decreasing the risk of heart failure and decreasing morbidities from transfusional iron overload.
5. Chelation therapy at the correct doses and frequency can balance iron excretion with iron accumulation from transfusion.
6. Absolute change in total body iron in response to chelation can be calculated based on change in LIC.
7. Direction of change in body iron in response to transfusion and chelation can usually, but not always, be estimated from the trend in serum ferritin.
8. Prevention of iron accumulation using chelation therapy is preferable to rescue treatment because iron mediated damage is often irreversible, and removal of storage iron by chelation is slow - particularly after it has escaped the liver.
9. Response to chelation is dependent on the dose applied and the duration of exposure.
10. Response to chelation is affected by the rate of blood transfusion.
11. Heart iron accumulates later than liver iron, and is rare before the age of 8 years; affecting a subset of patients.
12. Chelation of storage iron from the liver tends to be faster than from myocardium.
13. Heart storage iron concentration is directly related to the risk of heart failure, which can be reliably estimated by MRI (e.g. cardiac T2*), provided that the centre performing the measurement uses a validated method, which has been independently calibrated.
14. Chelation can rapidly reverse iron mediated heart dysfunction (within weeks) by rapid chelation of labile iron, if 24h chelation cover is achieved.
15. Chelation therapy removes myocardial storage iron slowly compared with liver iron.

THALASSAEMIA INTERNATIONAL FEDERATION

Cardiovascular Disease Assessment in Thalassaemia

Exracted from TIF's
"Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

Cardiovascular (CV) disease in thalassaemia is primarily determined by the following factors:

- The severity of the haematological defect dictated by the genetic background, and
- The applied disease-specific therapy including blood transfusions and iron chelation.
- The impact of patients' ageing, by increasing the occurrence of age-related conditions.

The spectrum of CV disease includes:

- Left and/or right ventricular dysfunction, with or without heart failure.
- Pulmonary hypertension.
- Tachyarrhythmias e.g. atrial fibrillation, and bradyarrhythmias e.g. atrioventricular block.
- Valvular disease.
- Pericarditis and myocarditis.
- Thromboembolic events, resulting from either venous or arterial thrombosis.
- Cerebrovascular disease, manifested as either ischaemic or haemorrhagic stroke.
- Vascular abnormalities, including endothelial dysfunction and increased arterial stiffness.

Regular assessment is within the multidisciplinary care program

- It includes taking the history, performing a full physical examination, ECG and echocardiogram.
- Cardiological examination is performed on an annual basis in all thalassaemia patients, regardless of the presence of history or symptoms. More frequent follow up if complications are detected.
- Check for co-morbidities which may affect heart function (endocrine or metabolic).

