Guy's and St Thomas' NHS
NHS Foundation Trust

Clinical Guidance

Thalassaemia intermedia: Guidelines on diagnosis and management

Summary
These comprehensive guidelines are intended for use as a reference for medical, nursing staff and all health care professionals.
(It is based on those in use at the Whittington Hospital London)

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Inclusion criteria:

Thalassaemia Intermedia patients are those with:
Beta thalassaemia intermedia

1. Homozygous mild beta globin variants or severe variants with an alpha deletion
2. Increased gamma production and homozygous beta globin mutations
3. Compound heterozygous with low synthesis variant such as HbE
4. Compound heterozygous with unstable variant
5. Compound heterozygous with triplicated alpha

Alpha thalassaemia Intermedia

1. HbH
2. HbH with Constant Spring
3. Homozygous alpha trait with other alpha variants

Background

Thalassaemia is an inherited disorder of haemoglobin (Hb) synthesis wherein mutations of the globin gene lead to various degrees of qualitative and or quantitative defects in globin production and an imbalance in α/β globin chain synthesis resulting in ineffective erythropoiesis, and a spectrum of anaemia. It is prevalent in many parts of the world and due to migration we have an increasing population of patients with thalassaemia phenotypes in our local area.

Patients with Thalassaemia intermedia are those who have clinical manifestations that are too severe to be termed minor yet too mild to be termed major. Hence this group has a diverse number of phenotypes with varying severity of anaemia and disease.

The management of thalassaemia intermedia differs depending on whether it is due to an alpha globin defect or a beta globin defect. Beta thalassaemia intermedia as a disorder is often associated with more morbidity and patients require more careful treatment plans.

These guidelines are an aid in ensuring that diagnosis is appropriate and timely and appropriate care plans are made for all patients with thalassaemia intermedia type syndromes.

If an adult patient with thalassaemia intermedia presents acutely unwell the haematology SpR on call must be called to inform them of the reason for admission and for advice about further interventions. *The on call haematology SpR must ensure the haematology consultant on call is aware of the admission.*

Diagnosis of Thalassaemia Intermedia

Although thalassaemia intermedia is generally diagnosed in childhood some patients are identified well into adulthood and often, in women, at the time of pregnancy.

Initial diagnosis:

Blood tests in all patients:

1. Full blood counts and group and save and Hb electrophoresis.
2. Blood for alpha, beta and XMN globin genotypes (4.5 ml EDTA)
3. If possible blood should be taken pre transfusion for the blood group phenotype. If not then a sample should be done post transfusion and sent to the national blood transfusion service for red cell genotype analysis. (7ml EDTA)
4. HepBsAg titres in adults and maternal HepBsAg antenatal result in young children born in the UK.
5. Hepatitis C and HIV in all patients who may have been transfused aboard.
6. Serum ferritin and biochemistry profile
7. Vitamin D
8. Abdominal ultrasound to assess spleen size accurately
9. Consider a Ferriscan liver iron assessment if ferritin is persistently raised above 400ug/l
10. Consider a bone density scan in adults who are post pubertal especially if history of fractures

Immunisations

In all patients hepatitis B immunisation should be offered as per The Green Book (DOH) 2011 recommendations:

- If hepatitis B surface antigen negative, start vaccination programme
- If the patient has already been splenectomised at another centre ensure patient is up-to-date with pneumococcal, meningitis and HiB vaccines
- Check HbsAb titres post vaccination to ensure that an adequate response has happened.

Decision to transfuse

Alpha Thalassaemia Intermedia

Patients with alpha thalassaemia Intermedia generally do not need regular transfusions. In exceptional circumstances patients may need this in which case formal investigation into the causes for worsening anaemia or worsening tolerability of anaemia must be looked into. If the patient does not have a simply correctable cause (hypersplenism, iron deficiency, folate or B12 deficiency etc.) then transfusions can be initiated as a supportive intervention.

