Clinical Commissioning Policy:

Allogeneic Haematopoietic Stem Cell Transplant for patients with X-linked cerebral adrenoleukodystrophy (Adults) [2203]

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Summary

Allo-HSCT is recommended to be available as a routinely commissioned treatment option for adult patients with C-ALD in within the criteria set out in this document.

The policy is restricted to adult patients of male sex (with an “XY” chromosome pattern) as C-ALD is only known to affect patients of male sex and allo-HSCT for this condition is already commissioned for patients less than 18 years of age.

For the purposes of this policy, the term ‘male’ refers to patients of male sex (with an “XY” chromosome pattern) unless otherwise stated.

Committee discussion

Please see Clinical Panel reports for full details of Clinical Panel’s discussion.

The Clinical Priorities Advisory Group committee papers can be accessed on the NHS England website.

What we have decided

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

The evidence review which informs this commissioning position can be accessed on the NHS England website.

Links and updates to other policies

This document is linked to:

NHS England Clinical Commissioning Policy B04/P/a: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised

NHS England. Service Specification No. B04/S/a: Haematopoietic Stem Cell Transplant (adults)

NHS England. Service Specification No. B04/S/b: Haematopoietic Stem Cell Transplantation (Children)

Plain language summary

About X-linked cerebral adrenoleukodystrophy

X-linked adrenoleukodystrophy (X-ALD) is a genetic (inherited) disease that affects the nervous system (brain, spinal cord and nerves throughout the body) and the adrenal glands (small glands located on top of each kidney). X-ALD is caused by mutations (changes) in the ABCD1 gene, which leads to very long chain fatty acids (VLCFA) building up in the body. This can lead to several effects including acute brain inflammation and demyelination (loss of the protective nerve coating), and progressive damage to the brain, spinal cord, nerves and the adrenal glands.

The most severe forms of X-ALD are seen in males. This is because the ABCD1 gene is on the “X” chromosome, which is why the condition is called “X-linked”. Men only have one copy of ABCD1 as they have an “XY” chromosome pattern and will be clinically affected if it is faulty. Women who have the “XX” chromosome pattern can have a working copy of ABCD1, as well as a faulty copy. This means women with X-ALD present at a later age with limited features of the disease which progress at a slower rate compared to males. Women are not known to be affected by C-ALD.

The clinical features of X-ALD are varied, with different aspects of the disease appearing at different times. There are three core clinical syndromes and patients may go on to develop any combination of these syndromes. Males with X-ALD may first present in childhood with adrenal insufficiency (problems with the adrenal gland functioning), which means they need life-long medications. They may also present with a second syndrome of rapid neurological damage due to an inflammatory leukodystrophy (loss of the white matter within the brain), which can affect learning, behaviour, vision and physical functioning. This is known as cerebral adrenoleukodystrophy (C-ALD). The third clinical syndrome is a slowly progressive spinal cord disease known as adrenomyeloneuropathy (AMN). AMN normally presents in men in their thirties who may or may not have adrenal insufficiency. AMN leads to stiffness and weakness of the legs, including problems with balance and difficulty controlling bladder and bowel function. Patients end up wheelchair bound and requiring catheterisation (a procedure to empty the bladder). This policy will focus on C-ALD.

C-ALD develops in approximately 35% of affected males younger than 12 years of age and in a smaller percentage of affected patients 12 years of age or older. Without early treatment, C-ALD leads to permanent disability and death. Median life expectancy in adults after onset is about 4 years. It is not possible to predict which patients will develop C-ALD or when it will occur. Approximately 20% of adult males with AMN will go on to develop C-ALD, but approximately 10.3% of adults will develop C-ALD with no prior AMN changes (Alex TLC database; Van Geel et al. 2001).

It is important to detect and treat C-ALD as early as possible to alleviate progression. Early-stage cerebral changes can be stabilised with allo-HSCT. A regular MRI scan of the brain is indicated for monitoring purposes in patients who are asymptomatic for C-ALD and in whom allogeneic haematopoietic stem cell transplantation (allo-HSCT) remains a treatment option. An MRI scan is currently recommended every 6 months for males between the ages of 3 and 12 years. After the age of 12 years the risk of C-ALD is lower and annual scans are indicated thereafter. An MRI scan is indicated at the earliest possible opportunity in individuals who develop physical symptoms of C-ALD. Allo-HSCT is currently commissioned for male paediatric patients with C-ALD.

