INTRAVENOUS ENZYME REPLACEMENT THERAPY (ERT)

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Lysosomal storage disorders (LSDs) are an assorted group of approximately 70 genetic metabolic disorders in which a single gene mutation leads to a deficiency in, or absence of specific lysosomal enzyme activity. For some of these LSD's, enzyme replacement therapy (ERT) may be a treatment option.
- Children with LSD's treatable by ERT are clinically supervised by the Genetic Metabolic Disorders Service (GMDS), specifically the Metabolic physicians based at SCHN.
- ERT is given as an intermittent intravenous infusion, weekly or fortnightly, depending on the disorder, and is **lifelong**.
- ERT infusions are administered, on average, over 2-6 hours. Duration of the infusion is dependent on ERT safety data, determined by the Department of Health Therapeutic Goods Administration (TGA), product information, dose, size of child and immunogenicity.
- Each child receiving ERT has an 'Individualised Infusion Protocol' (IIP) placed in their electronic Medical record (eMR) as a 'Management Plan' approved by a Metabolic physician.
- **ERT has specific storage and handling, preparation and administration requirements which, if not followed, can denature the product and render it inactive.**
- **ERT is administered as per a patient's Individualised Infusion protocol (IIP) and can be found in eMR/ Powerchart under 'Management Plans/ Enzyme replacement Infusion Protocol.**

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

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Risk of Anaphylaxis

- Life-threatening anaphylactic reactions have been observed in some patients receiving ERT, therefore all parents or patients (as appropriate) must be trained in anaphylaxis management. Anaphylaxis has been seen in some products up to 24 hours after the end of an ERT infusion.
- Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when ERT is administered because of the potential for severe anaphylactic reactions.
- The ERT education pathway includes read and acknowledgement of this practice guideline, viewing of the video 'How to do ERT' and quiz, attend demonstration session; and complete a supported administration of ERT.

CHANGE SUMMARY

- N/A – New Document

READ ACKNOWLEDGEMENT

- Training/Assessment Required – Registered and enrolled nurse must complete the ERT education pathway prior to administering ERT. This document forms part of the ERT Education pathway for nursing staff
- The document is relevant to all clinical staff involved in the storage and handling, preparation and administration of ERT
- Clinical staff must have completed:
  - Clinical Skill Assessment - **Aseptic Non-Touch Technique;**
  - Clinical Skill Assessment - Administration of Intravenous Therapy.

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

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Introduction

Lysosomal storage disorders (LSD's) are life-threatening metabolic disorders caused by insufficient activity of housekeeping enzymes required for the catabolism of materials that arise from the normal turnover of body constituents.

The highest specific activity of all of these enzymes is seen in lysosomes—subcellular organelles, which were discovered by Christian de Duve who first suggested that ERT might be helpful in such disorders, hence LSD's were named. The rationale for ERT is to restore a level of enzymatic activity sufficient to dissolve the accumulated substrate and to prevent further accumulation.

Currently, within the Sydney Children's Hospital Network (SCHN), we use specific ERT to treat metabolic conditions such as Pompe Disease (Glycogen Storage Disorder II- GSD II), Fabry Disease, Gaucher Disease, and Mucopolysaccharidosis (MPS) type I – Hurler-Scheie Syndrome, MPS type II – Hunter Syndrome, MPS IVa – Morquio A Syndrome, and MPS VI - Maroteaux-Lamy syndrome.

ERT is a high cost therapy and is coordinated by the GMDS team. Eligibility for treatment is based on disease-specific criteria determined by; the Federal Governments' Life Saving Drug Program (LSDP), clinical trials, or compassionate access.

All missed ERT infusions are to be notified to the relevant SCHN or local area Pharmacy contact, and the LSDP.

Training

Nursing staff

Prior to administering ERT nursing staff are to successfully complete the ERT education Pathway. ERT training and education pathway includes read and acknowledgement of this practice guideline, viewing of the video 'How to do ERT' and quiz, attending a demonstration sessions for preparation and administration of ERT; and completing a supported administration of ERT.

