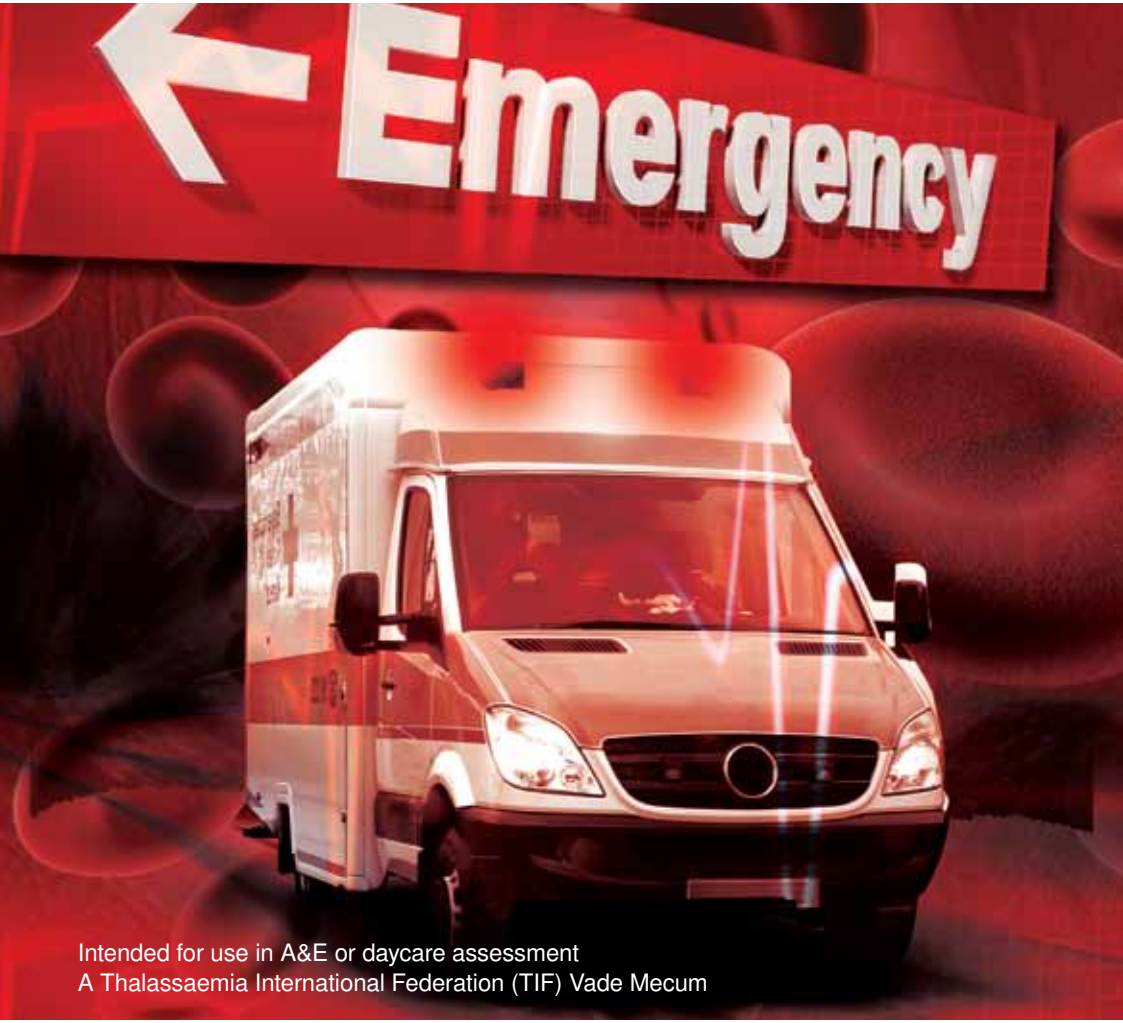
EMERGENCY MANAGEMENT OF THALASSAEMIA



Intended for use in A&E or daycare assessment
A Thalassaemia International Federation (TIF) Vade Mecum

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CONTENTS

FOREWORD

Over recent years there has been a steady improvement in the management of severe forms of thalassaemia, with the result that many patients now are surviving childhood and early adolescence and hence the age range of those with the disease is becoming much wider. This means that, particularly in countries with very limited numbers of special units for managing the disease, its acute complications may be encountered by a wide range of specialists both in paediatrics and adult general internal medicine. Since the haemoglobin disorders still play a relatively small role in general medical education it is likely therefore that many clinicians will be asked to manage patients with severe complications of the disease who have very limited knowledge about it.

I think that TIF have done an excellent job in producing this small and very simply written account of the major complications and their preliminary management. It should be widely distributed, particularly in countries with a high frequency of thalassaemia and in those where a few specialist centres exist. I congratulate TIF on this project and hope that this small booklet will be available in these countries and, indeed, anywhere where thalassaemia poses a problem."

Professor Sir David Weatherall FRS
Regius Professor of Medicine Emeritus
University of Oxford

MESSAGE FROM THE PRESIDENT OF THE EUROPEAN HAEMATOLOGY ASSOCIATION

The European Hematology Association aims to support research and education in all disciplines and diseases of hematology. This booklet is very important because of its focus on a frequent form of anemia which is unevenly distributed throughout Europe and the world. In a recent survey in which young hematologists in Europe have participated we noted considerable needs to enforce the knowledge of hematologists on the topic of thalassemia. The authors of this book have therefore contributed to education and the harmonization of training in Europe. I hope the book will be used by all our colleagues in Europe.

Ulrich Jaeger

PREFACE

The thalassaemias are hereditary conditions and amongst the most common serious monogenic disorders. However, the geographic spread of these conditions is uneven-rare in some populations and more common in others.

