Serum asparaginase activity monitoring in children and adolescents

UPDATED 2024 ANZCHOG GUIDELINE

ANZCHOG
Australian & New Zealand Children's Haematology/ Oncology Group

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This guideline has been written to assist Australasian clinicians in implementing best practice in the use of the different preparations of asparaginase and in using and interpreting serum asparaginase activity assays (SAA).

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Key recommendations

1. For patients receiving any asparaginase therapy as part of therapy for lymphoblastic leukaemia or lymphoma, consider performing Therapeutic Drug Monitoring (TDM).
2. Serum asparaginase activity is used as a surrogate for plasma asparagine depletion. The internationally accepted standard for sufficient depletion is asparaginase levels ≥ 0.1 IU/ml (100 IU/L).
3. The role of TDM is to:
   a. Identify silent inactivation.
   b. Help distinguish infusion reactions and guide management of grade 1-2 hypersensitivity reactions.
4. The suggested timing of TDM assessment is:
   a. 7 – 10 days after each dose of pegaspargase. If levels are adequate i.e. ≥ 0.1 IU/ml), no further monitoring is required for that dose (i.e. no nadir at day 14).
   b. Trough levels should be monitored once during each course of Erwinase, at 48 hours post a dose. Recommended timing of TDM varies (post dose 1, dose 5 or final dose).
   c. Enrylaze TDM should be performed once during each course, at 48 hours post a dose if dosing every 48 hours, or if dosing Mon/Wed/Fri then at 72 hours post the Fri dose (i.e. prior to subsequent Mon dose).
5. Premedication combined with TDM allows safe drug administration and monitoring of effectiveness without loss of efficacy.
6. For grade 1-2 hypersensitivity reactions, rechallenge with pre-medication and drug monitoring can be considered.
7. For grade 3 and above hypersensitivity reactions, switching to an alternative product with TDM is recommended.

Background

Asparaginase is a critical component of modern multi-agent chemotherapy regimens for leukaemia/lymphoma and has been shown to significantly improve outcomes.[1] Asparagine is required by all cells for protein production and cell growth. In contrast to healthy cells, leukaemia/lymphoma cells have limited capacity to produce endogenous asparagine and are fully reliant on an external supply.[2]

Asparaginase is an enzyme that hydrolyzes asparagine to aspartic acid and ammonia whilst also depleting glutamine (required for mitochondrial metabolism). By disrupting asparagine availability, asparaginase depletes malignant cells of this essential amino acid required for cell growth and replication. This, combined with reduced glutamine, leads to inadequate protein synthesis and leukaemic cells subsequently undergo apoptosis.[3]

PEGylated-asparaginases are derived from *Escherichia coli (E. coli)* with polyethylene glycol (PEG) attached to prolong drug activity and reduce immunogenicity.[4] Pegaspargase (Oncaspar®), often referred to as PEG-asparaginase, is currently the most common first line agent. Alternative long acting agents available overseas that may enter the Australasian market include calaspargase pegol-mknl (Asparlas®) which utilises an alternative linker to the PEG moiety, provides a longer half-life and is being incorporated into Children's Oncology Group (COG) protocols in North America.[5]

Crisantaspase (Erwinase®), often referred to as Erwinia, is an asparaginase derived from the bacterium *Erwinia chrysanthemi*. It is approved for use in combination with multi-agent chemotherapy in patients who are allergic to or have developed antibodies to PEGylated *E. coli* derived asparaginase. Erwinase is immunologically distinct from *E. coli* derived asparaginase, meaning there is no risk of cross reactivity.[6] Each dose of pegaspargase requires replacement with 6 or 7 doses of *Erwinia* asparaginase depending on the treatment protocol. Route (intravenous (IV) versus intramuscular (IM)) and frequency (doses 48 hours apart or a Monday/Wednesday/Friday schedule) vary depending upon unit preference.

There is evidence that IM dosing maintains plasma levels longer than IV. For sites using IV dosing with a Monday/Wednesday/Friday schedule, a combination of routes (IV Monday/Wednesday and IM Friday) may be more optimal to maintain therapeutic levels.[7]

Recombinant crisantaspase (Enrylaze®), an *Erwinia chrysanthemi* L-asparaginase, is produced in *Pseudomonas fluorescens* by recombinant DNA technology and is an alternative non-*E coli*. based asparaginase product. Dosing is either every 48 hours or a Monday/Wednesday/Friday schedule, with dosing varying between treatment regimens.[8, 9] Enrylaze is currently undergoing TGA evaluation.

