Management of Children with Thalassaemia

University Hospitals of Leicester NHS NHS Trust

EMSTN East Midlands Sickle Cell and Thalassaemia Network

Trust reference: E7/2019

Introduction & who this guideline applies to

Concise guideline for overall management of paediatric patients with Thalassaemia

Relates to paediatric haematology teams, paediatric emergency medicine, paediatric medicine and specialties (nephrology, urology, microbiology, endocrinology, surgery, gastroenterology, anaesthesia, orthopaedics, ophthalmology, ENT)

Guidelines based on:

- National Haemoglobinopathy Peer Review Standards 2014
- NICE:sickle cell acute pain episode: management of an acute painful sickle cell episode in hospital (2012)
- UK Thalassaemia Society - Standards for the Clinical Care of Children and adults with Thalassemia 3rd edition 2016
- Caring for people with Sickle cell and thalassaemia syndromes: RCN competencies: a framework for nursing staff (2011)
- A sickle cell crisis? A report of the National Confidential Enquiry into Patient Outcomes and Death (2008)
- Transition: improving the transition of young people with long term conditions (2006)
- BSH Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias

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1 INTRODUCTION

1.1 This clinical policy has been compiled by the paediatric haemoglobinopathy team. It has been formulated following reviews in service, based on current practice and research including the Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK (http://www.ukts.org).

1.2 It is intended for the guidance of in and out-patient management. Cases need to be assessed individually and the management tailored appropriately. The opinion of the paediatric haemoglobinopathy team should be sought where necessary.

2 DEFINITIONS

Haemoglobinopathy	A group of conditions where the pathology relates to abnormalities in haemoglobin production or function. Includes haemoglobin variants and thalassaemias.
Thalassaemia	A group of conditions characterised by quantitative defect in alpha or beta globin production resulting in impaired haemoglobin production.
Child	Trust transition age for adult care is > age 16. For the purposes of this policy a child is a person up to and including 16 years of age.
Adolescent	This includes teenagers and young adults age up to 18 years. Some of these will be managed in the paediatric service and some in adult service

3 THALASSAEMIA DISORDERS

3.1 The thalassaemias are genetic disorders of haemoglobin production. Most are inherited in an autosomal recessive pattern and in the case of β thalassaemia major are due to mutations of the β globin gene causing reduced or absent production of β globin and as a result, Hb A. This results in globin chain imbalance and subsequent ineffective erythropoiesis, anaemia and bone marrow expansion.

3.2 Most of the patients seen can be classed as having β thalassaemia major or β thalassaemia intermedia. Patients with β thalassaemia major need regular transfusions from infancy to maintain normal growth and development. Those with thalassaemia intermedia (usually Hb E / β thalassaemia) may only require transfusion for specific indications. Untreated anaemia results in cardiac failure.

3.3 Other than transfusion therapy, standard treatment also consists of iron chelation therapy usually started a year after regular transfusions have begun. Good compliance with this treatment is necessary to prevent iron induced toxicity to the heart, liver and endocrine organs.

3.4 Diagnosis of β thalassaemia is usually made in the neonatal period following identification of ‘at risk’ pregnancies, and by the neonatal screening programme. However not all cases of thalasaemia intermedia will be identified this way. Older children with thalassemia may also present following migration of families to the UK from high prevalence regions.

4 MANAGEMENT OF THE NEWLY DIAGNOSED CHILD

4.1 All infants identified by the neonatal screening programme should either have an initial home visit organised by the community specialist nurse counsellor/health visitor or be seen by the paediatric haemoglobinopathy team in secondary care. This should be planned within 2 weeks of the provisional diagnosis.

4.2 Following careful history and examination, particularly to monitor growth and development, the diagnosis should be established and confirmed as below:

Routine baseline investigations

- FBC and blood film
- Haemoglobin analysis by HPLC
- Genetic analysis for β globin mutations
- A thalassaemia genotype and Xmn status
- G+S and red cell phenotype
- G6PD screen

4.3 Of note the diagnosis of β thalassaemia major is **clinically determined** and dependent on failure to thrive, transfusion dependency and usually evident by the age 1 year. It is important not to label a neonate as thalassaemia major on receipt of the neonatal screening result.