A patient with thalassaemia is more likely to be of Mediterranean origin, from the Middle East or from Asia, specifically, from zones previously or currently endemic to malaria. People of Western and particularly Northern European origin rarely present with a thalassaemia syndrome. However, the process of migration has introduced the thalassaemias to Europe, the Americas and virtually every other part of the world. Over the course of decades of research, the key components of the effective prevention and treatment of the thalassaemia have been clearly identified, such that the appropriate management of these conditions today rests to a great extent on political will.

The multi-organ pathology of the thalassaemias means that the most successful patient treatment programmes involve a number of medical staff, led by paediatricians and haematologists, but including other specialists in a multidisciplinary approach. However, this means that medical professionals not involved in such multidisciplinary groups, including primary care physicians and the staff of Accident and Emergency departments, rarely treat patients with thalassaemia. As a result, their knowledge of how to address acute complications in such patients is extremely limited.

This handbook aims to provide a brief evaluation of the situations in which a thalassaemia patient may seek help beyond the specialised environment he/she is used to. The layout of the handbook is intended to enable the medical professional in a busy clinical setting to draw essential information at a glance, supporting rapid, accurate as possible, decisions on how to proceed. The focus of this guide is on the treatment of acute complications in β-thalassaemia major and β-thalassaemia intermedia. Of course, this handbook does not seek to replace the expert advice of a patient's regular medical specialist. But where time is of the essence, it aims to serve as a ready-reference to minimise errors.

Dr Androulla Eleftheriou
Executive Director
Thalassaemia International Federation
BSc, MSc, PhD, Dip Mgt

01.
SIMPLE OVERVIEW OF THALASSAEMIA

WHAT ARE THE THALASSAEMIAS?

The thalassaemias are an inherited group of conditions that result from an imbalance in globin synthesis of the haemoglobin molecule, causing varying degrees of haemolytic anaemia and expansion of the bone marrow.

Alpha thalassaemias result from insufficient alpha-globin chain synthesis. Beta-thalassaemias result from inadequate beta-globin chain synthesis.

- Mild, clinically insignificant forms usually include the heterozygote states of α and β thalassaemia, otherwise referred to as alpha or beta thalassaemia traits. The greatest majority of these individuals are healthy carriers without significant anaemia and it is only microscopically that their red cells exhibit certain characteristics e.g. they are small (microcytic) or variable in shape (poikilocytosis).

- Clinically significant forms include:

For β-thalassaemia:

• Beta-thalassaemia major (TM) which results in transfusion dependent anaemia, usually with requirement for transfusion every 2-4 weeks

• Intermedia forms (TI) which result from either mild beta mutations or interactions of beta thalassaemia with other haemoglobin disorders such as HbE. These are not initially transfusion dependent.

For α-thalassaemia:

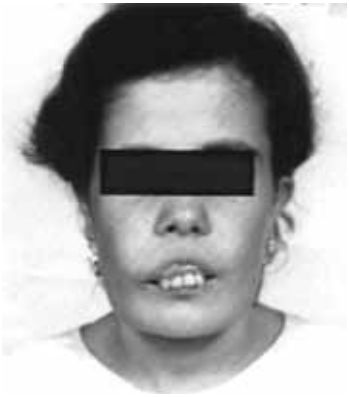
• HbH disease, which is a form of alpha thalassaemia and which may behave in clinical outcome as TI.

Patients with β-thalassaemia intermedia, HbE/β and HbH which are generally considered milder than TM, typically receive infrequent or sporadic transfusions, but may become increasingly transfusion dependent as (i) they age, (ii) if they develop an enlarged spleen or (iii) if they develop an acute infection.

Refer to TIF publications or website (www.thalassaemia.org.cy) for further details about the genetics of thalassaemia and more detailed information on the pathophysiology and clinical manifestation.

- Modern treatment with transfusion and chelation has radically altered the life expectancy and quality of life of patients with all clinically significant forms of thalassaemia and in particular of those with the most severe form, TM.

Dramatic advances in the medical treatment of thalassaemia have transformed the profile of the disease. It is now not uncommon for a patient to be an otherwise healthy parent.



WHAT ARE THE CONSEQUENCES OF THE THALASSAEMIAS?

1. Anaemia which results mainly from a combination of ineffective red cell synthesis and reduced red cell survival (haemolysis). Severe forms require regular transfusions of 2-4 units/month.

2. Iron overload which results from transfused blood (RBCs breakdown) and to a much lesser extent from increased dietary iron absorption (the latter being the main cause of iron load in patients with TI). One unit of blood (RBCs) contains 200mg of iron, which accumulates mainly in the heart, liver and endocrine tissues, unless appropriate chelation therapy is given.

- Heart failure from myocardial iron deposition is historically the commonest cause of morbidity and death in TM. This can be precipitated by inadequate chelation therapy, poor adherence to chelation therapy, infections or poor metabolic control (e.g. diabetic ketoacidosis).

- Liver disease can occur due to iron deposition in liver and infection from transfusion-transmitted viruses, especially hepatitis C and/or B.

- Common iron-related endocrine complications (mainly in TM) include:
  - diabetes mellitus - a significant percentage of patients are diabetic and on relevant medication.
  - hypothyroidism - many patients are already receiving thyroxine replacement.
  - hypoparathyroidism - may present with hypocalcaemia.

3. Spleen enlargement (variable)
   This used to be common in TM but is becoming less frequent since the improvement of clinical management protocols and the introduction of appropriate transfusion regimens. However, splenomegaly may still be common in TI patients.

- Always check for evidence of splenectomy. **If splenectomy has taken place**, consider infection with capsulated organisms. Otherwise note the spleen size - particularly for **infrequently-transfused patients**.