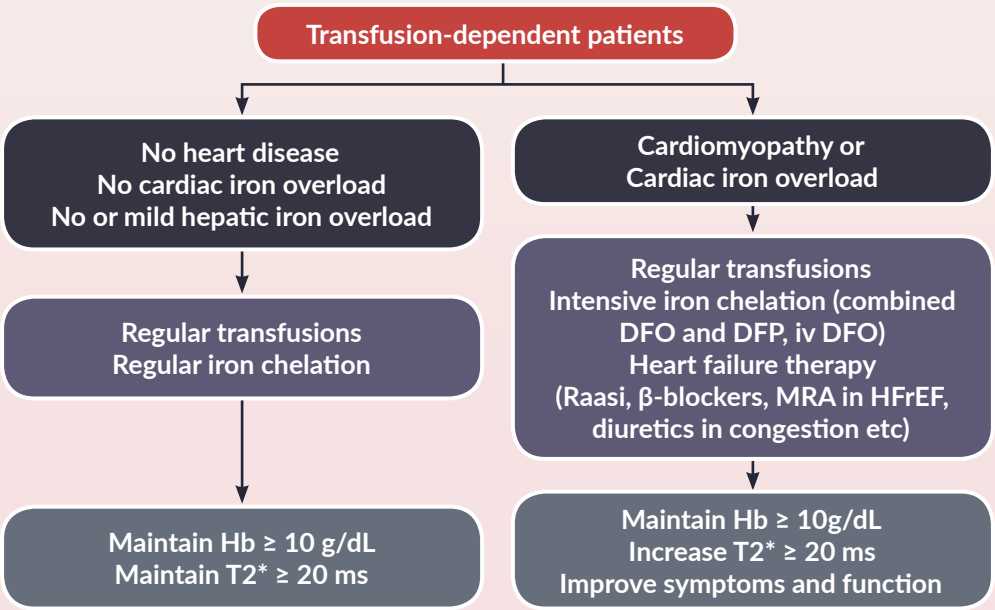
Examination	*Comments*
Resting ECG	Ambulatory ECG monitoring for the evaluation of frequent palpitations or known arrhythmias or to assess the arrhythmogenic risk of patients with systolic LV dysfunction or heart failure.
Transthoracic echocardiography (TTE)	Evaluation of function of cardiac chambers, valves and pericardium. Screening for pulmonary hypertension.
Cardiac MRI T2*	Assessment of cardiac iron overload. The first MRI T2* scan is performed 7-10 years after the initiation of blood transfusions repeated every 2 years*. Also used for the more accurate assessment of cardiac cavities, systolic LV function and myocardial tissue characterization.
Cardiac biomarkers	Cardiac troponins (e.g., in suspected myocarditis) Natriuretic peptides (e.g., for the evaluation of patients with known or suspected heart failure).
Exercise testing	Exercise ECG or ergospirometry for the assessment of functional capacity or arrhythmias.
Right cardiac catheterization	Evaluation of pulmonary artery pressure in patients with echo signs of pulmonary hypertension (e.g., TRV >3 m/s, despite optimal transfusion therapy and a pre-transfusional haemoglobin level close to 100 g/l).
Lung function tests	For the comprehensive diagnostic assessment of confirmed pulmonary hypertension.
Chest computed tomography (CT)	CT pulmonary angiography (or lung scanning) along with careful ventricular function evaluation: for the comprehensive diagnostic assessment of confirmed pulmonary hypertension.

** see also Iron Load Monitoring information*

Management

Optimize disease specific management:

- Regular blood transfusions aiming at a pre-transfusional haemoglobin level of 100 g/l.
- Iron chelation regimens aiming at a cardiac T2* value greater than 20 ms.
- Cardiac dysfunction due to iron overload may be reversed by intensification of iron chelation.
- Significant arrhythmias may require implantable cardioverter defibrillator (ICD) implantation, catheter ablation.
- Advanced heart failure may require permanent ventricular assist device implantation or cardiac transplantation.
- Anticoagulation in patients with atrial fibrillation. Non-regularly treated patients with previous splenectomy carry an increased risk of thromboembolism, while patients with pseudoxanthoma elasticum-like lesions may carry an increased risk of bleeding.
- Lifestyle choices that promote CV health (absence of smoking, physical exercise, weight control, healthy diet) should be vigorously promoted in thalassaemia patients.



A basic therapeutic algorithm for thalassaemia patients on regular blood transfusions modified from Farmakis et al.[1]

[1]Eur J Heart Fail 2017;19:479-489

(DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; Hb: haemoglobin concentration; ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers; AFib: atrial fibrillation).

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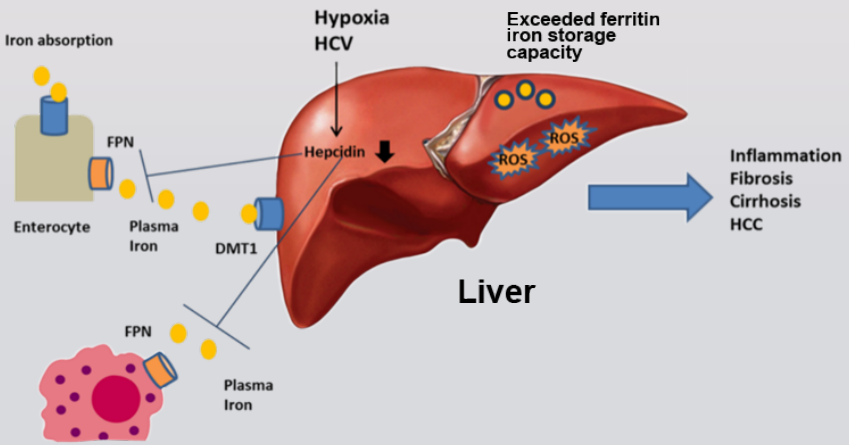
Liver Disease in Thalassaemia

