Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK (2016, 3rd edition)

Summary

Networks for care and commissioning

Every patient should have a key contact health professional and Local Haemoglobinopathy Team (LHT)

Role of Specialist Haemoglobinopathy Centres (SHC)
- Acting in a hub and spoke model with other linked providers
- Annual comprehensive review
- Specialist advice and transfer of complex care

Systems for information sharing, clinical governance, accountability and staff development

National Haemoglobinopathy Registry (NHR)
- Captures information on AEs, transfusion, medication, iron overload
- Provides information for future planning of service delivery
- Participation is voluntary > requires informed consent

Integrated care, audit, clinical guidelines, clinical pathways

Peer Support groups

Annual review

New symptoms
AEs over preceding 12 months
Transfusion management
Iron status
Iron chelation and adherence
Prophylaxis for splenectomised patients: vaccination (Hib, meningitis, pneumococcal) and antibiotics (Pen V or erythromycin)
Specialist referrals, eg cardiac, hepatology, endocrine, transplant
Growth (for children)
Clinical exam: cardiac, liver, pubertal status
Fertility, conception, partner testing
Psychosocial evaluation
Education, lifestyle > influence adherence to treatment

Quality Assessment

Independent external peer review of thalassaemia services every 2 to 3 years > Report to NHSE

Each SHC should be responsible for a defined geographical area
SHC should monitor annual patient data from their network: number of thalassaemia patients under active care, number having annual review, AEs in thalassaemia patients

Robust fail-safe mechanisms for appropriate clinical care pathways for babies identified by new-born screening programme

Psychosocial issues

Challenges: transition to adulthood/independence, poor self-esteem, low mood, health anxieties, needle phobia, treatment compliance, school and work difficulties, relationship problems, cultural issues

Milestones: Initial diagnosis, first transfusion, start of chelation, puberty, transition, pregnancy, other major life events

Core staffing of SHC to include a clinical psychologist with special interest in thalassaemia > They should be an embedded member of the MDT

Offer peer support groups

Empower patients, eg involve them in monitoring their own progress such as ferritin results

The newly diagnosed infant

Neonatal heel prick test is a screening test, not a diagnostic test
Diagnosis of a serious thalassaemia needs to be timely and accurate > include globin genotype
FBC, blood film, Hb electrophoresis or HPLC, β and α globin genotype, *Xmn1* polymorphism (see below)

Test parents > Genetic counselling regarding future pregnancies, other family members

Clinical phenotype cannot be predicted accurately in early stages > Close monitoring of child to determine clinical course

Family's importance as the central care-givers > Inform them

National Haemoglobinopathy Registry

Transfusion

Monitor infants with β-thalassaemia carefully for transfusion indications: severe anaemia (Hb <70 on two occasions), failure to thrive, thalassaemic bone deformity, cardiac failure
Consider other causes such as IDA or G6PD
Extended red cell phenotype and genotype before starting transfusions

Investigations
Serial Hb measurements; G6PD screen and assay if low
Full red cell extended phenotype and genotype (C, c, D, E, e, K, k, Jk^a, Jk^b, Fy^a, Fy^b, Kp^a, Kp^b, MNS, Lewis)
LFT and baseline ferritin assay
Hepatitis B surface antigen; Hepatitis C antibody; HIV antibody

Start (and ideally complete) course of hepatitis B vaccinations before first transfusion
Maintain Hb at trough 90 to 105 g/L
ABO compatible, fully matched for all Rh antigens and K, and antigen-negative for any clinically significant (historic or current) antibodies
RBC units should be < 2 weeks old
Good transfusion practice
Clinical review of patient before transfusion by HCP
Review of transfusion-dependent patients by designated clinician every 3 months, in addition to annual review

Iron overload

SHC/LHT information sharing
Inform patients about benefits and possible AEs of each treatment option
Support adherence to chelation: MDT approach, doctors, nurse specialists, clinical psychologists, play therapists for children, peer support
Use annual transfusion requirement to estimate iron stores

Indications for iron chelation:

- Serum ferritin >1000 ug/L on two occasions + 10-12 transfusions + Age>2yrs
- Alternatively TSAT>90% and/or when 1000 g pure red cells transfused

Ferriscan (R2 MRI) to evaluate Liver Iron Concentration: Normal LIC is 0.2-1.8 mg/g dry weight, but aim for 3-7 mg/g dw (to avoid chelator toxicity). Levels above 15 mg/g dw have been associated with increased morbidity/mortality.