4. Expansion of bone marrow can occur:
   - within bone (intramedullary).
   - outside bones (extramedullary) - more likely in infrequently-transfused patients.
   - marrow expansion may present with:
     - neurological complications e.g. loss of power or sensation in the legs.
     - loss of bladder control.
     - unexplained chest shadow.
     - osteoporosis and bone fractures.
     - March fractures in the feet - a common cause of foot pain.
     - rib (micro) fractures - a common cause of chest pain.
     - fractures or microfractures of vertebrae, which may be associated with back pain.

WHAT IS THE STANDARD TREATMENT OF THALASSAEMIA?

Heterozygotes or carriers require no treatment but β-thalassaemia carriers in particular do require genetic counselling, in order to allow them to make informed choices when in an 'at risk' partnership (i.e. with another carrier).

Blood Transfusion

- TI patients (i.e. patients with β-thalassaemia intermedia or HbE/β-thalassaemia) require carefully considered sporadic transfusions and iron chelation therapy according to their level of iron load, mainly in the liver (see below).
- TM patients require regular transfusion every 2-4 weeks - keeping the pre-transfusion Hb >9g/dl (9.5 - 10 g/dl) and post transfusion Hb <15g/dl. TM patients will also require lifelong, daily iron chelation therapy tailored to their needs (see below).

> *For more detailed information on the management of thalassaemia, see 'Guidelines for the Clinical Management of Thalassaemia 2nd Edition Revised (2008)' on TIF's website at www.thalassaemia.org.cy*

Iron Chelation

EMA and FDA approved chelators to-date include:

- Desferrioxamine (Desferal). This is not an orally absorbed drug and is effective when given sc or iv as slow infusions.

Recommended dose: 20-40mg/kg/day in children and up to 60mg/kg/day in adults **after growth is complete**. This daily dose is infused subcutaneously over 10-12 hours via a portable infusion pump (there are various kinds of pumps, and the patient will usually be carrying one when visiting the Emergency Department or any surgery room).

The drug is diluted at home by the parents or the patients themselves.
In situations where hygiene at home is anticipated to be poor, a low threshold of suspicion for infection is recommended, either local at the site of injection or systemic.

> *In emergency situations such as heart failure, Desferrioxamine may be given intravenously dissolved in 100-500mls of saline over 24h.*

Patients on this drug are particularly prone to infection with iron-philic pathogens including **Yersinia enterocolitica**. Such infections present with fever and abdominal pain and may mimic acute appendicitis.

Therefore, it is advisable **not to rush to surgery** before excluding this infection. **Overdosing** should also be considered as this may occur, relative to the patients' degree of iron overload, and can lead to **retinal** and **auditory toxicity**.

- Deferiprone (Ferriprox, Kelfer) is an orally-administered drug. The recommended standard dose is 75mg/kg/day given as capsules in three divided doses. In severe iron overload and heart failure, it may be given in combination with Desferrioxamine.

  Be alert to a patient on this drug who **presents with fever**. A serious (but not very common) associated toxicity is **agranulocytosis** or **neutropenia**. A **blood count** and a blood culture should be considered as a first step, while considering stopping the drug either temporarily or permanently according to the severity of the episode.

  Severe joint pains, especially in the knees, may require the drug to be stopped. Consider pain control.

- Deferasirox (Exjade) is an orally-administered drug. The recommended starting dose is 20mg/kg/day which may go up to 40mg/kg/day. It is available as tablets, which are dispersed in water, or apple or orange juice and usually given as a once-daily dose. This drug may cause **a rise in serum creatinine, usually not indicative of renal failure**. Rarely, rises in ALT may occur at high doses or if body iron stores are reduced too quickly. The most common adverse events are GI disturbance, nausea, vomiting and diarrhoea.

> *Initiation of chelation is rarely warranted in A&E. The possible exception is acute heart failure, but preferably after consultation with a medical specialist/treating physician, or if a long waiting period in the unit is anticipated.*

02.
WHAT TO ASK FOR IN THE HISTORY?

As with all patients, particularly those with a chronic disease, establishing a careful history is very important.

Key questions to ask in thalassaemia patients should include the following:

i. Is the patient feeling unwell, are there **rigours, chills, fever**? Ask leading questions for severe systematic illness.

If there are **symptoms of infection**, consider:

- Klebsiella sepsis, which is common in heavily iron-loaded patients. This can result in septicaemia, urinary tract infection (UTI) or abscesses (cerebral, liver);
- Yersinia enterocolitica, which may cause abdominal pain, diarrhoea and lymphadenopathy (more likely with desferrioxamine therapy).

ii. Has the patient had **splenectomy**? If so, is he/she taking antibiotic prophylaxis? Pneumococcal, meningococcal and haemophilus infections are common in splenectomised patients.

iii. Is the patient transfused regularly? If so at what age did this begin? When was the patient last transfused? Answers may explain Hb levels; consider the possibility of transfusion-related reactions (short-term or belated).

iv. Is the patient taking chelation therapy, and if so, which regime? Consider the following:

- **Desferrioxamine** - look for sites of sc or iv infusion
  - watch for **Yersinia** and other iron-associated bacteria, including **Klebsiella**
  - ask about changes in eyesight and/or hearing
- **Deferiprone**
  - check for consequences of **reduced neutrophil counts**
  - ask about joint pains (particularly knees and elbows)

- **Deferasirox**
  - investigate renal and hepatic function
  - ask about upper and lower gastrointestinal disturbances

v. What is the current status and consequences of iron overload?

- **Iron load status** is a very important piece of information. Adult thalassaemia patients usually know their iron assessment record, including serum ferritin level and MRI results. If such assessment is not available, the treating physician should be contacted as soon as possible. Otherwise, questions to ask include:
  - Has the patient not been adequately chelated recently? This can precipitate heart failure.
  - What is the recent trend of serum ferritin? Is it increasing or decreasing?
  - Has the patient had an MRI scan or used other tools to assess liver or heart iron recently?

