Clinical Commissioning Policy
Allogeneic Haematopoietic Stem Cell Transplantation (Allo-HSCT) for adult transfusion dependent thalassaemia [URN 2120]

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Commissioning position

Summary

Allo-HSCT is recommended to be available as a routine commissioning treatment option for adults with transfusion dependent thalassaemia (TDT) within the criteria set out in this document.

The policy is restricted to adults as allo-HSCT is already commissioned for a number of disorders including children aged up to 18 years with TDT.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Executive summary

This policy is focussed on allo-HSCT as treatment for adult TDT. The independent evidence review returned evidence for allo-HSCT which is presented for a routine commissioning position.

Plain language summary

About thalassaemia

Thalassaemia is a rare blood disorder passed down in families that affects the production of haemoglobin in red blood cells in the body. Haemoglobin is the protein present in red blood cells responsible for transporting oxygen around the body. Failure to produce enough haemoglobin leads to severe anaemia and/or complications which impact on life expectancy and quality of life. Significantly affected patients have TDT, a severe, life limiting condition which was previously fatal in childhood.

Patients with TDT can live up to 50 years or more. Thalassaemia is a complex multi-system disease and for older patients, heart, liver and bone disease are significant problems.

About current treatment

Blood transfusions and chelation therapy are the mainstay of treatment and are aimed at disease control. Regular blood transfusions are delivered as day case procedures and patients attend hospital on average every two to five weeks. This leads to a build-up of iron which can deposit in the liver, heart and the endocrine glands leading to damage and eventually if left untreated, organ failure.

Treatment with iron chelation medication is commenced to prevent and treat iron overload. Compliance with chelation therapy is required life-long to prevent organ damage. Regular monitoring with blood tests and screening for body iron burden with MRI imaging is necessary to monitor treatment efficacy and screen for complications.

About the new treatment

Allo-HSCT is also known as bone marrow transplantation (BMT). It is a curative intervention already used to treat a wide spectrum of disorders, including children with TDT up to the age of 18 years. Transplantation involves replacing the bone marrow stem cells of a patient with stem cells from a donor. Haematopoietic stem cells are found in bone marrow and blood in adults. They are delivered to a patient through intravenous infusion, to re-establish blood cell production in patients whose bone marrow or immune system is damaged or defective.

What we have decided

NHS England has carefully reviewed the evidence to treat adult TDT with allo-HSCT. We have concluded that there is enough evidence to make the treatment available at this time.

Links and updates to other policies

This document links to the following documents:

Haematopoietic Stem Cell Transplantation (HSCT) (All Ages)

Specialist-Haemoglobinopathy-Teams-Service-Specification.pdf (england.nhs.uk)

Haemoglobinopathy-Coordinating-Centres-Service-Specification.pdf (england.nhs.uk)

Committee discussion

Clinical Panel considered the evidence base and the recommendation was made to progress the policy as for routine commissioning. Please see the Clinical Panel report for full details of Clinical Panel's discussion. See the committee papers (link) for full details of the evidence.

The condition

Thalassaemia refers to a group of blood disorders characterised by decreased or absent synthesis of normal globin chains. The thalassaemias are named according to the chain whose synthesis is impaired, the two most relevant clinically are α- and β- thalassaemias. They result from the decrease of one of the two types of polypeptide chains that form the normal adult human haemoglobin molecule (Origa, 2021).

The thalassaemia syndromes are classified phenotypically based on their clinical severity and transfusion requirement into two main groups: TDT and non-transfusion dependent thalassaemia (NTDT). TDT requires regular blood transfusions, without which patients would suffer complications and a short life span.

TDT is a complex multi-system disease and for older patients cardiac, liver and bone disease are significant problems. Iron overload can cause tissue damage and impaired function of affected organs. In the heart this damage can lead to cardiac arrhythmias, pericarditis, dilated cardiomyopathy and ultimately heart failure. Liver involvement can lead to cirrhosis, portal hypertension and hepatocellular carcinoma. Endocrine gland involvement can present as hypogonadotropic hypogonadism, hypothyroidism, hypoparathyroidism, diabetes mellitus and complex bone disease.