Beta Thalassaemia Intermedia

Beta thalassaemia Intermedia patients are more likely to need transfusion support. The decision to transfuse is an individualised one and requires an understanding of the alpha and beta genotype, red cell allo-antibodies and red cell phenotype as well as careful discussion about risks and benefits.
It is important to rule out common causes for worsening anaemia such as folate deficiency, infection, hypersplenism, G6PD deficiency and other causes for increased red cell destruction. Once these have been excluded and the patient remains with symptoms then transfusions can be initiated.

Common indications for initiation of transfusion are either for short term support or long term management:

Short term support:

1. Leg ulcers
2. Intercurrent illness
3. Surgical intervention planned or unplanned
4. Pregnancy for either maternal support of anaemia or for foetal growth retardation.
5. Presence of extramedullary masses

Long term management:

1. Pulmonary hypertension
2. Extramedullay masses
3. Worsening anaemia....supportive care
4. Recurrent fractures
5. Thrombotic events

The risk of alloimmunisation is far higher in older patients who start transfusion and therefore a full red cell genotype should be done and blood should be matched for full Rh and Kell groups.

Monitoring Alpha and Beta Thalassaemia Intermedia patients

Adults with thalassaemia intermedia should be monitored depending on the degree of the anaemia and iron overload. If the anaemia is more symptomatic then more regular monitoring is needed and if the anaemia is less severe annual review may be sufficient.

Monitoring in clinic:

1. Height and weight
2. Energy levels

3. Spleen size
4. Haemoglobin
5. Review serial serum ferritin, renal, bone profile and liver function tests, vitamin D levels annually or more often if in high dose correction phase.
6. Immunisations in post splenectomy patients and hepatitis B results
7. Problems with Priapism, thrombosis, fertility, fractures, work and social issues
8. Patients on chelation should be monitored for chelation compliance and effectiveness in the same way as patients with beta thalassaemia major.
9. Dexa scan every 2 years
10. Yearly ophthalmology review if chelated
11. Pulmonary hypertension screening and cardiology review

Iron overload:
The ferritin is unreliable as a marker of iron overload and all new patients with thalassaemia intermedia should have a Ferriscan liver iron assessment if their ferritin is outside the normal range for their sex or if there are signs or symptoms that may suggest iron overload. If the liver iron is raised then chelation therapy should be discussed.

The decision to chelate will depend on the degree of iron burden and in general the aim should be to keep the liver iron < then 5mg/g/dw and consideration should be given to starting low dose chelation at liver iron values above this, all patients with Liver iron >7mg/g/dw should be on chelation (please refer to iron chelation protocol).

Once chelation starts then monitoring for complications of chelators should be undertaken and regular liver iron assessments to ensure that therapeutic goals are being achieved. It is possible that chelation could be stopped once iron burden falls into the target range however it is important to remember that the patients iron overload developed due to gastrointestinal iron absorption from the diet in a manner similar to patients with haemochromatosis. This will not resolve and the patient is likely to re-accumulate iron. It is probable (no clinical trial data) that using a low dose of chelator over the long term will be more effective at maintaining stable iron burden rather than intermittent episodes of chelation.

Pulmonary hypertension:
Myocardial iron is unlikely in patients with thalassaemia intermedia if occasionally transfused but poor ejection fraction is seen in this population often related to pulmonary hypertension. All patients should have a baseline cardiac review and thereafter screening on a bi-annual basis with echocardiograms (or more frequently on the advice of cardiology teams).

Osteoporosis:
Patients with thalassaemia intermedia do develop osteoporosis and this is often slow to respond to bisphosphonates. In osteoporotic patients refer to local osteoporosis guidelines and ensure that Calcium and vitamin D are replete and regular moderate impact exercise is taken. DEXA scans should be repeated following this intervention to see if improvement has occurred prior to starting on bisphosphonates or strontium.