Cardiac T2* MRI is expressed in milliseconds – the higher the reading, the lower the cardiac iron. Aim for >20 ms (low risk). 10-20 ms is mild/moderate risk, <10 ms is high risk of cardiac failure.

Pregnancy:

- If planned, then prior intensive chelation to reduce SF, LIC and myocardial iron
- Stop all chelators as soon as pregnancy diagnosed
- DFO can be considered from 20/40 gestation if iron load is high, to prevent cardiac complications. DFX should be avoided and DFP is contraindicated.

	Desferrioxamine (DFO) *Desferal*	Deferiprone (DFP) *Ferriprox*	Deferasirox (DFX) *Exjade*
Children age 2 – 6	First line	Insufficient information	Second line if DFO contra-indicated or inadequate
Children age > 6 and adults	First line	Second line: If DFO not tolerated or ineffective	First line
Route	s.c/i.m or i.v injection	Oral, tablet or liquid	Oral, dispersed tablet
Advantages	Most data Can be used IV in severe cardiac disease	Crosses cell membrane, can act as intracellular chelator Controls cardiac iron well	Crosses cell membrane Long half-life, once daily Cardiac control non-inferior to DFO
Disadvantages	Quality of life 12 hours/day for 5 to 6 days/week	Short half-life, tds or qds May not control liver iron Urine excretion: Red	
Adverse effects	Hyper-sensitivity Bone growth Sensorineural hearing loss Yersinia / Klebsiella Liver toxicity	Agranulocytosis Arthropathy	Hyper-sensitivity GI symptoms Less frequent: hepatitis, GI haemorrhage CI: Estimated creatinine clearance < 60ml/min
Monitoring	Monthly ALT Annual audiometry Annual opthalmology	Monthly ALT Audiometry/opthalmology not required if single agent	Monthly ALT, creatinine Annual audiometry Annual opthalmology
Pregnancy	Can consider from 20/40 in cases of high iron load	Contraindicated	Avoid unless necessary

Synergistic effect of DFO/DFP combination can reverse cardiac failure

Referral for Blood and Bone marrow transplantation

Offer to parents when child is 1-2 years of age

Growth, Development and Endocrine Function

Iron toxicity > pituitary damage > hypogonadotrophic hypogonadism, short stature, delayed puberty
Further pituitary failure can lead to secondary hypothyroidism and adrenal failure

Ideally joint clinic with experts in bone metabolism and endocrine
Regularly monitor growth and development of children
Minimum annual review for disturbance of hypothalamo-pituitary axis, calcium and bone homeostasis
Ask about menstrual history and impotence

Can give GH (to children), oestrogen, testosterone, cortisol, etc

Transition from Paediatric to adult services

Transition with named key worker should commence from 13 years age
Support and education for transition for taking responsibility for own health and choices
Close monitoring of adherence to iron chelation
Note that many toxic effects of iron accumulation can present at this age range

Fertility and management of pregnancy

Fertility: Hypogonadotrophic hypogonadism, diabetes, hypothyroidism, BM transplant
Paediatric endocrinologist: Closely monitor pubertal development, growth, endocrine function in boys and girls

For males, HCG injections can help with spermatogenesis. Should stop DFP/DFX 3/12 before conception, switch to DFO

For females, joint management of pregnancy and increased risks: cardiomyopathy, osteoporosis, haemosiderosis off-chelation, diabetes (risk for foetus), osteoporosis, infection
Review by cardiologist at 28/40 gestation
Can re-start DFO from second trimester and continue through breast-feeding (not DFP or DFX)

Acute clinical presentation

Discuss with SHC as soon as possible, and consider transfer
Enter serious acute complications on the NHR

Cardiac: High risk if MRI T2* <10 ms (see below)

Sepsis:
- Consider as immunocompromised.
- Consider line-related infections, Klebiella, Yersinia, malaria.