Splenomegaly has historically been a complication related to TDT, through the increased destruction of red blood cells and extramedullary haematopoiesis. Current treatment with regular transfusion is given to avoid this. Nevertheless, many TDT patients in the older cohort who developed splenomegaly were splenectomised to reduce transfusion requirement, ultimately reducing iron overload. These splenectomised patients are at significant risk of an overwhelming sepsis.

Outcomes are impacted by adherence to treatment, particularly chelation therapies. For younger cohorts where optimal treatment has occurred, the likelihood of end organ damage is less likely. A critical time for many patients with thalassaemia is the adolescent years and early adulthood where the impact of psycho-social factors can have a profound impact on treatment compliance.

Current treatments

Current management of adult patients with TDT is complex and generally involves supportive care. Patients require lifelong treatment with regular red blood cell transfusions every two to five weeks to maintain haemoglobin levels. The target for haemoglobin levels is to maintain it at around 95-105g/l in order to be sufficient to reduce bone marrow expansion whilst minimising transfusion iron loading (UK Thalassaemia Society, 2021).

Patients receiving regular red blood cell transfusions must adhere to an iron chelation therapy regimen to prevent complications due to iron overload. Iron can accumulate at a rate of 0.3-0.6 mg/kg per day in transfused patients and cannot be excreted by the body. Iron chelation therapy is very effective in preventing iron overload though requires a good compliance and adherence to treatment. This is very demanding of patient time and can have a profound impact on their quality of life (Taher et al, 2021).

Proposed treatments

Allo-HSCT is an established curative intervention for the treatment of many haemoglobinopathies. It is delivered in accredited transplant units and involves a four-to-twelve week inpatient stay and subsequent outpatient follow up. Allo-HSCT usually utilises bone marrow as the stem cell source. It involves replacing the bone marrow stem cells of a patient following high-dose therapy, with stem cells from a tissue-type matched or mismatched donor.

Allo-HSCT treats the underlying cause of the genetic defect. It is a curative intervention for patients with TDT and patients who undergo HSCT will have no ongoing transfusion or iron chelation requirement. Failure of the transplant, results in a recurrence of transfusion dependence and need for ongoing chelation therapy.

Allo-HSCT is intended to be offered to adult patients when an HLA-matched donor is found, and they are deemed fit for transplant (based on a medical, psychological and social assessment). Adult patients who have previously had an allo-HSCT but who experienced graft failure can have a second transplant if they meet the eligibility criteria within this policy.

Current guidelines recommend that in paediatric patients with TDT who have an HLA-matched sibling donor, allo-HSCT should be offered as soon as possible to avoid complications from both thalassaemia and iron overload. Experience of transplantation in children has shown that optimal medical management prior to transplantation is the most important factor for successful transplant outcomes. With advances in chelation treatments and monitoring strategies, young adult patients have sustained low iron burden and a reduced risk of organ damage. The improvement in supportive care alongside advances in transplant conditioning regimens and strategies to prevent graft rejection and graft vs host disease (GVHD) has made allo-HSCT an increasingly feasible option for adult patients.

Epidemiology and needs assessment

In the UK, there are 1614 people with thalassaemia registered on the National Haemoglobinopathy Registry (NHR), 1332 of whom are age 18 years and above. Of these it is estimated that there are 608 adults who are transfusion dependent (NHR, 2021).

Thalassaemia is more prevalent amongst Southern European, Middle Eastern, South American, Caribbean, Asian and South East Asian populations and prevalence in any locality will be affected by the proportion of the population that are genetically linked to susceptible populations. The high gene frequency in certain regions is likely to be related to the selective pressure from Plasmodium falciparum malaria.