Prerequisite Training:

- Clinical Skill Assessment (CSA) - Aseptic Non-Touch Technique
- CSA- Administration of Intravenous Therapy
- CSA- CVAD Core Skills
- IVC accredited or working towards

Parents/patients

All patients receiving ERT must be seen by the Anaphylaxis CNC for parental or patient training for treatment of severe reactions. This includes training in the use of **EpiPen's**, as age-appropriate or if applicable. Training is arranged by the Metabolic CNC's/ Metabolic NP.

Storage and Handling Guidelines

All IV enzymes are to be stored in monitored refrigeration at 2°C to 8°C. The products are not to be frozen or shaken, as this can denature the product and render it inactive. The enzymes should generally be protected from light prior to administration. Please refer to IIP's for product-specific information.

DO NOT USE Enzymes after the expiration date on the vial. The products contain no antimicrobial agents, therefore, once made up should be used as soon as practicable. The diluted solution can be stored in a monitored fridge for a maximum of 24 hours at 2°C to 8°C if necessary. Refer to the IIP or consult the metabolic team for product specific recommendations.

The product is for single use in one patient only. Any residual product must be discarded.

ERT is a high cost product, excess stock should not be stored at ward level, and must be returned to pharmacy. Pharmacy and the Metabolic service must be notified of any damage to ERT stock as soon as possible, and IMS+ submitted

Preparation and Administration

Preparation and administration of ERT is guided by a patient's Individualised Infusion Protocol (IIP)

1. **Prior to preparing the ERT**: **Assess the patient's current health status**

The child is at an increased risk of infusion associated reactions if they have an intercurrent illness, such as cold like symptoms, fever, vomiting, diarrhoea, or any other systemic infections. Prior to preparing ERT, assess the following to identify if the child is well enough to receive the scheduled infusion:

- Perform baseline observations on admission to the unit:
    - Height and weight, temperature, pulse, respirations (TPR), blood pressure (BP) and oxygen saturations (SaO2).

ERT dosing is weight-based, and usually rounded-up to the whole vial. If there is a significant discrepancy between the measured weight and the weight on the IIP, please notify the Metabolic CNC's/ NP

- Assess recent history for intercurrent illness including; vomiting, diarrhoea, temperature ≥38.0℃, respiratory symptoms or any other parental concerns
- Visualise patient's EpiPen and check expiry date (if applicable). If IV ERT is being administered in a ward environment, IV or IM Adrenaline must be readily available for administration, prior to product being made up.

If a patient receiving ERT has ANY alterations outside of normal 'BTF' parameters for vital signs on admission, or is visually unwell, please contact the Metabolic team ***PRIOR* to preparation of the Enzyme**

- If a child has had any accidents, injuries or variations precluding them from attending a Day stay Unit, the unit Co-ordinator/ Team Leader and Metabolic Team must be informed of changes to the patients' treatment day.

2. Review patient's Individual Infusion Protocol (IIP)

IIP's are version and date controlled.

The most current version is located in the patient's SCHN eMR under "Management plans/ Enzyme Infusion Protocol". Version control is maintained by the Metabolic Team. Any changes or updates to an IIP is conveyed to the nurses at the infusion location. Please ensure that the IIP is printed off and kept with the patient for each infusion.

The IIP outlines the following:

- The child's metabolic condition
- Information about the patient's IVAD
- Prescribed ERT and dose required
    - **Ensure** the dose on the protocol correlates with the dose ordered on the MAR/ medication chart.
- Description of ERT powder/ solution appearance, to enable appearance to be inspected by nurses prior to opening vials.
- Total volume of sodium chloride 0.9% intravenous fluid (IVF) that an enzyme is diluted in.
    - The volume is **dependent** on the specific enzyme used and the age or weight of the child

ERT is ONLY compatible with sodium chloride 0.9%

- **Premedications (if applicable):**
    - **Ensure** the premedications listed on the protocol correlate with the child's MAR/ medication chart.
    - **Oral** premedications are given **30 minutes prior** to commencing ERT.
    - **IV** premedications are given **20 minutes prior** to commencing ERT if indicated.