- Does the patient have heart complications?
  - Is the patient demonstrating decreasing exercise tolerance or breathlessness?
  - Is there peripheral oedema?
  - Is the patient experiencing palpitations?
  - Are there any symptoms of liver distension with abdominal discomfort?

- Does the patient have endocrine complications?
  - For diabetes, hypogonadism, hypothyroidism and hypoparathyroidism, check blood and urine sugar, plasma calcium and thyroid function tests

vi. Surgical history
- Has the patient had a splenectomy?
- Has the patient had gallstones or cholecystectomy?

vii. Fracture history - fractures are common in thalassaemia patients because of weakened bone structure. **It is important to know if the patient has a metal plate, which may exclude the possibility of an MRI examination.**

viii. Infections history
- Has the patient been infected with HBV, HCV or HIV?
- What vaccinations has the patient received? Most thalassaemia patients should have received meningococcal, pneumococcal, haemophilus influenzae and influenza vaccines.

- Has the patient travelled to malaria-endemic areas recently? Thalassaemia patients are vulnerable to malaria infection.
- Does the patient have an indwelling IV device (e.g. porta-cath)? Such a device may be used, albeit very rarely, to provide intensive chelation (when needed) with desferrioxamine. This, however is a potential source of infection and/or thrombosis.
- In the Mediterranean and Middle East regions, the possibility of Familial Mediterranean Fever (FMF) coexisting with thalassaemia should be considered in patients presenting with recurrent fever and pains.

Medications

- Is the patient being treated for hepatitis? Many thalassaemia patients are receiving the current standard for chronic HCV infection of combined Interferon and Ribavarin. Side effects such as flu-like symptoms (fever, chills, headache, muscle pains, nausea) or fatigue, depression, irritability, sleep disturbance and/or sexual dysfunction may be severe enough to bring the patient to the Emergency room. In addition, Ribavarin-associated haemolysis may increase a patient's need for blood transfusions and consequent intensification of iron chelation regime.
- Is the patient on anticoagulants? Heart disease and thrombotic conditions (more common in TI) may have necessitated anticoagulant treatment.
- Is the patient on antiplatelet drugs?
- Is the patient on hydroxyurea?
- Is the patient on any medication for the heart?
  e.g. ACE inhibitors, amiodarone, digoxin.
- Is the patient on medications for endocrine complications?
  e.g. insulin, thyroxin, calcium, vitamin D, oestrogens, testosterone.
- Is the patient being treated for osteoporosis? This is a common complication in thalassaemia patients and presents at a young age compared to the general population.

03.
WHAT TO LOOK FOR IN THE PHYSICAL EXAMINATION?

It is important to categorise the severity of the illness early. Look at the vital signs. Is the patient in a critical condition?

General appearance

- Skin may have a 'tanned' discolouration due to iron overload.
- Jaundice - from anaemia, liver complications or coexistence of Gilbert's syndrome.
- Short stature, short trunk and genu valgum (poor treatment in early life).
- Skull and facial changes (signs of TI or poorly treated TM).
- Skull enlargement with accentuation of the frontal and malar prominences and depression of the bridge of the nose. Upper maxillary enlargement affecting teeth spacing and leading to malocclusion.
- Signs of previous surgery – splenectomy, cholecystectomy, fracture surgery.
- Pubertal immaturity (as a sign of endocrine failure).

Vital signs

- Blood pressure - many TM patients have low BP in steady state. However this may also be a sign of cardiac decompensation or sepsis.
- Pulse - an irregular pulse is an iron-related complication of the myocardium and patients may be on anticoagulation for this.
- Temperature - sepsis is common and life threatening, particularly in iron overloaded and/or splenectomised patients.
- Respiratory rate, pulse oximetry, glucose check and level of consciousness (Glasgow Coma Scale) should be checks of priority.

Hepato-splenomegaly

- Most well-treated TM patients will not have had their spleen removed; assessment of its size may help guide diagnosis of the emergency problem.
- Assessment of liver size is also essential. Enlarged liver may result from cirrhosis, right-sided heart failure or extramedullary haematopoiesis.

Bone Marrow Expansion (BME)

BME is increasingly rare in well-transfused TM patients than in TI patients. Consequences include:

- Bone fractures, which are common in both TM and TI and often occur following trivial injury.
- Micro-fractures - back pain, rib/chest pain, March fractures of feet.

Neurological complications (see 4.5).

Other complications:

- Sepsis (see 4.1)

Potential sources/causes: cholecystitis, UTI, chest, teeth, endocarditis, brain abscess, meningitis.

Anaemia (see 4.2)

Evidence and consequences: pallor, jaundice, exertional dyspnoea, heart failure.

- **Heart** failure (see 4.3 and 4.4)

  - Cardiovascular examination is essential: arrhythmias and biventricular heart failure from myocardial iron may occur, usually after 10 years of age.
  - Clinical signs of congestive heart failure, including oedema, require emergency intervention (iv Desferal ± deferiprone orally).
  - Pulmonary hypertension is increasingly important, especially in TI.

- **Thrombosis** (see 4.7):

  DVT, chest pain, hypoxia, ECG changes.

- **Endocrine** complications (see 4.5)

  - Diabetic ketoacidosis? Hypocalcaemia? Hypothyroidism?

- **Neurological** complications (see 4.5)

  - Brain abscess (sometimes without fever) and stroke.

