

# ANZCHOG GUIDELINE:

## Serum asparaginase activity monitoring in children and adolescents

Reproduced by Servier for distribution, with permission from ANZCHOG



### AUTHOR:

#### Dr Siobhan Cross

on behalf of the Leukaemia-Lymphoma Group of ANZCHOG

### DATE OF PUBLICATION:

June 2020

### DATE OF REVIEW:

June 2022

*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.*

### KEY SUMMARY POINTS:

1. All patients receiving asparaginase preparations should have Therapeutic Drug Monitoring (TDM).
2. The recommended method is using a validated serum asparaginase activity assay.
3. TDM should be performed for each dose of PEG asparaginase for all patients and as recommended for each course of Erwinia asparaginase (see body of text for timing).
4. If TDM levels suggest silent in-activation then switching to an alternative product if possible is recommended.
5. If Grade 1-2 hypersensitivity reactions occur, then re-challenge after premedication for current and subsequent doses should be considered.
6. If grade  $\geq 3$  hypersensitivity reactions occur then switching to an alternative product is required by the Children's Oncology Group and recommended in the National Comprehensive Cancer Network (NCCN) guidelines, regardless of asparaginase activity.
7. Premedication may reduce the rate of clinical hypersensitivity and can be considered for routine use in the setting where TDM is available.

## Current laboratories with asparaginase activity assays and sample requirements:

1. **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:** (02) 9845 3287

#### Shipping address:

**Attention: 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 deg C before shipping in dry ice within 2 days of collection and accompanied by the completed CHW asparaginase Testing Request Form.

2. **Royal Brisbane & Women's Hospital, Brisbane – NATA accredited**

#### Contact details: Dr Carel Pretorius

**Email:** Carel.Pretorius@health.qld.gov.au

**Tel:** (07) 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 deg C before shipping in dry ice. Frozen samples should be thawed only once.

3. **Alfred Hospital, Melbourne – NATA accredited**

#### Contact details: Heather Aumann

**Email:** h.aumann@alfred.org.au

**Tel:** (03) 90763616

#### Shipping address:

**Central Specimen Reception,  
Pathology Department, Alfred Hospital**

55 Commercial Road, Melbourne VIC, 3004

**Sample requirements:** Please freeze serum, EDTA or lithium heparin samples within 2 hours of collection. Store at -20 to -80 deg C before shipping in dry ice. Please indicate on the request form the type of asparaginase given.

## Background:

While L-asparaginase is an important component of therapy for acute lymphoblastic leukaemia, its use is associated with several significant side effects. The commonest of these and the focus of this document is hypersensitivity reactions. The reported rates of clinically significant hypersensitivity vary widely, from 10-30% with the native *E. coli* product and 3-24% with the PEGylated *E. coli* product (PEGasp)<sup>1</sup>. A recent review reports the rate of grade  $\geq 3$  reactions at 2-10% in children and adults<sup>2</sup>. As well as hypersensitivity reactions there can also be the development of silent neutralizing antibodies that lead to a decrease in drug efficacy. The rate of silent inactivation is less certain but is reported to occur in approximately 10% of children who have no clinical evidence of hypersensitivity<sup>3</sup>.

### Clinical reactions to PEG-Asparaginase may represent:

1. True antibody mediated hypersensitivity to *E. coli* asparaginase
  - Such patients likely will not benefit from further PEG or *E. coli* asparaginase, so attempted re-challenge with pre-medication is not recommended
2. Antibody mediated reaction to polyethylene glycol
  - PEG antibodies are inactivating for this formulation<sup>4</sup> however *E. coli* asparaginase is no longer commercially available
3. Non-antibody mediated infusional reaction: complement/histamine/ammonia-mediated
  - Such patients retain benefit from all asparaginase formulations

To avoid decreasing the intensity of therapy by giving an ineffective drug to patients, recent guidelines recommend testing for serum asparaginase activity<sup>6</sup>.