Haemoglobinopathy screen, particularly for thalassaemia intermedia, should be repeated at 1 year.

4.4 Older children presenting with an uncomplicated thalassaemia and those scheduled to start transfusion therapy:

- viral hepatitis screen
- serum ferritin and LFTs

Additional Investigations

4.5 Other tests may be indicated based on presentation eg acutely presenting untreated patients:

- Bone profile (Ca, phosphate)
- Glucose
- TFTs
- ECG
- USS abdomen
- CXR
- Echocardiogram
- Septic screen
- Ferritin

5 MONITORING OF CHILDREN WITH THALASSAEMIA

5.1 All children with β thalassaemia major require initial monthly review with monitoring of:

- growth

- development
- feeding & weight gain
- history of infections
- bone deformity
- presence of organomegaly
- head circumference
- FBC

5.2 More frequent monitoring may be required for those with increasing symptoms.

5.3 Appropriate written information should be made available and details of community support networks explained. Hand held patient information records are encouraged. A copy of the clinic letter is sent to the parent and GP.

5.4 Family members should be offered screening, particularly parents and children.

5.5 For patients previously treated outside of the UK, enquiry should be made into:

- age/mode of diagnosis
- transfusion history
- chelation history
- history of complications

5.6 A careful evaluation for complications should be carried out.

6 TRANSFUSION POLICY

- Transfusion administration, monitoring and management of transfusion reactions should be according to the trust Blood transfusion UHL policy. http://insitetogether.xuhl-tr.nhs.uk/pag/pagdocuments/Blood%20Transfusion%20UHL%20Policy.pdf
- Phlebotomy for crossmatch should be done to minimise absence from school.
- Patients will be admitted to the ward by the allocated nurse, weight and observations recorded. A review by the junior doctor covering the day unit will be done only if required – routine transfusion is a nurse led service.
- Prompt cannulation within 30 minutes will be organised by the daycare team, with no more than 3 attempts by one person.
- If possible, Saturday transfusion sessions should be available to all patients.
- An accurate transfusion record will be recorded for each patient with documentation of transfusion date, volume, pre-transfusion haemoglobin, ferritin and monthly blood parameters for monitoring adverse effects of chelation.
- **All RBC units must be phenotypically matched (Rhesus and Kell).**

Decision to Start Transfusions

6.1 This is a clinical decision based on

- Evidence of severe anaemia (usually <70g/L measured 14 days apart)
- Failure to thrive
- Thalassaemic bone deformity

6.2 Patients will be monitored for signs and symptoms indicating need for transfusion. The aim is to initiate transfusion to prevent the complications of anaemia and bone marrow expansion. Attention should be paid to:

- Worsening fatigue
- Poor feeding and impaired growth
- Developmental delay or regression
- Frequent infections
- Worsening splenomegaly
- Facial bone expansion

6.3 Factors contributing to anaemia should be investigated

- Iron deficiency
- G6PD deficiency
- Intercurrent infection

Transfusion Algorithm

6.4 Aim to maintain pre transfusion Hb 95-100g/L. Transfusions are given 3-4 weekly.

Prior to commencing the transfusion programme, potential complications of transfusion must be discussed and documented:

1. Transfusional iron overload
2. Transfusion transmitted infection – aim for Hepatitis B/C + HIV screen prior to starting
3. Transfusion reactions
4. Antibody formation
5. Ensure hepatitis B vaccination status satisfactory

Annual Investigations (see Appendix 1)

6.5 The following should be organised at annual visit or the first transfusion in January:

- Average pre-transfusion haemoglobin
- Total blood volume transfused
- Average ferritin
- Annual virology (hepatitis B,C, HIV) and hepatitis B surface antibody
- Audiology and ophthalmology (for those on chelation therapy)

Iron Chelation

6.6 Follow the trust Iron chelation therapy in transfusional iron overload for inherited anaemias UHL childrens hospital guideline.

http://insitetogether.xuhl-tr.nhs.uk/pag/pagdocuments/Iron%20Chelation%20Therapy%20in%20Transfusional%20Iron%20Overload%20for%20Inherited%20Anaemias%20UHL%20Childrens%20Hospital%20Guideline.pdf

7 MANAGEMENT OF COMPLICATIONS

Endocrine Complications

7.1 Endocrine complications predominantly due to iron overload are not uncommon. Delayed puberty and hypogonadism are most commonly seen. Endocrine failure is difficult to reverse but can be prevented with iron chelation therapy and should be screened for and actively managed.