INITIAL APPROACH TO ANY PATIENT WITH THALASSAEMIA PRESENTING TO THE EMERGENCY DEPARTMENT

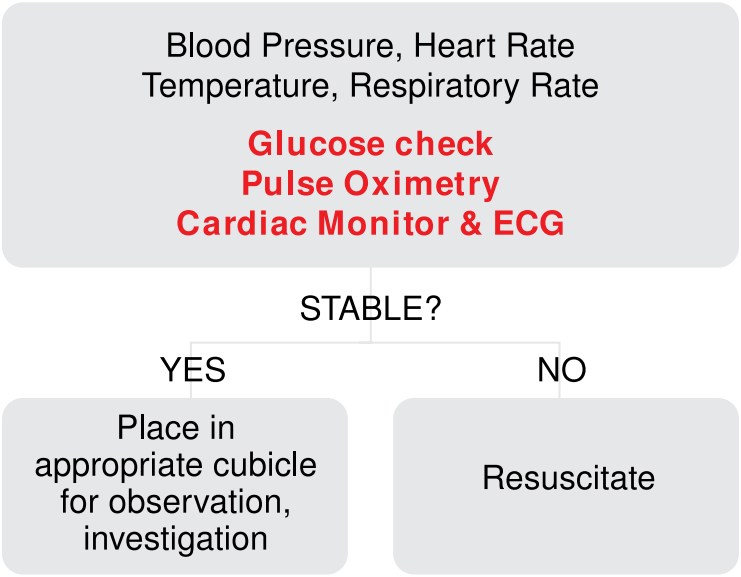
- **History** (see chapter 2)
- **Physical exam** (see chapter3)

Inform specialist or thalassaemia center as soon as possible.

Insert cannula or iv.

- **Labs** / Obtain sufficient samples for:

- **FBC** & differential (NB nuclated reds increase “white” count).
- **Group** extended phenotype & cross match.
- **Chemistry** BUN, Cr, eloctrolytes including calcium, LFTs blood glucose, TSH if necessary.
- **Urine** analysis for sugar, protein, haemolysis (chelation can give red urine) & pregnancy test.



04.
PROBLEM RELATED MANAGEMENT

4.1 SEPSIS

4.1 SEPSIS

Consider possible causes and investigations.

- Infections are typically bacterial and are often rapidly progressive and potentially fatal.
- Infections are the second cause of death in TM, after cardiac complications.
- Thalassaemia patients should be treated as if immunocompromised if they have a fever.

Common organisms involved include:

- Klebsiella, which may cause septicaemia and shock.
- A variety of other gram negative organisms.
- Cerebral abscesses.
- Yersinia enterocolitica, more commonly occurring in patients on desferrioxamine. Presents with fever, abdominal pain, diarrhoea lymphadenopathy. May mimic acute appendicitis. Difficult to detect and the microbiology laboratory must be alerted to this possibility when receiving samples of stool or blood.
- A variety of gram positive encapsulated organisms may cause infection, particularly in splenectomised patients.

Common foci of infection include:

- Renal tract - UTI, renal stones
- Respiratory tract
- Abdomen
  i. cholecystitis
  ii. colitis, appendicitis (but consider first excluding yersinia)
- Indwelling lines/catheters
- Cerebral (abscess)
- Heart (myocarditis and endocarditis)
- Septicaemia without a focus – consider splenectomy and severe iron load.

To address Sepsis follow **EGDT guidelines** (Early Goal Directed Therapy). [Rivers E et al NEJM 2001, 345(19)]:

- Provide early fluids (avoid overload since many patients have cardiac involvement due to iron toxicity - each case must be assessed according to cardiac status).
- Administer early antibiotics.

- Monitor parameters e.g. mean arterial pressure, central venous pressure, lactate.
- Provide inotropic agents if indicated.

Antibiotics

When giving antibiotics in the emergency unit to a thalassaemia patient, care should be taken to always cover for pneumococci, Haemophilus influenzae and meningococci if splenectomised.

Acute septicaemic patients should be covered for a range of gram negative pathogens including Klebsiella (ciprofloxacillin is often effective).

Should Yersinia - an intracellular organism - be suspected, ciprofloxacillin or trimethoprin are usually effective.

Local antibiotic sensitivities should be also considered and an infectious disease specialist may need to be consulted.

If there is an indwelling catheter, Teicoplanin or Vancomycin are the antibiotics of choice, especially if the patient has recently been hospitalised, requiring cover for MRSA.

If a patient has a fever always admit, unless you are advised by the treating thalassaemia specialist that there is no need to do so.

SUSPECTED INFECTION/FEVER

Always admit except for cases cleared by thalassaemia specialist.

Send: cbc, chem, urine

SEPTIC FOCUS?

NO

- Chest X-ray PA & lat
- Urine Culture
- Blood Cultures x 2
- Stool & Blood Yersinia Cultures
- FOCUS STILL UNCLEAR - ü Consider U/S or CT, Echo, LP, panoramic (dental), non-infectious causes e.g. drugs, DVT

(see next chart)

YES

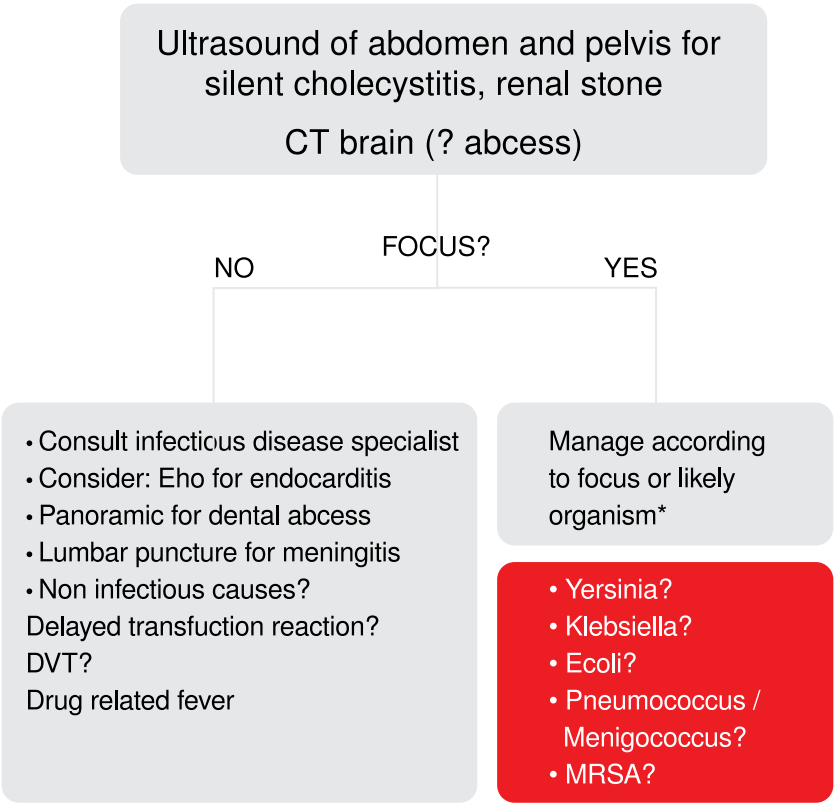
- Rt Hypochondrial pain?
  Cholecystitis
- GI symptoms?
  Yersinia
- Neurological symptoms?
  Cerebral abscess, meningitis
- Renal pain?
  Stones
- Indwelling catheter?
  Infected
- Respiratory symptoms?