Exracted from TIF's "Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

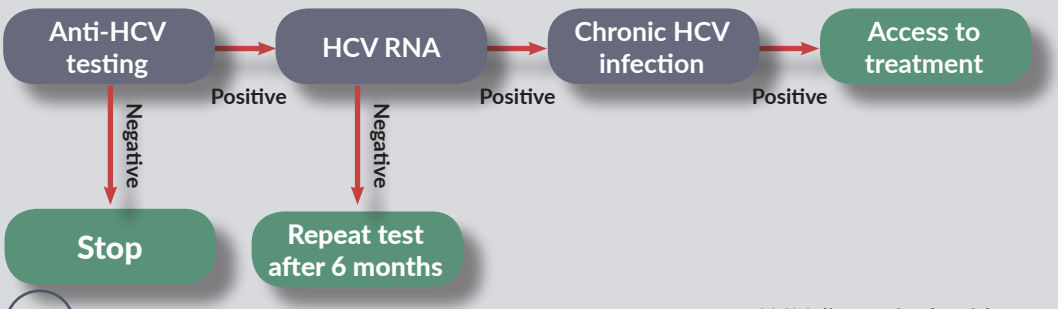
Causative factors:

1. Iron overload with cellular damage due to free iron radicals (reactive oxygen species). Hepatic inflammation and cell necrosis lead to fibrosis and cirrhosis
2. Viral hepatitis due mainly to HCV and HBV (more rarely HEV). Transmitted mainly through blood transfusion they cause inflammation and in combination with iron overload accelerate liver fibrosis.



Diagnosis and assessment:

Examination	*Comments*
Physical examination	May reveal hepatomegaly, palmar erythema, spider naevi etc.
Liver enzymes	Elevations 2-3 x upper limit of normal, mild increase in γ GT.
Serum ferritin	>2000ng/ml are associated with liver iron overload.
HBV, HCV serology	At least every 12 months with PCR to follow if serology is positive.
Abdominal ultrasound	Performed every 6 months in cirrhotic patients or those with risk factors positive for the presence of viruses and in NTDT patients with LIC >7mg/g dw (danger of HCC).
MRI monitoring*	To measure liver iron concentration (LIC) annually. The method of choice to also monitor chelation therapy effectiveness. Values: 1. 7mg/g dw = moderate iron overload 2. 15mg/g dw = severe iron overload See "Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)" Important also for liver morphology: early detection of HCC.
Transient elastography (TE)	For the assessment of liver fibrosis.
Liver biopsy	Gold standard for the assessment of liver morphology e.g. fibrosis but also iron content. Invasive examination replaced by MRI & TE
Duplex U/S or Doppler imaging	For diagnosis and assessment of portal hypertension



HCV diagnosis algorithm

** see also Iron Load Monitoring information*

Recommendations

- MRI R2 or R2* is the method of choice to assess liver iron concentration (LIC) and monitor chelation therapy effectiveness.
- Deferoxamine, deferiprone and deferasirox are effective in decreasing total body iron burden as well as LIC.
- Screening for HCV and HBV chronic infection is recommended in thalassaemic patients.
- Vaccination against hepatitis B is recommended in all patients with thalassaemia who are seronegative for HBV markers.
- If anti-HCV antibodies are detected, the presence of HCV-RNA in serum or plasma should be determined to identify patients with chronic infection.
- The new IFN-free, ribavirin-free direct acting anti-viral drugs for hepatitis C are effective and safe in patients with thalassaemia.
- Serum transaminases, HBV DNA levels and liver fibrosis assessment by transient elastography are the main tools to guide treatment decision in HBV-chronic hepatitis.
- Oral nucleoside and nucleotide analogues are well tolerated and effective drugs for HBV-chronic hepatitis, though loss of HbsAg remains a rare event.
- Biannual ultrasound screening for hepatocellular carcinoma should be performed in all thalassaemic patients.