Definition of optimal activity

Serum asparaginase activity (SAA) is used as a surrogate for plasma asparagine depletion. The current internationally accepted standard threshold for sufficient depletion is a serum asparaginase activity of ≥ 0.1 IU/ml (100 IU/L). Any level greater that this is considered sufficient for complete asparagine depletion and is the same for all preparations of asparaginase.[10, 11]

Laboratory listings / contacts

Serum asparaginase activity is currently being performed at the laboratories listed below.

CRITICAL INFORMATION FOR TESTING:
drug type (e.g. pegaspargase versus Erwinia) and date of dose MUST be included in the sample request form.

AUSTRALIA

The Children's Hospital at Westmead

NATA accredited and international eQAP performed
Contact details: Dr Christa Nath
Email: christa.nath@health.nsw.gov.au
Tel: +61 (2) 7825 3287
Shipping address:
Dr Christa Nath
Department of Biochemistry, The Children's Hospital at Westmead, Cnr Hawkesbury Rd and Hainsworth Street, Westmead, NSW 2145
Sample requirements: Please freeze lithium heparin plasma and store at -20 to -80°C before shipping in dry ice within 2 days of collection and accompanied by a completed CHW asparaginase Testing Request Form.

Alfred Hospital, Melbourne

NATA accredited
Contact details: Mayumi Knight
Email: heam.lab.managers@alfred.org.au
Tel: +61 (3) 9076 3616
Shipping address:
Central Specimen Reception, Pathology Department, Alfred Hospital, 55 Commercial Road, Melbourne, VIC 3004
Sample requirements: 5mL blood collected in SST gold top gel tube (EDTA or lithium heparin samples acceptable). Centrifuge within 2 hours of collection. Aliquot serum and freeze immediately. Store at -20 to -80°C before shipping on dry ice.

Royal Brisbane & Women's Hospital

NATA accredited
Contact details: Dr Carel Pretorius
Email: carel.pretorius@health.qld.gov.au
Tel: +61 (7) 3646 0083
Shipping address:
Pathology Queensland Central Laboratory,
Herston Hospital Campus, Level 3, Block 7,
Herston Road, Herston, QLD 4029
Sample requirements: Please freeze serum or lithium heparin samples as soon as possible after collection. Store at -20 to -80°C before shipping in dry ice. Frozen samples should be thawed only once. (N.B. Freezing not required if reaches lab and is processed within 8 hours of collection).

PathWest Laboratory Medicine, Perth

NATA accredited
Contact details: Conchita Boyder
Email: conchita.boyder@health.wa.gov.au
Tel: +61 (8) 6383 4113
Shipping address:
PathWest, PP Block, QEII Medical Centre
Verdun Street, Nedlands, WA, 6009
Sample requirements: Serum is ideal, however EDTA or lithium heparin are acceptable. Please separate and freeze samples within 2 hours of collection. Store at -20 to -80 °C before shipping on dry ice and accompanied by a PathWest Asparaginase Activity request form. A minimum of 0.5 mL of sample is required for the analysis. Please contact laboratory if outside Perth.

NEW ZEALAND

Canterbury Health Laboratories, Christchurch

IANZ accredited
Contact details: Chris Sies
Email: chris.sies@cdhb.health.nz
Tel: +64 (3) 3630332
Shipping address:
Canterbury Health Laboratories
Cnr of Hagley Ave and Tuam Street,
Christchurch 8140, New Zealand
Sample requirements: 1 x 4.5ml LiHep PST – separated sample on dry ice. Please contact laboratory for shipping requirements.

Drug preparations

Bacterial source	Generic names	Brand name	PEGylated	Linker used	Vial size	Route of administration
E. coli Asparaginases	pegaspargase	Oncaspar®	Yes	Succinimidyl succinate (SS) linker	3,750 IU per 5 ml	Intramuscular Intravenous
	calaspargase pegol-mknl	Asparlas®	Yes	Succinimidyl carbonate (SC) linker	3,750 IU per 5 ml	Intramuscular Intravenous
Non-*E. coli* derived Asparaginases	crisantaspase	Erwinase®	No	–	10,000 IU	Intramuscular Intravenous
	recombinant crisantaspase	Enrylaze®	No	–	10mg in 0.5 ml	Intramuscular Intravenous

Pre-medication

Pre-medication has been shown in some studies to reduce the rates of severe reaction, allowing increased numbers of patients to continue asparaginase therapy without compromising efficacy,[12] however there is ongoing debate in the literature as other studies showing limited benefit have recently been published.[13] However given the minimal cost and relative ease, the majority of Australian/New Zealand centres are using pre-medication (combined with TDM) as per the below pre-medication schedule for each dose of asparaginase.