Manage according to focus

Once appropriate cultures obtained **DO NOT DELAY** starting antibiotics until focus/organism identified. Start broad spectrum antibiotics.

FEVER: FOCUS STILL UNCLEAR

Always admit except for cases cleared by thalassaemia specialist.



04.
PROBLEM RELATED MANAGEMENT

4.2 ANAEMIA

4.2 ANAEMIA

Consider possible causes and investigations.

Patients with TM should be on a regular transfusion program to keep Hb >9.0g/dl (9.5 – 10 g/dl) - see TIF Guidelines for the Clinical Management of Thalassaemia 2nd Edition Revised (2008).

Values below this may result from:

- delayed transfusions
- delayed transfusion reactions
- bleeding (e.g. GI from peptic ulcer)

Patients with TI have a wide range of steady state Hb (6-9g/dl).

- Ask the patient, family or treatment centre the patient's usual Hb level.
  A sudden decrease in Hb may result from
  - parvovirius infection (B19) (may lead to Aplastic crisis)
  - other acute infections
  - delayed transfusion reactions
  - enlarged spleen (subacute)
  - folate deficiency
  - G6PD deficiency

Transfusion should only be given as a life-saving measure, for example in cases of severe bleeding or anaemia with instability. Before embarking on transfusion:

- Consult with the treating physician and blood bank specialist
- Ensure that the Hb is significantly lower than the steady state
- Establish patient history of transfusion reactions
- Request extended red cell phenotype

TM patients usually receive blood <10 days old that is at least Kell negative and matched for extended rhesus phenotype - refer to TIF Guidelines for the Clinical Management of Thalassaemia 2nd Edition Revised (2008).

04.
PROBLEM RELATED MANAGEMENT

4.3 DYSPNOEA

4.3 DYSPNOEA

Consider possible causes and investigations.

- Heart failure resulting from cardiomyopathy. This has a potentially rapid progression from severe to fatal.
- Check BP, pulse rhythm (associated dysrhythmia is common), JVP, liver congestion.
- Abdominal pain may be presenting feature of congestive cardiac failure (CCF).
- Peripheral oedema.
- May be precipitated by myocarditis, sepsis, poor recent chelation or poor chelation adherence.
- Consider immediate iv DFO infusion unless contraindicated (allergy, suspected Yersinia infection) - 40-50mg/kg day as a continuous iv infusion dissolved in 100-500ml of saline.
- Ask if a recent cardiac MRI has been done.
- Consider MRI or echocardiogram if MRI is not available.

- Dysrhythmia - patients with myocardial iron loading (present or past) are at increased risk of a variety of dysrhythmias, which can precipitate heart failure.

Check ECG – consider 24h monitoring.

- Pericarditis (see section 4.3) - occasional complication of iron-mediated cardiomyopathy.
- listen for pericardial rub (inflammation) or faint sounds (effusion).
- consider echocardiogram.

- Pulmonary embolism
- thalassaemia patients, particularly TI, are susceptible.

- Pulmonary hypertension
- thalassaemia patients, particularly TI, are susceptible.

- Anaemia (acute - see section 4.2)

- Rib micro-fractures and splinting

04.
PROBLEM RELATED MANAGEMENT

4.4 OEDEMA

4.4 OEDEMA

Consider possible causes and investigations.

- Congestive heart failure (see 4.3)

- Venous thrombosis
- red cells are prothrombotic, so more likely in TI.
- may present with typical leg DVT.
- other sites include mesenteric blood vessels.
- multiple small pulmonary emboli (PE).

- Hypoalbuminemia
- renal protein loss - check urine protein.
- liver failure - check LFTS.

- Leg ulcers more common in TI - examine the legs.

- Acute renal failure

04.
PROBLEM RELATED MANAGEMENT

4.5 CHEST PAIN

4.5 CHEST PAIN

Consider possible causes and investigations.

- Pulmonary embolism
- may be a single, large embolus but often repeated small emboli.
- consider requesting d-dimer, high resolution CT.

- Rib (micro) fracture
- palpate chest wall - pain on gentle pressure.

- Pericarditis
  A complication of iron overload.
- listen for heart sounds, do ECG, echocardiogram.

- Congestive heart failure
  May present as abdominal rather than chest pain, caused by distension of the liver capsule.

- Acute coronary syndrome
  Very unlikely but should be considered.

04.
PROBLEM RELATED MANAGEMENT

4.6 ABDOMINAL PAIN

4.6 ABDOMINAL PAIN

Consider possible causes and investigations.

- Cholecystitis
- pigment gallstones are common.
- consider abdominal ultrasound.
- if obstructed (bilirubin in urine, ± ↑ Alk Phos), consider ERCP.