In the UK, most new diagnoses of thalassaemia are through the newborn screening programme. Nevertheless, population migration has led to an increasing number of adults living in the UK who were diagnosed and initiated on treatment abroad.

An approximate figure of up to 10 patients per year aged 18 years and over would be eligible for an allo-HSCT (according to clinical consensus of the policy working group).

Evidence summary

An independent evidence review was conducted for the use of allo-HSCT for adults with TDT.

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication.

The evidence review which informs this commissioning position can be accessed here.

Implementation Criteria

Inclusion criteria

Patients who are aged 18 years and over and who meet the below criteria should be considered for allo-HSCT:

- Diagnosis of transfusion dependent thalassaemia

AND

- Comprehensive organ assessment including but not limited to cardiac, liver, renal assessment[1]

AND

- Agreement at National Haemoglobinopathy Panel (NHP)

AND

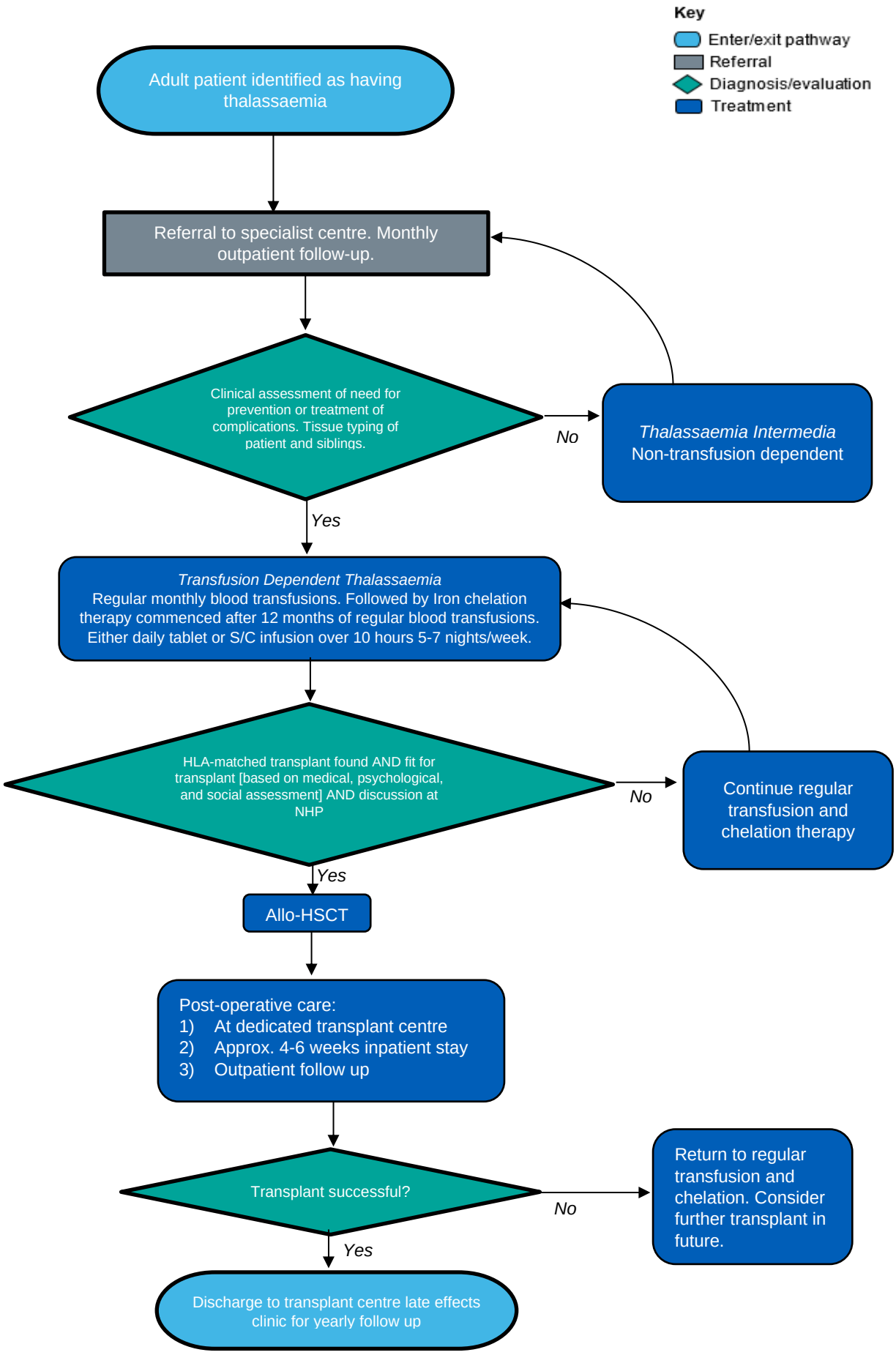
- At least one first degree relative willing to act as a donor and confirmed as a fully matched sibling donor.