Confirm dosing with local prescribing guide e.g. Australian Medicines Handbook, prior to prescribing.

Drug	Dose
Famotidine	oral, 1 mg/kg, max 20 mg
Cetirizine	oral, 2.5 mg – 10 mg (according to age as per Australian Medicines Handbook)
± Hydrocortisone	intravenous, 1 mg/kg, max 100 mg
± Paracetamol	oral, 15 mg/kg, max 1000mg
PRN Adrenaline	1:1000, 0.01 ml/kg up to 0.5 ml as per Advanced Paediatric Life Support (APLS)

Age	Cetirizine dose
1-2 years	2.5 mg
2-6 years	5 mg
> 6 years	10 mg

It is recommended to combine pre-medications with TDM for effective drug administration.[14]

Clinical reactions to asparaginase

There are two different types of clinical reactions to asparaginase therapy, hypersensitivity and infusion reactions. The reported rate of clinical hypersensitivity reactions varies greatly in the literature, but can occur in 3-37% of patients receiving asparaginase preparations.[6] Distinguishing between true hypersensitivity and acute non-antibody mediated infusion reaction can be extremely difficult due to overlapping signs and symptoms. Careful case-by-case consideration is required.[6,15]

True hypersensitivity	Non-antibody mediated infusion reaction
Potential development of neutralising antibodies	No antibody production
Systemic reaction	Typical clinical signs can include flushing, nausea, rash
Most often occurs after previous exposure to asparaginase	May occur with first exposure
Reduced asparaginase levels on TDM	Good levels of asparaginase depletion after dose
	Elevated ammonia levels
No benefit from further *E. coli* asparaginase	**Retain benefit from current asparaginase preparation**

Grading of asparaginase reactions[16]

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0					
	Grade I	**Grade II**	**Grade III**	**Grade IV**	**Grade V**
Anaphylaxis or allergic reaction	Transient flushing or rash. **No systemic intervention required**	Transient rash or flushing, urticaria, dyspnoea, drug fever ≥ 38°C. **Oral intervention**	Symptomatic bronchospasm, urticaria, hypotension, oedema/ angioedema, hospitalisation. **Intravenous intervention required**	Life-threatening anaphylaxis. **Critical intervention required**	**Death**
Infusion related reaction	Mild, transient. **Infusion not interrupted**	Therapy interrupted. **Improvement with symptomatic therapy**	Prolonged and recurrent symptoms after infusion interrupted. **Intervention and hospitalisation**	Life-threatening. **Critical intervention required**	**Death**

Accurate grading of reactions is important, particularly between grades 2 and 3 which determines if re-challenge can be considered or not.

Management recommendations in the setting of clinical allergy

1. Stop the infusion immediately.
2. Press emergency buzzer to obtain assistance and request urgent medical review with consideration of MET/CODE call.
3. Aspirate asparaginase if intravenous administration.
4. Full set of observations and continuous monitoring (blood pressure, heart rate, oxygen saturations, respiratory rate, temperature).

Grade I to II reactions

1. Medical review +/- intervention.
2. Ongoing monitoring for signs of severe allergic reaction (haemodynamic and respiratory compromise).
3. Document reaction grading in the medical note.
4. Consider admission for 24 hours if PEGylated product administered.
5. In consultation with paediatric oncologist, consider rechallenging with the same asparaginase preparation and premedications.
    a. Slow infusion to run over two or more hours.
    b. Addition of hydrocortisone if not used previously.

Early therapeutic drug monitoring (day 4-7) for confirmation of effective asparagine depletion.

Grade III to IV reactions

1. Emergency management of anaphylaxis as per APLS anaphylaxis algorithm.
2. Admit to paediatric ward or intensive care unit depending upon clinical status.
3. Switch to alternative asparaginase product if available with therapeutic drug monitoring.

Indications for switching to alternative asparaginase therapy

- Grade III to IV adverse reaction to PEGylated asparaginase products.
- Silent inactivation by anti-asparaginase antibodies confirmed by undetectable asparaginase level.
- Administered PEGylated-asparaginase product otherwise not tolerated.