- Yersinia infection
- iron-loving organism more commonly seen in patients receiving desferrioxamine.
- requires specific culture conditions for diagnosis from blood or faeces. Contact microbiology for Yersinia culture procedures.
- desferrioxamine should be stopped until diagnosis is confirmed or excluded

- Portal vein thrombosis
- more commonly seen in TI and splenectomised TM patients.

- Mesenteric infarction
- more commonly seen in TI and splenectomised TM patients.

- Renal stone
- common in TM due to hypercalciuria.
- consider renal ultrasound and urine microscopy (red cells).

- Peritonitis
  Especially in splenectomised patients.

- Gastroenteritis

- Acute appendicitis
  Should be considered after exclusion of Yersinia.

04.
PROBLEM RELATED MANAGEMENT

4.7 HEADACHES

4.7 HEADACHES

Consider possible causes and investigations.

Clues in patient history: consider duration, whether recurrent, whether increasing in severity ("the worst headache I have ever had"), whether onset is sudden and whether the episode is accompanied by vomiting.

Clues in physical examination: check for pyrexia, neurological signs, papilloedema, altered level of consciousness, stiff neck.

Investigations: computerised tomography (CT) with contrast (more common in hospital settings and more rapid than MRI), although MRI is more sensitive to cerebral abscesses.

- Cerebral abscesses
  Klebsiella may be the causative agent. Cerebral abscess commonly presents as headache, fever and/or neurological features, but often with a non-specific prodromal phase.

  Iron overload, especially in TM, increases patient susceptibility to infection with Klebsiella and other iron-loving micro-organisms. A high index of suspicion should therefore exist to confirm or exclude diagnosis with these pathogens.

- Meningitis - especially if the patient is splenectomised.

- Sinusitis - more commonly seen in TI due to distortion of sinuses (extramedullary erythropoiesis).

- Otitis media - more commonly seen in TI patients due to distortion of sinuses.

- Extramedullary haemopoietic mass - rarely occurs intra-cranially.

- Drug-related headaches
  (e.g. interferon, used in the treatment of chronic HC and/or HB).

- Consider other common non-thalassaemia related causes.
  e.g. migraine

HEADACHES

- Worst Headache ever
- Neurological Deficits
- Signs of increase intracranial pressure

→ Physical Examination
- Full neurological examination
- Fundoscopy Consult Neurologist

Insert I.V.
Blood Studies (Creatinine)

Brain (CT) without contrast

→
- Rule out sub-arachnoic Haemorrhage
- Rule out Intra-cranial Bleeding
- Rule out Ischemic Stroke

If CT Scan Negative
- Do Lumbar Puncture
- Start antibiotics if infection suspected

CT with contrast or MRI if available

→
- Rule out cerebral abscess
- Rule out Tumour
- Rule out Sinus thrombosis
- Rule out Sinusitis

04.
PROBLEM RELATED MANAGEMENT

4.8 SYNCOPE AND ALTERED LEVEL OF CONSCIOUSNESS

4.8 SYNCOPE AND ALTERED LEVEL OF CONSCIOUSNESS

The patient with syncope or pre-syncope symptoms must be admitted for investigation.

Consider causes include the following.

- Tachydysrhythmias, such as atrial fibrillation or ventricular tachycardia.
  - may result from iron-mediated cardiomyopathy, even after iron has been removed with intensive chelation.
  - may be exacerbated by electrolyte disturbances such as hypocalcaemia.
  - consider 24h motoring.

- Repeated pulmonary emboli - small pulmonary emboli are quite common in TI but may also occur in TM (red cells are prothrombotic in thalassaemia).

- GI bleed
  - drugs - e.g. non-steroidal (also take into account side-effects of iron chelation drugs, such as upper GI ulceration).
  - varices - some older patients have varices secondary to portal hypertension.

- Postural hypotension or vasovagal syndrome
  - many TM patients have low resting blood pressure, and inadequate postural response may cause syncope.

- Brain abscess (see section 4.9)

- Hypovolaemia (fluid loss, acute severe anaemia)

In all cases call an expert, get clearance from next of kin and admit.

04.
PROBLEM RELATED MANAGEMENT

4.9 NEUROLOGICAL COMPLICATIONS

4.9 NEUROLOGICAL COMPLICATIONS

Causes to consider.

Focal deficits

- Extramedullary haematopoiesis - may occur anywhere but often results in spinal deposition with weakness, paraesthesia and sensory loss in the legs. Difficulty in bladder control or urgency may also be a presenting feature.

- Cerebral abscess - bacteraemia may result in central brain abscess, often reported with Klebsiella pathogen. Symptoms may be non-specific, such as malaise and headache. Brain MRI is recommended where available.

- Meningitis - more likely to be seen in splenectomised patients

- Spinal thrombosis - rare complication which presents with acute motor or sensory feature, often with a neurological dimension. MRI is the initial investigation of choice.