It is important to note that X-ALD is progressive (gets worse) over time and treatment which is targeted at the cerebral changes of C-ALD would have little impact on the progressive AMN symptoms. The aim of treatment would be to reverse the cerebral changes (if possible) but also to halt or slow down the progression of cerebral disease.

About current treatment

There is no current standard active treatment for adult patients with C-ALD other than supportive and palliative care.

About allogeneic haemopoietic stem cell transplantation

HSCT involves destroying the patient's unhealthy blood cells and replacing them with stem cells (special cells which can turn into different types of blood cells) which are removed from the blood or bone marrow (a spongy tissue found in the centre of some bones) of a healthy individual. This allows the damaged blood cells to be replaced by healthy ones.

A stem cell transplant can be performed from a tissue-type matched or mismatched donor (termed allogeneic transplantation or allografting) or using the patient's own bone marrow cells which have been stored before high dose chemotherapy and are returned afterwards to speed bone marrow recovery (termed autologous transplantation or autografting). Allo-HSCT is an established therapeutic intervention for male paediatric patients with C-ALD. The aim is to provide a haematopoietic system which has a normal ABCD1 gene. If successful, this can halt brain inflammation. Evidence has shown that allo-HSCT is most effective when performed as soon as possible following MRI evidence of cerebral changes that indicate the development of C-ALD.

Planning and counselling for allo-HSCT should begin for at risk individuals as soon as possible after the initial diagnosis of X-ALD. Identification of potential matched donors must have already been started so that when the indication for transplant emerges, rapid organisation is possible and does not delay initiation of allo-HSCT.

Allo-HSCT is a complicated procedure. In order to perform the transplant an individual's immune system (the defence against infection) is suppressed both during the transplant and for many months after allo-HSCT. This can lead to a significant increase in risk of infection and transplant rejection (failure to engraft). Complications include infection and failure of other organ systems and in some cases can lead to death.

Allo-HSCT is proposed as a one-off intervention for the treatment of C-ALD, and patients with progressive C-ALD after allo-HSCT would not be eligible for a further round of treatment. However, patients who experience failure to engraft would be eligible for a second transplant, in line with NHS England HSCT (All Ages) Policy (B04/P/a).

Epidemiology and needs assessment

X-ALD is a rare disorder with a prevalence of 1 in 20,000 and a higher incidence in patients with African or Latino descent. C-ALD develops in approximately 35% of affected boys younger than 12 years of age and in a smaller percentage of affected patients 12 years of age or older. As the phenotype (expression) of X-ALD is variable, it is difficult to predict the precise number of adult patients with C-ALD who would be suitable for allo-HSCT. Clinical experience suggests that there would be one to three patients each year, who might be eligible for the intervention.

Implementation

Eligibility criteria

Patients eligible for treatment must meet **ALL** the following criteria:

- Adult males (≥18 years) with an MRI confirmed diagnosis of C-ALD [1]
- Assessed by a Multi-disciplinary Team (MDT) to be suitable for allo-HSCT based on concurrent health, social and psychological needs
- Individuals with early C-ALD, defined as:
    - Loes score[2] grading of cerebral MRI findings ≤ 10 **AND**
    - Expanded Disability Symptom Score (EDSS)[3] < 6
- The individual and/or their family can participate in informed decision making regarding the risks and benefits of allo-HSCT based on their individual circumstances.

Exclusion criteria

Individuals with concurrent health or other issues for whom the MDT determines that allo-HSCT cannot be delivered safely.

