Table of Contents

INTRODUCTION .................................................................................................................... 3
SCOPE ................................................................................................................................... 3
DEFINITIONS .......................................................................................................................... 4
RECOMMENDATIONS ............................................................................................................ 5
METHODOLOGY .................................................................................................................... 14
COLLATERAL TOOLS & RESOURCES (AS APPROPRIATE) .............................................. 17
APPENDIX A. GRADING OF COMMON ASPARAGINASE TOXICITIES .............................. 18
APPENDIX B. ASPARAGINASE TOXICITY MONITORING STRATEGY SUMMARY .......... 19
APPENDIX C. ASPARAGINASE TOXICITY MANAGEMENT SUMMARY ............................ 20
REFERENCES ....................................................................................................................... 21
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Introduction
Asparaginase products pegylated-asparaginase (pegaspargase) and asparaginase Erwinia chrysanthemi (Erwinia asparaginase) are medications utilized in treatment protocols for various hematologic malignancies. These products have been an integral aspect of multiagent therapy yielding high survival rates in pediatric acute lymphoblastic leukemia (ALL).1, 2 Of the two available asparaginase products in the US, pegaspargase is recommended as first-line therapy due to its longer duration of action, less frequent administration, and flexibility in route of administration (i.e., intramuscular and intravenous).3,9

The limiting factors to using asparaginase for both adult and pediatric patients are the toxicities associated with the drug, which include hypersensitivity, pancreatitis, hyperglycemia, hypertriglyceridemia, hepatotoxicity, hyperbilirubinemia, hyperammonemia, and thrombotic events.1, 9-13 In pediatric patients, hyperammonemia and hypersensitivity are among the most common toxicities that occur. The Children’s Oncology Group (COG) discourages pre-medication with antihistamines as this may mask a possible systemic allergy to pegaspargase, which often signals the presence of asparaginase neutralizing antibodies. Many pediatric patients are often switched to Erwinia asparaginase at the first sign of a hypersensitivity reaction, regardless of the severity.6, 7

Compared to pediatric patients, adult patients being treated for ALL have traditionally used little to no asparaginase in their treatment regimens. This is because the toxicities associated with asparaginase have been reported more frequently in adults than in children, and it has been shown that toxicity frequency with asparaginase has a proportional relationship with patient age.9, 13 Depending on the grade of these toxicities, patients may temporarily discontinue asparaginase therapy and initiate at a later date, switch asparaginase products, or simply discontinue asparagine-depleting therapy altogether.3, 5-7, 9 Along with discontinuation of asparaginase therapy correlating with a higher mortality rate, inappropriately switching patients to Erwinia asparaginase has been shown to be associated with higher health care spending due to drug acquisition cost and a more frequent dosing regimen.14 The historical lack of asparaginase in adult ALL regimens is believed to be a strong contributing factor to the worse prognosis of adults being treated for ALL compared to pediatric patients.1, 9, 10, 12, 15 Much of the recent literature has looked at treating adults with “pediatric-inspired” regimens to elucidate the toxicity profile in adults and showcase various strategies, such as changing dosing, monitoring practices, or toxicity management, to allow adult patients to better tolerate the toxicities of asparaginase products, ultimately decreasing mortality through prolonged asparaginase therapy.1, 4, 9-12, 14-21

Scope
Intended User(s): Advanced Practice Providers, Pharmacists, Physicians, Registered Nurses

Objective(s): To maximize outcomes and minimize toxicity associated with asparaginase-containing regimens. In addition, this guideline aims to avoid inappropriate use of Erwinia asparaginase.

Target Population: Adult and pediatric oncology inpatients and clinic patients receiving asparaginase products
Clinical Questions Considered:

- What are appropriate monitoring practices for adult and pediatric patients on asparaginase products?
- What types of hypersensitivity reactions are appropriate to facilitate transition of patients from pegaspargase to Erwinia asparaginase?
- What grades of hypersensitivity reactions facilitate obtaining an asparaginase enzyme activity level in a patient?
- How should an asparaginase enzyme activity level be interpreted and what should the resulting action be?
- What are appropriate management practices for patients experiencing various toxicities (hepatotoxicity, pancreatitis, hyperglycemia, CNS/non-CNS thrombosis, CNS/non-CNS bleeding, hyperammonemia) due to asparaginase therapy?