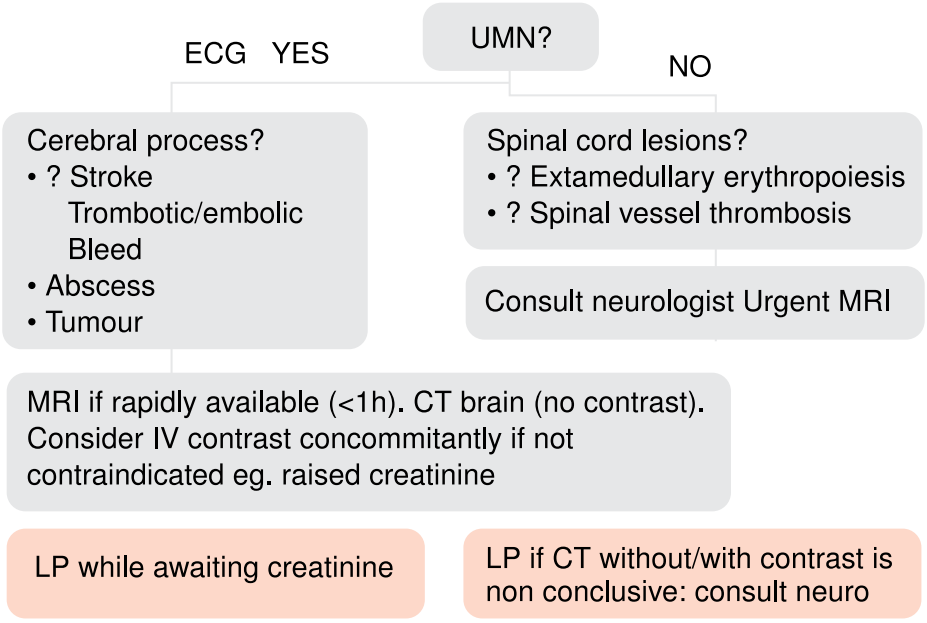
Other neurological complications

- Deteriorating hearing or tinnitus.
  - known side-effect of desferrioxamine overdosing - consider iron chelation regimen.
  - stop desferrioxamine and seek audiometry assessment.

- Change in visual acuity or colour vision.
  - known side-effect of desferrioxamine overdosing - consider iron chelation regimen.
  - stop desferrioxamine and seek electro-retinography.
  - consider diabetic retinopathy, which may also result in sudden visual deterioration.

FOCAL NEUROLOGICAL DEFICIT

Upper Motor Neurone (UMN)



04.
PROBLEM RELATED MANAGEMENT

4.10 BACK PAIN

4.10 BACK PAIN

Causes to consider

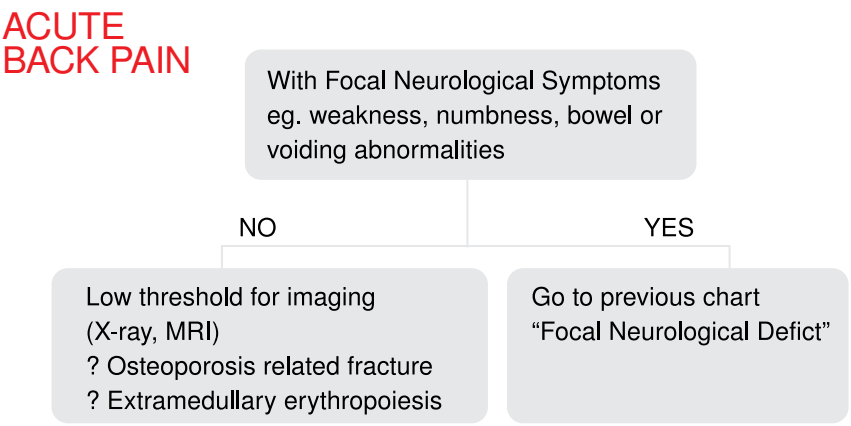
- Osteoporosis
- reduced bone mineral density of the spine is reported in around 50% of adult thalassaemia patients.
- causes micro-fractures and full compression fractures of the vertebral bodies.

- Degenerative changes of the intervertebral disc - a common cause of back pain.
- More common in the lower thoracic and upper lumbar spine (compared to non-thalassaemic patients, more commonly affected in the two lower lumbar discs).

- Extramedullary haemopoietic masses
- may cause spinal cord compression.
- neurological signs of cord compression more likely to be present than pain.

Flattening of the vertebral bodies (platyspondyly) in the lumbar and thoracic regions.

- Investigations
- exclude neurological deficit on examination.
- spinal X-ray and MRI (best method of assessing extramedullary haematopoiesis and also disc degeneration).



04.
PROBLEM RELATED MANAGEMENT

4.11 TRAUMA

4.11 TRAUMA

In thalassaemia, be alert to possible:

- Splenic rupture

- Bone fracture
- occurs with relatively minor trauma
- sites include:
- ribs
- spine
- hips
- metatarsals

Adhere to Acute Trauma Life Support (ATLS) guidelines
(see www.facs.org/trauma/atls/information.html)

Early involvement of general surgeon.

Special transfusion requirements (see section 4.2).

ABOUT THALASSAEMIA INTERNATIONAL FEDERATION

TIF

The Thalassaemia International Federation (TIF) is a non-profit, non-governmental organisation founded in 1987 by a small group of patients and parents representing mainly National Thalassaemia Associations in Cyprus, Greece, UK, USA and Italy - countries where thalassaemia was first recognised as an important public health issue and where the first programmes for its control, including prevention and clinical management have started to be promoted and implemented.

MISSION

The development of National Control Programmes, including both components of prevention and management and the promotion of their establishment across 'affected' countries.

VISION

Establishment of equal access to quality health care for every patient with thalassaemia wherever he or she may live.

OBJECTIVES

The objectives of the Federation in addressing effectively the needs of the world thalassaemia family have since its establishment remained the same and include:

• The establishment of new and promotion of existing National Thalassaemia Patient/Parents Associations

• Encouraging, motivating and supporting studies and research for further improving prevention strategies, clinical care and for achieving the long-awaited final cure and • Extending the knowledge and experiences gained from countries with successful control programmes to those in need.

TODATE

TIF has developed into an umbrella federation with 102 member associations, from 60 countries of the world, safeguarding the rights of patients for

quality health care. TIF since 1990 has organised 60 national/local, 6 regional workshops and 14 international conferences. TIF has an extensive range of educational material including 15 books published, translated some in more than 25 languages and distributed worldwide as free of charge service. Target audience: patients/parents, medical professionals and the community at large.

JOIN US, become a member of our world thalassaemia family

‘’Knowledge is our power’’
‘’Unity is our strength’’

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