There have also been studies published recently suggesting that premedication with antihistamines may decrease the rate of development of hypersensitivity reactions. This may improve exposure to asparaginase as fewer patients may be unnecessarily changed to Erwinia as the PEG-asp product leads to higher and more consistent serum asparaginase activity<sup>6-8</sup>.

## Summary of recommendations in an Australia/New Zealand (ANZ) context:

### 1. What is the best way to measure asparaginase activity?

Asparaginase activity levels – methods include reaction of Indoxine<sup>9</sup> (CHW method), B-nicotinamide adenine dinucleotide<sup>10</sup> (Brisbane Method), both of which are NATA accredited, or a commercial assay (AIBio Tech now Granger Genetics). All assays are NATA accredited and all laboratories have participated in inter-laboratory comparisons and/or external quality control programmes. These methods are preferred to direct measurement of the substrate, asparagine, as ongoing activity of the

asparaginase enzyme ex vivo may lead to ongoing depletion and falsely low readings. Asparaginase antibodies can also be measured but there are no clinically validated methods and the development of antibodies has poor correlation with asparaginase activity with some antibodies appearing to have no effect on enzyme activity.

### 2. What is the definition of optimal activity?

Currently a nadir level of  $\geq 0.1$  IU/mL ( $>100$ U/l) (at 14 days post PEG-asp administration or taken prior to each dose of native *E. coli* or Erwinia Asparaginase) is considered desirable. Consideration should be given to measuring asparaginase activity at day 7 and day 14 post PEG-asp as a level of  $<0.1$ U/ml at day 7 would be highly suggestive of inactivation.

### 3. What is the recommendation in the setting of a clinical allergy?<sup>11</sup>

For grade 1 and 2 reactions (rash, flushing, urticaria, and drug fever  $\geq 38^{\circ}\text{C}$ ) without bronchospasm, hypotension, oedema, or need for parenteral intervention) continuation of asparaginase with premedication and re-challenge with subsequent dose may be considered. TDM for inactivation is recommended.

If anti-allergy premedication is used prior to PEG or Erwinia administration, consideration should be given to TDM using commercially available asparaginase activity assays, since premedication may “mask” the systemic allergic reactions that can indicate the development of neutralizing antibodies.

Grade 3 and 4 reactions merit permanent discontinuation of the type of asparaginase that caused the reaction.

Asparaginase TDM can be useful when attempting to distinguish between an infusion reaction as opposed to true hypersensitivity particularly if  $>50\%$  of the dose has been given.

### 4. Silent inactivation

All patients should undergo TDM for silent inactivation. The recommendations for measuring for silent inactivation for PEG-asp are:

- An activity level within 7 days of the dose.
- A nadir level at D14.
- If the first level and/or the nadir is  $\leq 0.1$  IU/mL then silent inactivation is considered likely and product switching is recommended. (The level prior to D7 allows for switching of product for the current dose if early TDM levels are low).

## 5. Monitoring Erwinia asparaginase activity

Monitoring Erwinia asparaginase activity can inform individualisation of dosing amount and/or frequency, as clearance varies between individuals. If silent inactivation occurs, there is no alternative product currently available. Levels should be  $\geq 0.1$  IU/ml. **Dose adjustments are not currently performed on protocols used in Australia and New Zealand and are beyond the scope of this guideline.**

Monday, Wednesday, Friday regimens are commonly used for convenience. Several publications have demonstrated trough levels of  $< 0.1$  IU/ml after a three day interval between doses especially if using IV rather than IM dosing. Consideration should be given to 48 hourly dosing.

Recommendations for monitoring of Erwinia asparaginase activity are 2 weekly on continuous regimens or at the end of a 2 week block on intermittent regimens. Level should be taken 48 hours after the last dose and should be  $\geq 0.1$  IU/ml.

### Summary regarding the use of premedication to decrease the development of clinical and silent asparaginase antibodies

The consensus guidelines do not recommend the use of premedication for asparaginase without using TDM for serum asparaginase activity<sup>6</sup>. The use of premedication is based on an increasing body of literature<sup>6-8</sup>.