Exclusion criteria

- Current cardiac iron overload T2* < 20 milliseconds
- Glomerular Filtration Rate < 40 ml/min/1.73m²
- Current pregnancy or breastfeeding

[1] Assessment to include an echocardiogram, cardiac T2*, liver ultrasound and GFR.

Patient pathway



Governance arrangements

The governance arrangements are described within the Service Specification B04/Sa NHS Standard Contract for Haematopoietic Stem Cell Transplantation (ADULT) (NHS England, 2014). This can be accessed: Haematopoietic Stem Cell Transplantation (Adult).

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

Audit requirements

Complete data must be submitted to the BSBMT registry for all transplants carried out by centres in England. This will enable better evaluation of clinical outcomes broken down by patient and disease-related variables. All centres must undergo regular JACIE inspection. All centres must provide the data required for the BMT Quality Dashboard. Audit requirements are described in more detail in the BMT service specification.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Allogenic Haematopoietic Stem Cell Transplantation	A procedure which replaces the patient's own blood stem cells and immune system with those from a healthy donor, enabling the establishment of normal blood and immune system functions.
Bone Marrow	Soft tissue found within bones in the body containing immature cells called stem cells. These cells can turn into many different types of cells in the body.
Graft-versus-host disease	This is a common complication following an allogenic transplant where white blood cells (immune cells) in the donor cells (the graft) recognize the recipient host as "foreign". The transplanted white blood cells then attack the host's body cells.
Haematopoietic stem cells	Cells in the bone marrow that can develop into different types of blood cells.
Iron chelation therapy	This is the treatment given to patients to remove excess iron. There are 3 drugs currently used for iron chelation and they can be used as monotherapy or in combination to help control the iron burden.
Quality of Life	The individual's perception of their well-being with respect to daily life.

Cardiac T2*	This is a non-invasive MRI measurement used to identify cardiac iron accumulation in iron storage diseases such as thalassaemia.
Thalassaemia intermedia	Encompasses a wide clinical spectrum between thalassaemia major and thalassaemia minor. Patients may require occasional blood transfusions.
Thalassaemia major	The most severe form of thalassaemia requiring regular blood transfusions and other treatments.

References

Origa, R. (2021). Genetic Basis, Pathophysiology and Diagnosis. In: Cappellini, MD. Farmakis, D. Porter, J. and Taher, A. *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT)*. 4th ed. Cyprus: Thalassaemia International Federation. p20-36.

Taher, A et al. (2021). Improving outcomes and quality of life for patients with transfusion-dependent beta-thalassaemia: recommendations for best clinical practice and the use of novel treatment strategies. *Expert Review of Haematology*. 14 (10), p897-909.

UK Thalassaemia Society. (2021). *Blood Transfusion Therapy.* Available: https://ukts.org/blood-transfusion-therapy/. Last accessed 7th Dec 2021.