Hydroxycarbamide:
In adult patients the Xmn1 polymorphism should be known and consideration given to hydroxycarbamide offered to patients. Patients with this polymorphism can improve

their Hb by anywhere between 1 and 3 g. If there is no change in Hb after 6 months on a dose of 15 - 35mg/kg/day then hydroxycarbamide should be stopped.
Hydroxycarbamide should also be part of standard management in patients with extramedullary haemopoiesis.

Contraception and sexual health:
Advice on contraception and sexual health should be provided to the patient in a relaxed environment and complete confidentiality assured in the case of adolescents. Patients should be referred to local sexual health clinics for more complicated issues.
All adolescents once sexually active and all adults should be counselled on the need to ensure that they are in optimal health prior to conception. This should include a discussion on risks of having a child with a serious haemoglobinopathy and the need for partner testing antenatally.

Indications for splenectomy:
The decision to remove the spleen in a Thalassaemia intermedia patient should only be made by a consultant haematologist with experience managing such patients. There is now clear evidence that splenectomy in Thalassaemia intermedia is associated with long term increases in mortality and morbidity, in part because of the increased thrombotic risk, hence splenectomy should be avoided if possible.

Splenomegaly alone is not an adequate reason for splenectomy, the main indication historically has been hypersplenisim, where increases in blood transfusion requirement prevent adequate control of body iron even with optimum chelation. Other causes should be considered including low pre-transfusion haemoglobin, raising this to 9.5-10g/dl may resolve the problem.

Patients with hypersplenisim may have moderate neutropaenia and thrombocytopenia but clinically significant pancytopenia may be a consideration for splenectomy.

All patients should be immunised as per the splenectomy guidelines (against Strep Pneumoniae, HiB and Neisseria meningitides) and maintained on prophylactic antibiotics – penicillin v 250mg BD post operatively.

Patients should be advised to seek medical help early for any febrile illness and due to the development of a thrombophilic state in thalassaemia patients post splenectomy adequate care must be taken during high risk periods to reduce this risk.

Pregnancy in thalassaemia intermedia patients

Pre conception management for all pregnancies:

1. Genetic screening of partner.
   - If the partner is a carrier of a haemoglobinopathy that may adversely interact with the patients genotype the counselling should be offered and the couple referred for pre-implantation genetic diagnosis
2. Oral glucose tolerance test.
   - If glucose level at 120 minutes >7.8 but <11.1 mmol/l the patient should be advised regarding low carbohydrate diet and referred to diabetes CNS and dietician.
   - If glucose level > 11.1 mmol/l the patient should be referred for specialist diabetic advice.
   - Patients with established diabetes mellitus should have serum fructosamine levels <330 µmol for at least 3 months prior to conception.

3. Viral Screening
   - HIV
   - Hepatitis B antibody titre/core antibody and hepatitis C antibody. If positive, test for hepatitis C RNA.
   - HbSAg negative patients should be immunised
4. Start daily folic acid 5mg daily, 3 months prior to conception.
5. Ensure that vitamin D and B12 levels are normal.
6. Refer to the assisted conception unit for fertility issues and Mr Oteng-Ntim and Dr S Robinson for management of pregnancy
7. Stop any oral chelation or bisphosphonates (oral or IV) for 3 months prior to conception.
8. Arrange Ferriscan liver iron assessment if ferritin above normal range for a female(>150 umol/l)
9. Arrange cardiac t2* assessment if previous history of regular transfusions and previous cardiac status unknown

Unplanned conception

Attempt to complete as many of the points for planned conception as soon as possible. Main issues are to:

- Stop bisphosphonates and any chelation,
- Start folic acid and
- Genetic screening of partner