Monitoring:

- Growth monitoring from birth/diagnosis
- Sitting and standing height / weight from age 10
- Annual assessment of pubertal development from age 10
- Random glucose 3-6 monthly from age 10
- Glucose tolerance test from puberty or age 10 if positive family history of diabetes
- Bone profile 3-6 monthly from age 10
- Annual TFTs from age 10
- Vitamin D annually from age 2
- DexaScan from age 16
- Annual morning cortisol from age 2

7.2 All complications should be discussed and jointly managed with the paediatric endocrinology team.

7.3 Declining height velocity should be investigated. Desferrioxamine toxicity and growth hormone deficiency should be considered.

7.4 Delayed puberty should be investigated. Hormone replacement therapy should be considered.

7.5 Exercise and adequate consumption of diet rich in Vitamin D / calcium should be encouraged.

Liver Complications

7.6 Liver disease is more common in adults. Hepatic fibrosis can be found in children who are not well chelated. This is due to iron loading, biliary disease, viral hepatitis and potential drug toxicity.

7.7 Clinical presentation includes acute and chronic hepatitis, obstructive jaundice, cholangitis, portal hypertension, hepatic failure and hepatocellular carcinoma.

Monitoring:

- Monthly LFTs
- Ferriscan monitoring for iron load assessment with aim to maintain liver iron between 3-7mg/g dry weight
- Annual serological testing for viral hepatitis (anti-HCV, HBsAg and HepB core antibody)

7.8 All complications should be discussed and jointly managed with the tertiary paediatric hepatology team.

7.9 Liver biopsy may be needed for unexplained changes to liver function.

7.10 Hepatitis C should be actively treated.

7.11 USS should be considered to screen for gallstones if obstructive picture.

Cardiac Complications

7.12 Cardiac complications are less commonly seen in children.

Monitoring:

- Cardiac T2* MRI monitoring should be organised from age 8
- Assessment by paediatric cardiology team indicated if symptoms or signs of cardiac disease are present

Acute Decompensation and Sepsis

7.13 There is increased risk of sepsis and subsequent increased mortality particularly in splenectomised patients.

Risk factors include:

- Previous splenectomy
- Use of central venous catheters
- Iron chelation therapy
- Transfusion transmitted infection

7.14 Fever should be investigated and treated promptly.

7.15 Splenectomised patients with fever should be admitted for IV administration of broad spectrum antibiotics as per **Sepsis UHL Childrens Hospital Guideline**.

7.16 For central venous catheter associated sepsis vancomycin/teicoplanin should be considered.

Chelation therapy should be interrupted during acute illness due to sepsis

7.17 Yersinia infection should be considered in patients presenting with fever and abdominal pain. Stoolculture can be tested but the request form must specifically state for Yersinia to ensure correct incubation.

7.18 All patients presenting with fever on chelation therapy with deferiprone and deferasirox should have an urgent FBC organised to exclude neutropenia/agranulocytosis.

7.19 Other presenting complications include:

- Dysrhythmias, heart failure
- Acute hepatitis (consider viral, chelation associated)
- Endocrinopathy (tetany due to hypoparathyroidism, hyper/hypoglycaemia)

7.20 Urgent specialist haematology input is necessary with input from paediatric specialists when managing these complications.

8 SPECIALIST ANNUAL REVIEW (SEE APPENDIX 1)

8.1 Annual specialist outpatient review should be organised for all patients. In addition, a consultation should be offered for patients scheduled to commence regular transfusion, initiation or planned change of chelation therapy or for difficult management issues eg decision for splenectomy, endocrine, liver, cardiac complications, planning for complex surgery.

8.2 Copies of correspondence should be sent to parent, local centre, GP and community services.

At this review:

8.3 Enquire into symptoms, tolerance of transfusion therapy (venous access issues, transfusion reaction), tolerance of chelation therapy (compliance, side effects), school attendance and progress.