Acute back pain/spinal cord compression:
- Osteoporotic fracture
- Extramedullary haematopoiesis should be treated with hyper-transfusion (aim for Hb 120 g/L) +/- hydroxycarbamide, but give radiotherapy if there is spinal cord compression. Surgical decompression is rarely an option.

Endocrine: Diabetes, hypocalcemia, hypothyroidism

Gallstones and renal stones/hydronephrosis

Liver

Anaemia

Cardiovascular management

Access to cardiology service with experience in management of cardiac consequences of thalassaemia
Age 7 to 10 years: first cardiac evaluation, including clinical, ECG, echo and MR T2* (see above)
High risk is age 16 to 25 > minimum annual assessments
Myocardial iron and LV impairment require urgent review by SHC team > inpatient intensive chelation
Note that chronic anaemia leads to hyperdynamic circulation and cardiac chamber dilatation: lower limit of normal EF is 63%
Address lifestyle factors
Full anticoagulation if indwelling venous lines or AF

Acute decompensated heart failure:
- IV DFO, oral DFP, adrenocorticoid therapy, thiamine, potassium and magnesium replacement
- Inotropic support should be used cautiously

Pulmonary HTN:

- More common in untransfused patients
- Treatment includes intensive transfusion, life-long anticoagulation
- Refer to national pulmonary HTN centre for query Sildenafil.

Pregnancy: Should have T2* >20 ms and EF >65% before conception

Glucose Tolerance and Diabetes Mellitus

Annual check for impaired glucose regulation and diabetes from puberty, or from age 10 years if family history.

Diabetes review: BM control, CVS risk factors (smoking, bp, cholesterol), diabetic complications (retinal screening, foot), sexual health

Diagnosis: Oral glucose tolerance test
Monitoring: Fructosamine levels (HbA1c or glycated Hb are unreliable after transfusion and should be avoided in thalassaemia patients)

Bone problems

Focus on achieving peak bone mass
Lifestyle advice eg smoking cessation, ETOH, undertaking weight bearing exercise

Optimal transfusion during childhood to prevent irreversible bone deformities of skull and face
Avoid desferrioxamine bone toxicity (eg pseudorickets) by not exceeding recommended DFO dose

Vitamin D supplements if needed (aim for 80 nmol/L, higher than 'normal range' 50 nmol/L)
HRT for hypogonadism

Monitor adult patients for osteoporosis: DEXA scan, consider bisphosphonates

Liver

Monitor LFTs monthly on oral chelation and every 3 months on DFO
Ferriscan (see above)
Hepatitis A and B vaccination

Designated specialist hepatologist in cases of chronic active HBV or active HCV > consider antiviral therapy
HCV can be treated with Harvoni (Ledipasvir–sofosbuvir) oral agent, but will require i.v. Ribavirin if there is cirrhosis
Monitor AFP and USS six-monthly in patients with cirrhosis

Prenatal diagnosis and preimplantation genetic diagnosis

Thalassaemia disorders: β-thalassaemia major/intermedia, haemoglobin E/β thalassaemia, α^0 thalassaemia hydrops fetalis or severe haemoglobin H disease
All couples at risk of having children with thalassaemia disorder > Refer to specialist genetic counsellor with expertise in haemoglobin disorders
Inform of prenatal diagnosis and preimplantation genetic diagnosis as options
If prenatal diagnosis shows an unaffected fetus and the couple already have a child with thalassaemia, then perform fetal HLA typing > Collect cord blood cells at birth if the fetus and the affected child are HLA-compatible, to provide future BM transplant option
Offer PGD if female partner is aged <50 years and there is no living unaffected child from the current relationship

Previously treated outside the UK

Thorough assessment in SHC asap after arrival in UK
Focus on transfusion history, chelation, co-morbidities, medications, developmental history, splenectomy, complications of iron overload, bone problems, family history

Baseline investigations/assessments (see below)