Therapeutic drug monitoring

Serum asparaginase activity is used as a surrogate for plasma asparagine depletion. The internationally accepted standard is an asparaginase level ≥ 0.1 IU/ml (100 IU/L).[1, 2,10,17] Measuring asparaginase levels when less than 50% of a dose has been received may result in an uninterpretable result.

Monitoring of serum asparaginase activity is used to

- Distinguish infusion reactions that maintain adequate asparagine depletion from hypersensitivity reactions with development of neutralising antibodies.
- Identify patients without overt signs of reaction but with development of neutralising antibodies (silent inactivation).

Monitoring of asparaginase activity for guiding a switch to alternative asparaginase therapy has been shown to improve patient outcomes and reduce preparation switching.[15]

Timing of therapeutic drug monitoring

Pegaspargase (Oncaspar®)

- 7 – 10 days after each dose of Pegaspargase.
- If levels are adequate (i.e. ≥ 0.1 IU/ml), no further monitoring is required for that dose.

Asparaginase *Erwinia chrysanthemi* (Erwinase®)

- Trough levels should be monitored once during each course of *Erwinia*, at 48 hours post a dose.
- There is no clear consensus regarding timing of measurement within a course, with variations in practice including pre dose 2, pre dose 6 or 48 hrs post the last dose.

Asparaginase *Erwinia chrysanthemi* (recombinant)-rywn (Enrylaze®)

- When administered every 48 hours, a trough level should be performed once at 48 hours post dose.
- When dosing on a Monday/Wednesday/Friday schedule, a trough level should be measured 72 hours after the Friday dose and prior to administration of the following Monday dose.

Silent inactivation

Most studies suggest rates of silent inactivation to asparaginase products are low (0-8% of patients). When identified (i.e. a day 7 level < 0.1 IU/ml and/or below limit of quantification at day 14 after administration of pegaspargase), switching to an alternative asparaginase product with TDM is recommended.[10,18] There is no alternative product available for patients who develop silent inactivation to *Erwinia* or Enrylaze asparaginase products (i.e. 48 hour post dose SAA below limit of quantification).

Nursing preparation and administration

Wherever possible, asparaginase products should be prepared in a pharmacy cytotoxic suite. All information below is a guide only, refer to product information and local guidelines prior to use.

Pegaspargase (Oncaspar®) preparation

- Unopened Oncaspar vials should be kept refrigerated (2-8°C). Do not freeze. Unopened vials can be stored at room temperature (up to 25°C) for up to 48 hours.
- After reconstitution, the product should be ideally used immediately. The reconstituted product can be stored for up to 24 hours at 2-8°C or up to 6 hours below 25°C.
- Reconstitute each 3750 international unit vial with 5.2 mL of water for injection to make a 750 international units/mL solution.
- Prepare in 100 mL of sodium chloride 0.9% for intravenous use.
- Swirl gently until the powder is reconstituted. Do not shake.
- Visually inspect the vial for particulate matter, cloudiness or discolouration prior to use. If the solution is not clear and colourless, contact the pharmacist.
- Oncaspar does not contain antimicrobial preservative. It is for single use in one patient only. Discard any unused solution.

Asparaginase *Erwinia chrysanthemi* (Erwinase®) preparation

- Unopened *Erwinia* asparaginase vials should be kept refrigerated.
- After reconstitution, the product should be ideally used within 15 minutes. If there is delay of more than 15 minutes, the solution should be withdrawn into a syringe and used within 8 hours. The reconstituted product should be stored below 25°C.
- Reconstitute each 10 000 international unit vial with 1 mL of sodium chloride 0.9% to make a 10 000 international units/mL solution.
- Add sodium chloride 0.9% solution for injection slowly against the inner vial wall. Do not squirt directly onto or into the powder. Allow the contents to dissolve by gentle mixing or swirling while maintaining the vial in an upright position. Avoid contact with the stopper. Avoid froth formation due to excessive or vigorous shaking.
- Swirl gently until the powder is reconstituted. Do not shake.
- Visually inspect the vial for particulate matter, cloudiness or discolouration prior to use. If the solution is not clear or colourless, contact the pharmacist.

Asparaginase *Erwinia chrysanthemi* (recombinant)-rywn (Enrylaze®) preparation

- Ready-to-use vial (no reconstitution or filtration required).
- Undergoing TGA evaluation for intramuscular and intravenous use.
- Enrylaze should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter, cloudiness or discolouration are present, discard the vial.
- Discard the remaining unused Enrylaze in the single-dose vial.
- Do not shake or freeze.