THALASSAEMIA INTERNATIONAL FEDERATION

Assessing Growth and Development in Thalassaemia

Exracted from TIF's "Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

The child with Transfusion Dependent Thalassaemia (TDT) has a particular growth pattern, which is relatively normal until age 9-10 years if regularly transfused; after this age a slowing down of growth velocity and reduced or absent pubertal growth spurt are observed.

Three phases of growth disturbances with different aetiologies:

Phase 1. Young children: growth disturbance is mainly due to hypoxia, anaemia, ineffective erythropoiesis and nutritional factors.

Phase 2. Late childhood: growth retardation is mainly due to iron overload affecting the GH-IGF-1 axis and other potential endocrine complications.

Phase 3. After the age of 10-11 years delayed or arrested puberty is a contributing factor to growth failure in adolescent thalassaemics, who do not exhibit a normal growth spurt.

Factors affecting growth:

- Onset of disease and the need for blood transfusions. Patients with the β^0/β^0 genotype have a significantly higher prevalence of growth retardation compared to those with the β^0/β^+ and β^+/β^+ genotypes.
- Pre-transfusion haemoglobin level → Chronic Anaemia.
- Chelation therapy (type, dose, compliance).
- Iron Overload.
- Associated comorbidities (endocrine complications, chronic liver disease, chronic cardiac failure, human immunodeficiency virus (HIV) infection).
- Nutritional Deficiencies.
- Emotional and psychosocial factors.

Assessment:

Six-month measurement of:

1. Standing and sitting height. Growth data are plotted on ethnically adjusted charts or internationally (WHO) adjusted charts. Interpretation of absolute height must consider the height of the parents. Measurements of standing height and sitting height with Harpenden stadiometer in absence of sitting height table. Growth velocity curve in adolescents.
2. Pubertal staging in males and females according to Tanner charts
3. The following tests and assessments are recommended, annually:
   iv. Serum thyroid stimulating hormone (TSH) and free thyroxine (T4).
   v. Serum calcium, ionized calcium, inorganic phosphate, magnesium and alkaline phosphatase.
   vi. Serum IGF-1 and insulin-like growth factor-binding protein 3 (IGF BP-3) in growth screening are useful indicators of growth hormone secretion and nutrition, bearing in mind that chronic liver diseases and malnutrition may interfere with their secretion.
   vii. Serum zinc (in selected cases).
   viii. Screening for coeliac disease.
   ix. X- ray of wrist and hand, tibia and spine should be evaluated in patients with TDT who have body disproportion to exclude the presence of platylospondylosis or metaphyseal cartilaginous dysplasia changes.
   x. Assessment of growth hormone (GH) secretion: significant GH insufficiency may be diagnosed by a reduced response of GH to two provocative tests (GH peak <10 ng/ml) in children and adolescents and 3 ng/ml in adults).
   xi. Magnetic resonance imaging (MRI) of the hypothalamic–pituitary region is useful to evaluate pituitary iron overload as well as the size of pituitary gland (atrophy).
   xii. Luteinising hormone (LH), follicle-stimulating hormone (FSH) and sex steroids, starting from the pubertal age.