Vaccinate and re-start transfusion without delay

Immediate investigations	FBC, blood film, haemoglobin HPLC (although may not be informative if recently transfused; family study may help)
	Serum or plasma ferritin assay
	Blood group and antibody screen. Red cell genotyping, offered through the NHSBT.
	Hepatitis B and C serology to include Hep B surface antibody titre.
	HIV serology preceded by pre-test counselling.
	Full renal, liver, bone, sex hormone profiles, TFTs, random glucose, fructosamine if diabetic, PTH, vitamin D level, G6PD level.
	Globin genotyping (α and β globin genotype, -158 $^{G}\gamma$ *Xmn*1 C→T polymorphism). Parental samples may be informative.
Semi urgent investigations	Glucose tolerance test if not established diabetes mellitus
	Abdominal and pelvic ultrasound to assess for gallstones, liver fibrosis or cirrhosis, spleen size and renal tract pathology (renal stones) and uterine/ovarian tissue in females
	Cardiac T2*
	Liver iron quantification using T2* or R2
	DXA scan
Other specialist assessments and clinical reviews	Audiology
	Ophthalmology
	Cardiac review
	If diabetic, specialist diabetic clinic
	If impaired glucose tolerance, dietician and diabetes nurse review
	If other endocrinopathies, endocrine clinic
	If hepatitis B antigen or C antibody positive, hepatology clinic
	Patient and family members should be offered genetic counselling, as appropriate

Management of non-transfusion-dependent thalassaemias

Comprehensive DNA diagnosis (β globin, α globin genotype, *Xmn1* C→T polymorphism) can help predict for a NTDT:

Homozygote (or compound heterozygote) for mild β-mutation (such as IVS1-6 T>C, Codon 9 C>T)	
Homozygote for severe β mutation but persistence of Hb F due to:	Homozygote for *Xmn*1 polymorphism
	HPFH
	Other factors increasing HbF
Co-inheritance of β thalassaemia (heterozygote) and a thalassaemia-like Hb variant (these may result in a major or intermedia phenotype)	Hb E/β thalassaemia
	Hb Lepore β thalassaemia
Co-inheritance of α thalassaemia mutations (homozygous α^{+} or heterozygous α^{0}) with homozygous β thalassaemia resulting in decreased globin chain imbalance	
Co-inheritance of extra α gene(s) with heterozygous β thalassaemia resulting in increased globin chain imbalance	
Inheritance of a 'dominant thalassaemia' mutation (hyperunstable β globin variant)	

Clinical phenotype may not always be predictable from genotype > Monitor children carefully during first 5 years of life for evidence of transfusion need

Monitor older children, adolescents and adults with NTDT regularly as follows:

	Frequency	Age at start
Clinical examination to include: • Height • Weight • Spleen size • Liver size • Assessment of facial bone deformity and dental state	3 monthly, but according to severity of clinical syndrome, can be less frequent if mild	from birth or time of diagnosis
Pubertal development	6 monthly	Age 10
Cardiac assessment including echocardiogram	moderate severity : 1 – 2 yearly, mild phenotype: 5 yearly.	Age 15
Blood tests	3 monthly, but according to severity of clinical syndrome, can be less frequent if mild	from birth or time of diagnosis
FBC		
Liver function, renal function, urate		
Ferritin		
Formal assessment of liver iron concentration by MRI	2 – 5 yearly or more frequently if abnormal	Age 10
Cardiac iron assessment by MR T2*	2 – 5 yearly depending on previous results	Age 20 + or earlier if needing > 3 transfusions per year
DXA bone density	5 yearly	Age 15

Indications for transfusion:
- Before splenectomy
- Growth delay
- Pulmonary HTN
- EMH masses

Clinical phenotypes on NTDT are as follows:
- Moderate/Severe (10% of β/β, majority of E/β, very small proportion of HbH) can only just about manage without transfusions, but have significant problems such as reduced exercise tolerance, hypersplenism, poor growth
- Mild (small proportion of β/β, some with E/β, most patients with HbH) do not require transfusion but can experience long-term complications usually after age 30, including pulmonary HTN, gallstones, osteoporosis, VTE and iron overload

Monitoring iron overload in NTDT:
- Low hepcidin levels > increased iron absorption from GI tract and release from RES > relatively low serum ferritin but high iron load in the liver (irrespective of RBC transfusion)
- LIC is most important parameter in NTDT, and Ferriscan should be repeated every 2 to 5 years from age 10
- Annual SF should be correlated with LIC
- Iron chelation is recommended where LIC is >5 mg/g dry weight, and DFX (not DFO) is first line for this patient group
- Myocardial T2* MRI should be reserved for older patients and those who require 3 to 6 transfusions per year