#### Premedication (in Australia and New Zealand) can include:

- **Antihistamine (e.g. Cetirizine (2.5mg -10mg according to weight or Promethazine 0.5 mg/kg, max 25 mg)**
- **H2 blocker (e.g. Famotidine 1 mg/kg, max 20 mg)**
- **Hydrocortisone 1 mg/kg, max 100 mg.**

## Appendices:

### Appendix 1 – CTCAE grading

### Appendix 2 – Premedication schemas

## References

1. Vrooman LM et al. Erwinia asparaginase after allergy to E. coli asparaginase in children with acute lymphoblastic leukemia. *Pediatric Blood and Cancer* 2010;54(2):199-205.
2. Heo YA, Syed YY, Keam SJ. Pegaspargase: a review in acute lymphoblastic leukaemia. *Drugs* 2019;79(7):767-777.
3. Tong WH et al. A prospective study of drug monitoring of PEGasparaginase and Erwinia asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. *Blood* 2014;123(13):2026-2033.
4. Armstrong JK, Hempel G, Kolling S, et al. Antibody against poly(ethylene glycol) adversely affects PEG-asparaginase therapy in acute lymphoblastic leukemia. *Cancer* 2007;110:103–111)
5. Van der Sluis IM et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica* 2016;101(3):279–285.
6. Cooper SL et al. Universal premedication and therapeutic drug monitoring for asparaginasebased therapy prevents infusion-associated acute adverse events and drug substitutions. *Pediatric Blood and Cancer* 2019;66(8):e27797.
7. Marini BL et al. A single-center multidisciplinary approach to managing the global Erwinia asparaginase shortage. *Leukemia and Lymphoma* 2019. doi: 10.1080/10428194.2019.1608530
8. Stock W et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood*. 2019;133(14):1548–1559.
9. Lanvers C et al. Analytical validation of a microplate reader-based method for the therapeutic drug monitoring of L-asparaginase in human serum. *Analytical Biochemistry* 2002;309(1):117- 126.
10. Fernandez CA et al. High-throughput asparaginase activity assay in serum of children with leukemia. *International Journal of Clinical and Experimental Medicine* 2013;6(7):478-487.
11. National Comprehensive Cancer Network *Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia v2.19* May 2019.

## Appendix 1

**CTCAE V5** – has both allergic reaction and infusion related reaction options however asparaginase reactions biologically usually fall into the first category.

CTCAEC Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Systemic intervention not indicated	Oral intervention required	Bronchospasm; hospitalisation indicated for clinical sequelae; intravenous intervention indicated	Life threatening consequences; urgent intervention indicated	Death

**Definition:** A disorder characterised by an adverse local or general response from exposure to an allergen.

**Navigation Note:** If related to infusion, use injury, poisoning and procedural complications: Infusion related reaction. Do not report both.

Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
---------------------------	--	---	--	--	-------

**Definition:** A disorder characterised by an adverse reaction to the infusion of pharmacological or biological substances.

## Appendix 2

PEG-asparaginase administration:	For acute reactions:
<p><b>Pre-medications:</b></p> <ul style="list-style-type: none"> <li>Cetirizine 2.5mg -10mg according to weight or Promethazine 0.5 mg/kg, max 25 mg</li> <li>Famotidine 1mg/kg/dose (max 20mg)</li> </ul> <p><b>If previous grade 1-2 reaction with same product add:</b></p> <ul style="list-style-type: none"> <li>Hydrocortisone 1mg/kg(max 100mg)</li> </ul>	<p><b>Administer:</b></p> <ul style="list-style-type: none"> <li>Further dose of Promethazine 0.5 mg/kg, max 50 mg</li> </ul> <p><b>For reaction with haemodynamic instability:</b></p> <ul style="list-style-type: none"> <li>Follow APLS allergic reaction algorithm</li> </ul>

\*Adapted from Marini BL et al. A single-center multidisciplinary approach to managing the global Erwinia asparaginase shortage. Leukemia and Lymphoma 2019.