Monitoring

As C-ALD is a progressive disease and HSCT requires donor cells to establish and repopulate the brain, it takes time for allo-HSCT to stabilise cerebral changes. Therefore, clinical response should be determined no sooner than 12 months post intervention. It is expected that the monitoring would include MDT assessment for activities of daily living (ADLs), neurological assessment including scoring tools (e.g., EDDS or Severity Score System for Progressive Myelopathy (SSPROM)[4]), radiological assessment of cerebral changes (e.g., MRI monitoring to assess disease progression) and a formal cognitive assessment (e.g., in the form of neuropsychological testing.) These measures should be compared to baseline pre-intervention assessments and can be used for the purposes of audit and data submission to the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) registry, the European Society for Blood and Marrow Transplantation (EBMT) registry and other relevant registries.

The MED-A form for minimum dataset reporting for the EBMT registry requests reports on day 0 (or within 1 week of day 0) post-transplant, then post-transplant information at day 100, plus yearly thereafter.

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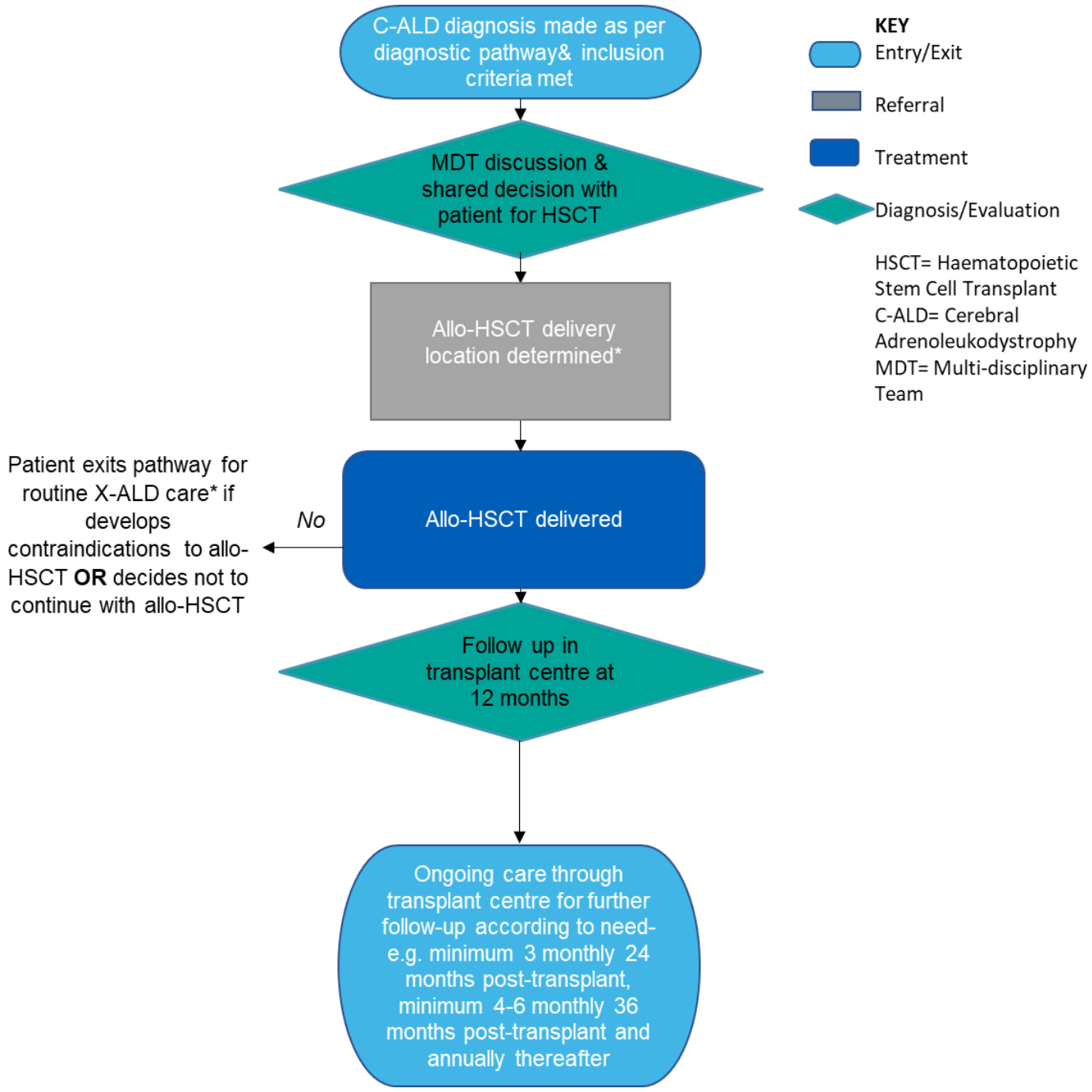
[1] **X-linked Cerebral Adrenoleukodystrophy** (C-ALD), also known as Adult CALD (ACALD) would be diagnosed with elevated concentrations of very long chain fatty acids (VLCFA) and ABCD1 gene mutations. Cerebral ALD includes cerebral, cerebellum and brain stem lesions on MRI (this might be described as white matter lesions or lesions with gadolinium enhancement on brain MRI).
[2] **Loes MRI severity score** please refer to the definitions section.
[3] **Expanded Disability Symptom Score (EDSS)** please refer to the definitions section.
[4] **Severity Score System for Progressive Myelopathy** please refer to the definitions section.