Management

- Adequate blood transfusion to maintain pretransfusion haemoglobin level > 90 g/l.
- Adequate chelation to attain serum ferritin < 1,000 ng/ml.
- Use of oral iron-chelators with lower toxicity on the skeleton and with better patient compliance.
- Correction of nutritional deficiencies when suspected.
- Oral zinc sulphate supplementation for patients with proven zinc deficiency.
- Correction of hypersplenism.
- Appropriate and timely management of pubertal delay in boys and girls with TDT and appropriate induction of puberty to attain normal pubertal growth spurt and normal bone accretion.
- Accurate diagnosis and early management of hypothyroidism and abnormal glucose homeostasis (impaired glucose tolerance and diabetes mellitus).
- The management of GH deficiency (GHD): The linear growth velocity attained after exogenous GH administration in children with thalassaemia is reported to be lower than that seen in children with primary GH deficiency, possibly due to GH insensitivity.
- At present, there are no guidelines in the literature for the use of recombinant human GH in adult patients with TDT and GHD. However, due to the possible positive effects of GH on the heart, it could be speculated that GH treatment may be useful in some patients with cardiac failure.
- During GH treatment, patients should be monitored at 3-4 monthly intervals with a clinical assessment and an evaluation for parameters of GH response and adverse effects.

THALASSAEMIA INTERNATIONAL FEDERATION

Splenomegaly and Splenectomy

Exracted from TIF's
"Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

Increased destruction of red blood cells by the reticuloendothelial system, in particular the spleen, together with extramedullary haemopoiesis result in splenic enlargement: splenomegaly.

The size of the spleen should be carefully monitored and recorded on physical examination and, as needed, by ultrasonography.

Steps to reduce or delay the onset of splenomegaly include:

- Adequate transfusion, maintaining pre-transfusion haemoglobin concentration (Hb) 90 g/l as a minimum. Splenomegaly may be reversible by increasing transfusion, albeit at the cost of increased iron load.
- Transfusion of red cells with a minimum haemoglobin content of 40 g.
- Use of as fresh as red cells as possible and those that have been stored for less than 2 weeks.
- In patients in whom pre-transfusion Hb is kept at adequate levels and yet the spleen size is increasing, a short period of a few months of hypertransfusion with the aim of increasing the rough Hb and reducing further the extramedullary erythropoiesis might be needed

Diagnosis and assessment:

Indication	*Comment*
Increased blood requirements that prevent adequate control with iron chelation therapy, having made sure that the increased requirements are not due to allo/auto-antibodies or blood loss.	Annual transfusion volume used to flag an increased blood requirement (200-275 ml/kg/yr red cells). However, if effective chelation therapy continues to be maintained despite increased transfusion, splenectomy may not be necessary.
Hypersplenism	Cytopenias causing clinical problems.
Symptomatic splenomegaly	Accompanied by symptoms such as left upper quadrant pain or early satiety. Massive splenomegaly causing concern about possible splenic rupture.

In recent years splenectomy is not recommended as a standard procedure in patients with thalassaemia. There is large amount of evidence that links splenectomy to a variety of complications such as pulmonary hypertension, silent brain infarcts, venous thrombosis and sepsis. Physicians should keep a guarded approach towards splenectomy.

Adverse events of splenectomy and prophylaxis

Complication	*Prophylactic measure*	*Comment*
Reduced cellular and humoral immunity: danger of fulminating sepsis	1. Splenectomy should be avoided in children less than 5 years of age	1. Considerably greater risk of fulminant post-splenectomy sepsis.
	2. Pre-operation vaccinations	
	2a. Strep pneuminiae: 23 polyvalent vaccinet	2a. 4-6 weeks pre-op repeat every 5 years
	2b. Haemophilus influenzae type b,	2b. 4-6 weeks pre-op but no recommendations for repeats
	2c. Neisseria meningitides	2c. 4-6 weeks pre-op repeat every 5 years
	3. Antibiotic prophylaxis	3. A broad-spectrum antibiotic should be given pre- and continued post-operatively. Prophylactic oral penicillin up to the age of 16 years or lifelong if considered high risk Alternative antibiotics for patients unable to take penicillin include amoxicillin, trimethoprim-sulfamethoxazole and erythromycin
Thrombocytosis	Low-dose aspirin (80 mg/d) for patients with high platelet counts	Common, with platelet counts often reaching 1,000-2,000 × 109/l.
Pulmonary hypertension		Advancing age and a history of splenectomy are major risk factors in this population
Iron overload	Monitoring and effective chelation	Spleen as a major organ of iron storage. Following splenectomy, the total body iron storage capacity is reduced Iron will be redirected and accumulated in the liver, heart and other organs and a higher incidence of myocardial iron load.