8.4 Monitor growth (weight, sitting / standing height) and pubertal development (from age 10).

8.5 Examine for facial bone / dental deformity, organomegaly.

8.6 Review transfusion record for the year (ml/kg – use mid year wt), review average pre-transfusion Hb.

8.7 Review chelation regimen and outcome of efficacy monitoring investigations. Assist adherence by reviewing complications and instituting appropriate management.

8.8 Review investigations for monitoring of chelation safety eg audiometry, ophthalmology, renal function, liver function.

8.9 Review vaccination status – Hepatitis B, pneumovax (for splenectomised patients).

8.10 The annual transfusion record should be reviewed and updated.

8.11 Referrals for specialist care (endocrinology/hepatology/cardiology) should be organized following review in the paediatric haemoglobinopathy MDT clinic.

8.12 Patients who are not brought on 3 consecutive occasions or young infants on the first appointment should be followed up by the community/haemoglobinoapthy nursing team and a letter sent to GP and family/patient. Referral of children who move to another region should be organised by the specialist centre and community teams to ensure appropriate local community input.

9 SURGERY INCLUDING SPLENECTOMY

9.1 All elective surgical procedures under general anaesthetic should be discussed and planned to ensure patients are optimised prior to the intervention to prevent acute decompensation (particularly due to cardiac and endocrine disturbance).

9.2 The procedure should be planned no later than a week after a scheduled transfusion to ensure optimal haemoglobin.

9.3 A thromboprophylaxis risk assessment should be carried out and treatment instituted as appropriate.

9.4 Patients with high and/or increasing transfusion requirement should be considered for splenectomy following a careful evaluation of post splenectomy sepsis.

9.5 If not previously vaccinated, 1 month prior to scheduled splenectomy the patient should receive pneumococcal, HiB conjugate, Men C conjugate vaccinations at the GP surgery.

9.6 5 yearly pneumococcal vaccination and antibiotic prophylaxis should be recommended in line with trust guideline B13/2007 Guidelines for the prevention of infection in patients with absent or dysfunctional spleen. http://insitetogether.xuhl-tr.nhs.uk/pag/pagdocuments/Spleen%20(Absent%20or%20Dysfunctional)%20Infection%20Prevention%20UHL%20Guideline.pdf

First line antibitoic prophylaxis choice is phenoxymethylpenicillin.

Dosage:

- Birth to 1 year 62.5mg phenoxymethylpenicillin suspension BD
- 1 to 4 years 125 mg phenoxymethylpenicillin suspension BD
- > 5 years 250 mg phenoxymethylpenicillin suspension/tablets BD

For those children who are genuinely allergic to Penicillin, Erythromycin is prescribed instead.

Dosage:

- < 2 years 125 mg Erythromycin BD
- 2-7 years 250 mg Erythromycin BD
- > 8 years 500 mg Erythromycin BD

9.7 Thrombocytosis is common post splenectomy. Discuss management with haematology team.

10 BONE MARROW TRANSPLANTATION

10.1 The option of bone marrow transplantation as a curative intervention should be discussed with all families.

10.2 Tissue typing of parents, child and siblings should be considered from age 12 – 18 months.

10.3 Referral to Birmingham Children's Hospital for a detailed discussion of this intervention should be considered.

10.4 Collection and storage of cord blood from siblings should be offered if available.

11 TRANSITION TO ADULT SERVICES

11.1 Use trust Transitional care UHL policy.

http://insitetogether.xuhl-tr.nhs.uk/pag/pagdocuments/Transitional%20Care%20UHL%20Policy.pdf

12 THALASSAEMIA INTERMEDIA / NON-TRANSFUSION DEPENDENT THALASSAEMIA

12.1 This heterogeneous group of patients are not dependent on lifelong transfusions. Transfusions are usually required intermittently.

12.2 The genetic mutations responsible for the phenotype can be variable and can include homozygous beta thalassaemia with milder beta globin gene mutations. Many additional genetic mutations can ameliorate the severity of thalassaemia.

12.3 Some of the patients in this group have a severe phenotype with severe anaemia requiring transfusions, extramedullary haemopoesis and problems with growth and development. The vast majority, however, have moderate symptoms.