Patient pathway



*Routine X-ALD care continued throughout, alongside specialist care in the transplant centre.

Governance arrangements

Governance arrangements for HSCT are outlined in the adult Service Specification for Haematopoietic Stem Cell Transplantation (B04/S/a).

Provider organisations providing HSCT are required to be JACIE accredited.

Mechanism for funding

Funding for stem cell transplantation is through the NHS England teams responsible for specialised commissioning.

Audit requirements

Complete data must be submitted to the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) Registry for all transplants carried out by England centres. This will allow a review of the clinical outcomes by patient and disease factors. Audit requirements are described in detail in the BMT service specification.

All centres must maintain JACIE accreditation.

All centres must provide the data required for the BMT Quality Dashboard.

Provider organisations should register eligible patients within the European Bone Marrow Transplant (EBMT) Register.

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.

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.

Definitions

X-linked adrenoleukodystrophy (X-ALD)	A rare genetic disease caused by changes in the ABCD1 gene, located on the X chromosome. This leads to a varied presentation of brain, adrenal and spinal cord demyelination (loss of the protective coating).
Cerebral adrenoleukodystrophy (C-ALD)	Describes the progressive brain changes which happen in individuals with X-linked ALD. This is the most severe presentation of the disease and has a varied pattern of symptoms which affect learning, behaviour, vision, and physical functioning.
Adrenomyeloneuropathy (AMN)	Describes the progressive spinal cord disease seen in individuals with X-ALD. This leads to stiffness and weakness of the legs, including problems with balance, and difficulty controlling their bladder and bowel function.
Allogeneic Hematopoietic stem cell transplantation (allo-HSCT) (also known as Bone Marrow Transplant (BMT)	A complex procedure which replaces the patients' own blood stem cells and immune system with those from a healthy donor.
Loes MRI Severity Score	This is a 34-point scale that assigns a score to an MRI based on the extent of white matter lesions (higher scores indicate more significant ALD involvement). A Loes score of a maximum of 10 is used to be considered for HSCT and shows evidence of MRI gadolinium enhancement around a consistent lesion.
Expanded Disability Symptom Score (EDSS)	This is a clinical scoring system. Scored from 0-10 points; 0= no deficits 6= inability to walk without assistance; 10= death.
Severity Score Symptom for Progressive Myelopathy (SSPROM)	This scoring system measures the severity of myelopathy ranging from 0 to 100, with lower scores indicating a higher degree of impairment.

References

NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplant (HSCT) (All Ages), 2013 (revised 2015) B04/P/a [online]. Available at: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/b04-haematp-stem-cll-transplt.pdf. Accessed 7/3/22.

NHS England. Service Specifications for Haematopoietic Stem Cell Transplant (adults). B04/S/a [online]. Available at: https://www.england.nhs.uk/wp-content/uploads/2013/06/b04-haema-adult.pdf. Accessed 7/3/22.

Snowden J, et al. 2022. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant; 57(8) 1217- 1239.

Van Geel B, Bezman L. 2001. Evolution of phenotypes in adult patients with X-linked adrenoleukodystrophy. Annals of Neurology; 49(2) 186-194.