ERT can cause anaphylactic reactions. Please ensure premedications are given as per the IIP

- **Rate of infusion:** These are determined by the specific Enzyme product listed in a patient's IIP, and patient's tolerance to a product. Rates are increased slowly to allow for desensitisation to a product, due to the high risk of reaction.
- Frequency of vital sign monitoring required for the patient during, and post infusion.
- Length of observation period post infusion completion, if required
- Recommended management of allergic reactions

3. Intravenous Access- (PIVC/ CVAD)

Children receiving ERT require regular intravenous access. Consider Child Life therapy support for children distressed by these procedures.

- Apply topical anaesthetic cream as per local policy guidelines a minimum of 20 minutes prior to cannulation or port access.
- Access port according to SCHN CVAD practice guideline using surgical ANTT.

If there are any difficulties or concerns in relation to port/CVAD access, escalate concerns to Metabolic CNC, Vascular Access nurse or Metabolic RMO

- Cannula insertion by accredited nurse according to SCHN Intravenous Cannulation procedure. If there are any issues with cannulation, escalate to Metabolic Registrar.

4. Preparation of ERT

- ERT is prepared following the SCHN ANTT policy.
- Ensure successful placement of cannula / access of IVAD prior to commencing the preparation of ERT.
- Collect required equipment for infusion:
  - This includes use of Clave™ Connector IV Bag access device which allows for syringe luer-lock access to IV bag, minimising risk of needle-stick injuries, or IV bag leakage.
  - **Please note** that if this adapter is not available, please contact Metabolic nurses to check if it is a requirement for the enzyme being given.
- **Adhering to the following practice points will reduce the risk of denaturing the enzymes:**
  - If the enzyme is powdered and requires reconstitution, direct the diluent towards the glass side of the vial to reduce the force with which the diluent contacts the enzyme.
  - Gentle swirling or rolling of the vial can assist the powdered enzyme to dissolve**. Avoid shaking or vigorous movement of the vial.**
  - Slowly withdraw the enzymes from the vial, **being cautious to avoid agitation and bubbling.**
  - Do not use a filtered needle when drawing up the enzyme as this may increase agitation.
  - Whilst slowly injecting the enzyme into the additive port of the 0.9% sodium chloride bag, hold the bag at a 45 degree angle. This will ensure the enzyme is delivered into sodium chloride 0.9% solution rather than air, to minimize agitation from bubbling.
  - Once the enzyme has been added to the bag, facilitate even diffusion of the enzyme by gently rotating the bag, **do not shake the bag.**

The enzymes are fragile and can be denatured during the preparation process. Any vigorous shaking, agitation or bubbling of the enzyme can result in the enzymes becoming biologically inactive

- **Enzyme batch numbers** to be recorded into child's eMR, or Medication/ IV fluid chart under 'Comment' section when signing for medication on MAR or IV fluid chart if electronic record is not available.
- Some enzymes are sensitive to light- check IIP to see if the enzyme requires protection from light.

ERT must not be mixed with any other medications in the same infusion, infusion line or burette

5. Administration of ERT

Ensure special considerations during reconstitution and dilution outlined in previous sections are adhered to

- Prime administration set including **0.2 micron filter** with ERT.
- Ensure a second needleless access device (NAD) proximal to the patient's IV administration line is available, for emergency access.

Ensure no more than 1 hour of enzyme is in the burette on completion of priming

- Explain administration procedure to child and parent.
- Ensure premedication timeframe has been adequate.
- If more than 1 hour has passed since observations, repeat vital signs.
- If vital signs remain 'Between the flags', connect ERT to the patient's IV access site, following ANTT guidelines.
- Reset volume of administration smart pump prior to commencement to enable volume infused to be monitored.
- Commence infusion at initial rate specified in IIP
- Assess vital signs at frequency specified in IIP.
- If vitals remain stable, increase the rate of infusion as per IIP.

Please contact the metabolic team if there has been a significant change in the observations or you are concerned, as per CERS guidelines

- Assess child's PIVC/CVAD site hourly for signs of extravasation as per extravasation practice guideline.
- Patients are not to leave the ward or Day Stay unit with ERT infusing without explicit consent from the Metabolic consultant. If consent has been given for a patient to leave the ward or Day Stay Unit, a nurse-escort who has an understanding of how to manage adverse events related to ERT. These include management of:
    - Reactions- Mild (i.e urticarial rash) to Severe (anaphylaxis)

- PIVC or port needle dislodgement or extravasation.