Monitoring

12.4 Patients with thalassaemia intermedia should be seen in the outpatient clinic 3 monthly:

- Enquire into symptoms
- Monitor growth (height, weight) and development (Tanner staging for puberty from age 10) 6 monthly
- Examine for facial bone and dental deformity, organomegaly
- Iron overload assessment from age 10 (repeat 1-2 yearly if moderate loading). Otherwise repeat 5 yearly
- From age 15: cardiac assessment including ECHO and DEXA scan
- Routine blood tests (FBC, reticulocyte count, U+E, LFTs, urate, ferritin) 3-12 monthly depending on symptoms

12.5 All non-transfused patients should receive folic acid.

12.6 An acute anaemic episode should be investigated.

12.7 Consider viral sepsis including parvovirus, acute haemolysis eg due to G6PD deficiency when unwell. Depending on symptoms a transfusion may be necessary.

Indications for regular transfusion therapy

- Worsening symptomatic anaemia, eg <70g/L
- Faltering growth, delayed puberty
- Bone expansion due to medullary erythropoiesis
- Pulmonary hypertension
- Symptomatic extramedullary haemopoiesis

12.8 This should be carefully discussed with the patient/parents.

12.9 The same transfusion principles apply for thalassaemia intermedia patients.

12.10 Compression symptoms due to extramedullary masses should be investigated with MRI. Symptomatic growth should be managed with a period of regular transfusion, radiotherapy and hydroxycarbamide.

12.11 Patients with symptomatic splenomegaly, increasing transfusion requirement or hypersplenism may benefit from splenectomy. All cases should be discussed at EMSTN Regional MDT.

12.12 Hydroxycarbamide therapy may benefit some patients (requires discussion at EMSTN Regional MDT).

Iron chelation for thalassaemia intermedia

12.13 Use trust Iron chelation therapy intr asnfusional iron overload for inherited anaemias UHL childrens hospital guideline.

http://insitetogether.xuhl-tr.nhs.uk/pag/pagdocuments/Iron%20Chelation%20Therapy%20in%20Transfusional%20Iron%20Overload%20for%20Inherited%20Anaemias%20UHL%20Childrens%20Hospital%20Guideline.pdf

13. REFERRAL BETWEEN ORGANISATION

13.1 All encounters with the patient including in-patient admissions, daycase attendance for transfusion, out-patient clinics and annual reviews are documented by electronic letter.

13.2 Copies of these electronic letters should be sent on to the patient/parents and be made available when referring between organisations.

14. EDUCATION AND TRAINING

Regular teaching provided in emergency department, ward 27 training days, paediatric specialist trainees training days and nursing training programmes.

15. MONITORING AND AUDIT CRITERIA

Key Performance Indicator	Method of Assessment	Frequency	Lead
100% Annual Review completion	Prospective data collection by data manager	Monthly	Dr K Bhuller
National Peer review standard audits (vaccination, iron chelation outcomes)	Prospective data collection by data manager	Monthly	Dr K Bhuller

16. KEY WORDS

Thalassaemia, transfusion

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Dr Kaljit Bhuller – Consultant in Paediatric, Teenage & Young Adult Haematology	**Executive Lead** **Chief Nurse**
Details of Changes made during review: ○ **Signpost to trust iron chelation guideline for patients with haemoglobinopathy** ○ **Reference BCSH iron chelation guideline**	

APPENDIX 1 TABLE 1: INVESTIGATION AND INTERVENTION

Investigation or Intervention	**1st appt**	**1yr**	**2yr**	**3yr**	**4yr**	**5yr**	**6yr**	**7yr**	**8yr**	**9yr**	**10yr**	**11yr**	**12yr**	**13yr**	**14yr**	**15yr**	**16yr**	**17yr**
Serial Hb measurement (Initially monthly)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Full red cell extended phenotype & Genotype	●																	
Weight/Height assessment (6 monthly)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Vitamin D Level	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Growth Hormone stimulation test (If declining growth velocity)									●									
Assessment of puberty											●	●	●	●	●	●	●	
Oral glucose tolerance test											● If family history of diabetes	● From puberty	●	●	●	●	●	●
Plain X-Ray of wrist											● If concern about fall in height velocity		●		●		●	
Thyroid function test											●	●	●	●	●	●	●	●
Bone profile & PTH if calcium low 6 monthly													●	●	●	●	●	●
Morning cortisol level			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Sex hormone levels														●	●	●	●	
DEXA scan (2-3 yearly from puberty)																	●	