THALASSAEMIA INTERNATIONAL FEDERATION

Managing Pregnancy in Thalassaemia

Exracted from TIF's "Guidelines for the Management of Transfusion Dependent Thalassaemia (4th Edition, 2021)"

Pre-Pregnancy Counselling:

- Issues of fertility must be resolved and fertility treatment offered to patients who are keen to have a child, provided that their state of health allows them to be eligible.
- The issue of whether the partner is a carrier so that prenatal diagnosis or preimplantation diagnosis may be necessary, should be discussed with both patients.

Steps preceding counselling:

1. Evaluation of eligibility.
2. An opportunity for physicians to review the medications involved and
3. Time for a discussion between physician/s, patient and partner regarding the risks associated with induced fertility and pregnancy.

Eligibility evaluation includes the following examinations:

- Cardiac function: ECG, echocardiogram.
- Liver function tests, ultrasound of the liver.
- Vessels : clotting factors (Prothrombin time, INR, Protein C , Protein S, Homocysteine, Thrombophilia panel) and doppler.
- Endocrine: thyroid function, calcium homeostasis, vitamin D levels.
- Pancreas: glucose tolerance test and optimisation of diabetic control.
- Status of viral infections: HBV, HCV, HIV, Rubella. Test for other possible infections including toxoplasmosis.
- Iron status assessment and optimisation of iron chelation therapy.
- Review medications.
- Screen for acquired red cell antibodies (risk of haemolytic disease of the fetus and newborn).
- Check partner for haemoglobinopathy.
- Arrange genetic counselling if necessary.

Medication review for pregnancy focus points:

- Emphasize folic acid supplementation even before conception.
- Oral iron chelating agents (DFP, DFX) should be discontinued 3 months before conception.
- Stop angiotensin-converting enzyme (ACE) inhibitors.
- Can safely continue metformin, but may need to change oral hypoglycaemic drugs to insulin.
- Stop bisphosphonates at least 6 months prior to planned pregnancy.
- Give calcium and vitamin D supplementation.

Potential risks associated with pregnancy include:

- Pregnancy does not alter the natural history of the disease.
- Requires intense/vigilant monitoring.
- Cardiac complications.
- Risk of pregnancy-specific complications same as background population.
- Risk of miscarriage same as background population.
- Risk of fetal malformation: no increase.
- Risk of fetal growth restriction: two-fold increase.
- Preterm labour risk: two-fold increase.
- Risk of transmission to the fetus/baby of hepatitis B/C, HIV.
- Risk of iso-immunisation.
- Risk of prematurity and growth restriction is increased in multiple births.
- Thrombotic risk may be increased.

Key points for pregnancy care include:

- Check cardiac, liver and thyroid function once each trimester
- Screen for gestational diabetes.
- Increase frequency of blood transfusion to maintain pre-transfusion haemoglobin above 100 g/l.
- Serial ultrasound scans to monitor fetal growth.
- Higher incidence of caesarean section.
- Encourage breastfeeding unless HIV positive and/or HCV RNA and/or HBsAg positive.
- Resume DFO after delivery.
- Discuss contraception, where appropriate with either the progesterone-only pill (POP) or barrier method.
- Avoid intrauterine devices and oestrogen-containing preparations.
- Implement a multidisciplinary approach with all specialists involved in the medical care of thalassaemic women.

Women with thalassaemia should be considered at high risk for venous thromboembolism and should receive low-molecular-weight heparin prophylaxis while in hospital. In addition this treatment should be administered for 7 days post discharge following vaginal delivery or for 6 weeks following caesarean section.

Recommendations:

- Factors to be taken into considered before pregnancy, include the degree of pre-existing cardiac impairment and of liver dysfunction, as well as the possibility of vertical transmission of viruses.
- Pregnancy does not alter the natural history of thalassaemia – it is safe, provided they have normal resting cardiac function. If cardiac function deteriorates during pregnancy, deferoxamine may be used cautiously after the first trimester.