Asparaginase *Erwinia chrysanthemi* (Erwinase®) and Pegaspargase (Oncaspar®) administration

For intravenous administration

- Withdraw the required dose and dilute in 100 mL of sodium chloride 0.9% or glucose 5%. Infuse over 1-2 hours as per treatment protocol or local practice.
- Note: Some centres deliver 10% of the dose in the first hour and 90% of the dose in the second

For intramuscular administration

- Withdraw the required dose and administer undiluted.
- It is highly recommended that intramuscular administration be given in a treatment room rather than the child's bed space.
- Maximum volume at each injection site is 2 mL. If the volume is greater than 2 mL administer at multiple injection sites as per local policy.
- It is preferable to give intramuscular asparaginase into deep muscular tissue. The upper/outer buttock region (ventrogluteal) or upper/outer thigh (vastus lateralis) are preferred sites.

The route of administration varies between institutions, with IV associated with increased emetogenicity and IM associated with the pain/discomfort of injection.[19] Please refer to local hospital administration guidelines.

Preparing for drug administration

Hypersensitivity reactions are the most common dose limiting toxicity and thus resuscitation facilities must be close at hand when administering asparaginase products.

Preparing the environment for potential adverse reactions

- Ensure all baseline investigation requirements have been met:
  - Platelets > 30 x 10^9/L for IM injection. If a platelet transfusion is required, it is recommended to administer IM asparaginase at least one hour after the platelet transfusion to allow clear identification of cause if a reaction occurs.
- The child is located in a space/area which is conductive to a potential emergency situation (i.e. sufficient room for emergency team to initiate resuscitation/APLS).
- Emergency equipment (oxygen, suction) is available in the correct size and is functioning at the patient's bedside.
- The location of the emergency trolley is known and has the correct sized equipment for the patient.
- Emergency drugs (i.e. adrenaline, hydrocortisone) and dosing are readily available in the emergency trolley or on ward.
- Medical staff members are aware a high risk therapy is occurring and are available to provide care on the ward/clinic during administration, as per local guidelines.

Preparing the patient and carer for potential adverse reactions

- Ensure the child and their carer are aware of the signs and symptoms of hypersensitivity reactions and the actions to take, including utilisation of the emergency bell.

Monitoring requirements

Nursing care during administration

- Baseline observations must be recorded immediately before commencing the infusion/administration of IM injection.
- Observation of the patient during administration is essential.
- Nurses must remain in the room or in immediate proximity for the first 15 minutes of the infusion. A full set of observations should be recorded at 15 minutes.
- If the child is stable after 15 minutes, a full set of observations should be recorded every 30 minutes thereafter, until one hour after the end of the infusion/IM injection. Examine the site of drug administration with each set of observations.
- The child must remain within the supervised hospital setting for at least 1 hour post the completion of asparaginase administration.

Patient care following administration and discharge planning

Post administration, ensure that

- The child and carer are aware of the potential side effects of asparaginase occurring immediately or in the days after administration e.g. loss of appetite, nausea/vomiting, allergic reaction, localised skin reaction/reaction, abdominal pain, hyperglycaemia (and associated signs such as frequent urination, thirst and lethargy). The patient or family must know to contact their treating oncology centre or their shared care hospital if they experience any side effects and are aware of the actions to take if there is a delayed anaphylactic reaction outside the hospital setting (i.e. calling an ambulance).
- The process of administration is documented in the patient's clinical record and the chemotherapy/medication chart is signed appropriately.

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Abbreviations

APLS: Advanced Paediatric Life Support; **ANZCHOG:** The Australian and New Zealand Children's Haematology/Oncology Group; **CHW:** Children's Hospital at Westmead; **COG:** Children's Oncology Group; **CTCAE:** Common Terminology Criteria for Adverse Events; **DNA:** Deoxyribonucleic acid; **EDTA:** Ethylenediaminetetraacetic acid; **eQAP:** External Quality Assessment Project; **PEG:** Polyethylene glycol; **IM:** Intramuscular; **IV:** Intravenous; **IU:** International units; **L:** Litre; **MET:** Medical Emergency Team; **ml:** Millilitre; **NATA:** National Association of Testing Authorities; **SAA:** Serum asparaginase activity; **SC:** Succinimidyl carbonate; **SS:** Succinimidyl succinate; **SST:** Serum-separating tube; **TDM:** Therapeutic Drug Monitoring.

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