Extravasation injuries can occur at any time, though there is no known association or increased risk with any particular enzyme

- Inspect burette at each rate change to ensure expected volume has been delivered and correlate with infusion pump. Refill burette to contain a maximum of 1 hour of volume.
- The rate and duration of the ERT is determined by the product used and the guidelines for administration as per the product information. Each patient's IIP has the specified rate of administration, which is determined by a patient's response to ERT, such as adverse events or infusion-associated reactions.

The rates of the ERT are not to be changed by ward clinical staff, unless under the guidance of, or consultation with the Metabolic team

- Once no further ERT remains in the bag or burette, a flush can be commenced. A significant volume of the Enzyme remains within the administration set. Priming volume of administration lines vary amongst products and brands. To ensure the child receives the full dose of ERT,

At CHW:

- Add 30mL sodium chloride 0.9% to the burette using ANTT, and continue infusion at final specified rate.

At SCH:

- Add an appropriate volume of sodium chloride 0.9% for the relevant administration line;

- **Do not increase the rate of infusion during the flush.**
- An observation period is specified within an IIP. Note the time, and communicate to parent and child the timeframe of observation.
- Ensure a positive-pressure flush when disconnecting IV administration line from IVAD.
- During the observation period, some patient's may be able to attend other appointments within the hospital after discussion with the Metabolic Team. This is considered on an individual patient basis for each episode.

If a parent/ patient refuses to remain in the Day Stay unit for the observation period, please document this in the patient's medical record & inform the Metabolic team

Infusion Associated Reactions (IAR's)

There are two types of IAR that have been observed with ERT.

- Hypersensitivity reactions that occur during the infusion are usually minor and respond quickly to oral anti-pyretics or antihistamines, and/or reduction of the infusion rate. The patients generally develop symptoms 5 – 60 mins after starting the infusion.

- Delayed or Biphasic reactions can occur, these tend to present as a rash, pyrexia, and occasional respiratory symptoms. The second wave of symptoms usually occurs 1 – 24 hours after the first symptoms but this delay can be longer.

An IAR is more common if ERT is administered when there is evidence of intercurrent illness. The infusion should be given with caution in children with asthma and/or eczema, or if the child has had an immediate hypersensitivity reaction previously to another drug.

Types of IAR's and their immediate management

All IAR's are to be notified to the metabolic CNC's/NP, and or Metabolic RMO

Symptoms	Action (**All Actions must be confirmed with the Metabolic Team**)
Mild reaction • Flushing • Fever and/or shivering • Nausea, abdominal pain • Irritability (especially in young children) • Headache	• **Stop infusion** • Give oral anti-pyretic and/or anti-histamine. • Reduce rate as determined by Metabolic Team • Consider pre-medication with oral antihistamine and/or antipyretic prior to next infusion
Moderate reaction • Chest pain • Itching and/or raised urticarial rash • Severe headache • Gastrointestinal symptoms, vomiting, diarrhoea, abdominal cramping.	• **Stop infusion** • Give oral antihistamine and consider IV corticosteroids • Record all details in infusion log • Pre-treat with oral antihistamine and/or antipyretic prior to next infusion. •
Severe Anaphylactic Reaction • Respiratory symptoms: Shortness of breath, stridor, wheezing, laryngeal oedema/ spasm. • Respiratory arrest, • Cardiac Arrhythmias • Anaphylactic shock with hypotension and circulatory collapse.*	• **Stop Infusion** • **Call 'Code Blue' as per BTF-CERS escalation policy** • **Give Adrenaline – Use Epipen if available** • **Give IV antihistamines and or corticosteroids if indicated** • **Close vital sign and patient monitoring** • **Obtain bloods for IgE status 3-5 days later**

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. Please contact the Metabolic CNC's/NP/ Metabolic registrar for further instructions and discussion.

Refer to Adverse Drug Reaction Practice Guideline

Reference List

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