Antenatal management

- All pregnant women with thalassaemia will be followed up in the specialist obstetric haematology clinics run by a Consultant haematologist and Consultant Obstetrician throughout the antenatal period
- Specialist cardiac assessment to be performed at 28 weeks gestation for all thalassaemia patients and thereafter according to cardiology advice
- If red cell antibodies are present (esp. Rhesus, Kell, S, Duffy, Jk) on baseline booking, then monitor titre levels monthly until 28 weeks gestation and fortnightly thereafter. If no antibodies are present then no need to monitor further.
- If patient is diabetic perform monthly serum fructosamine levels and ensure monitoring in the specialist diabetic pregnancy clinic.
- Thalassaemia intermedia patients to be reviewed monthly.
  - Assessments of Hb
  - patients symptoms re fatigue, shortness of breath
  - palpitations
  - careful monitoring of fetal growth for evidence of impaired growth

IF patient is unable to tolerate anaemia or there is evidence of poor fetal growth regular transfusion should be started with pre transfusion Hb target of 9.5g/dl.

The main complications having implications for obstetric care are:

1. Anaemia
2. Prothrombotic tendency especially in splenectomised patients
3. Diabetes
4. Infection
5. Osteoporosis
6. Pelvic disproportion

Intrapartum Management

The intrapartum care should be the same as for any other woman and there is no reason why caesarean section should be performed other than for obstetric causes.
Clearly if there are medical complications such as cardiomyopathy or diabetes then these will have been addressed antenatally and a management plan should be in the notes.

Any sign of infection should be treated promptly with antibiotics.
Patients with thalassaemia intermedia and a low Hb should have been reviewed and a formal plan outlined in the notes with regards blood transfusion in the pre delivery stage. In general if the patient Hb is >8g/dl at 36 weeks then a top up transfusion can be avoided prior to delivery and patient transfused if needed post partum. If Hb is less then 8g/dl and patient has no antibodies then aim to give a top up transfusion of 2 units at around 37 to 38 weeks.
In transfused thalassaemia intermedia patients depending on when the last blood transfusion was the woman may well have low haemoglobin and blood should be cross-matched on admission to the labour ward.

Specific Management

- Inform haematology team that patient is in labour ward
- Insert IV cannula
- If haemoglobin less than 10.0g/dl cross match 2 units
- If diabetic then will need to check blood glucose level and follow the diabetic protocol
- Active management of the third stage of labour to minimise blood loss
- All patients should be considered as high risk of venous thromboembolism and should be given appropriate prophylaxis whilst an inpatient.

Post Partum

All patients should be given a follow-up appointment in the haemoglobinopathy (sickle) clinic.

OPD monitoring (please see OPD guidance):

Baseline

- Haemoglobin
- Ferritin
- Gamma GT
- AST/ALT
- Vitamin D
- DEXA
- HepB sAb titre
- HCV ab
- HIV

Speciality review

- Cardiology for pulmonary hypertension and other cardiac complications
- Endocrine
- Reproductive

Vaccinations

- Hep B booster

- Pneumococcal booster
- HIB
- Meningitis C
- Influenza

Iron load

- Ferritin
- Liver R2
- Cardiac T2*

Chelation therapy
Hypogonadism
Cardiac failure or pulmonary hypertension
Extramedullary haemopoiesis
HCV RNA positive
Red cell antibodies
Any life threatening events

References:

1. *Thalassaemia intermedia guidelines on diagnosis and management: The Whittington Hospital NHS Trust. Dr F Shah*

2. Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the OPTIMAL CARE study. *Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, Daar S, Saned MS, El-Chafic AH, Fasulo MR, Cappellini MD. Blood. 2010 Mar 11;115(10):1886-92. Epub 2009 Dec 23.*

3. Standards for the clinical care of children and adults with thalassaemia in the Uk 2nd edition 2008

4. Pregnancy outcome in patients with beta-thalassemia intermedia at two tertiary care centers, in Beirut and Milan. *Nassar AH, Naja M, Cesaretti C, Eprassi B, Cappellini MD, Taher A. Haematologica. 2008 Oct;93(10):1586-7. Epub 2008 Aug 12.*