Definitions

<table>
<thead>
<tr>
<th>Enzyme Activity Level</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>&lt; 0.1 IU/mL</td>
<td>Subtherapeutic</td>
</tr>
<tr>
<td>0.1 – 1 IU/mL</td>
<td>Therapeutic, re-draw level within 14 days</td>
</tr>
<tr>
<td>&gt; 1 IU/mL</td>
<td>Therapeutic, continue therapy</td>
</tr>
</tbody>
</table>

1. CTCAE: Common Terminology Criteria for Adverse Events
2. BSA: Body Surface Area
3. COG: Children’s Oncology Group
4. PT: prothrombin time
5. PTT: partial thromboplastin time
6. FFP: fresh frozen plasma
7. LMWH: low molecular weight heparin
8. ULN: upper limit of normal
9. ADL: activities of daily living
Recommendations

1. Asparaginase product choice
   1.1 It is recommended that pegaspargase be utilized as a first-line agent for asparaginase therapy in adult and pediatric patients.\(^3\)\(^-\)\(^9\) (UW Health very low quality evidence, strong recommendation)
   1.2 It is recommended to switch from pegaspargase to Erwinia asparaginase in adult and pediatric patients that have experienced a severe grade 2 hypersensitivity reaction or a true grade 3 or 4 hypersensitivity reaction.\(^3\)-\(^7\), \(^9\), \(^22\), \(^27\) (UW Health low quality evidence, strong recommendation)
   1.3 The substitution of Erwinia asparaginase for pegaspargase after adverse events other than hypersensitivity should be avoided.\(^3\), \(^5\)-\(^7\) (UW Health very low quality evidence, strong recommendation)

2. Asparaginase product dosing and administration
   2.1 Pegaspargase should be dosed based on UW Health protocols utilized for the treatment of various hematologic malignancies.\(^5\)-\(^7\) (UW Health very low quality evidence, strong recommendation)
   2.2 In adult patients, intramuscular administration should be recommended over intravenous administration due to the potential increased risk and faster onset of hypersensitivity of intravenously-administered pegaspargase.\(^5\) (UW Health very low quality evidence, strong recommendation)
   2.3 In pediatric patients, intravenous infusion over 2 hours should be utilized to minimize hypersensitivity, hyperammonemia, and injection site trauma associated with intramuscular injections of pegaspargase.\(^6\), \(^7\), \(^28\) (UW Health very low quality evidence, strong recommendation)
   2.4 Erwinia asparaginase should be dosed based on protocols UW Health utilizes for treatment of various hematologic malignancies.\(^5\)-\(^7\) (UW Health very low quality evidence, strong recommendation)
   2.5 Dose adjustments for both adult and pediatric patients should be guided by the patient’s treatment protocol and the grade of toxicity that the patient experienced.\(^3\), \(^5\)-\(^7\) (UW Health very low quality evidence, strong recommendation)
   2.6 It is reasonable to consider capping the dose at 1 vial (3750 IU/m\(^2\)) or banding the dose to 10\% as it has been shown to yield effective asparagine depletion while having a potentially lower toxicity risk in adult patients due to decreased drug exposure.\(^1\), \(^9\), \(^10\), \(^17\) (UW Health very low quality evidence, strong recommendation)

3. Monitoring of toxicity for patients receiving asparaginase products
   3.1 Pediatric patients with a BSA ≥ 1.6 m\(^2\) should be monitored with the same frequency as adults due to an increased risk for toxicity.\(^1\), \(^10\), \(^16\), \(^18\) (UW Health very low quality evidence, strong recommendation)
   3.2 Asparaginase toxicity grades may be determined using CTCAE and the expert recommendations by Stock et al (see Appendix A).\(^9\), \(^26\) (UW Health very low quality evidence, weak/conditional recommendation)
   3.3 Hypersensitivity
      3.3.1 It is recommended that the patient be observed for 1 hour after administration of an asparaginase product and have an anaphylaxis kit available if needed.\(^3\)-\(^7\), \(^9\) (UW Health very low quality evidence, strong recommendation)
   3.3.2 Adult patients
      3.3.2.1 It is recommended that patients receive pre-medication with oral acetaminophen 650 mg and oral diphenhydramine 25 mg prior to asparaginase doses to decrease the risk of allergic reactions.\(^5\), \(^9\) (UW Health very low quality evidence, strong recommendation)
3.3.2.2 It is recommended to draw an asparaginase enzyme activity level after seven days of the first administered dose of pegaspargase to assess neutralizing antibodies and identify possible silent inactivation.1, 9, 22-25

3.3.2.3 If the asparaginase enzyme activity level after seven days is less than 0.1 IU/mL, consider switch to Erwinia asparaginase.1, 22-25 (UW Health very low quality evidence, weak/conditional recommendation)

3.3.2.4 If asparaginase enzyme activity level is between 0.1 and 1 IU/mL after seven days, redraw the level at 14 days post-dose to assess accelerated clearance.1, 9, 22-25 (UW Health very low quality evidence, weak/conditional recommendation)

3.3.3 Pediatric patients

3.3.3.1 COG discourages pre-medication to decrease the risk of allergic reactions as this may mask the appearance of systemic allergy, indicating the possible presence of asparaginase neutralizing antibodies.6, 7 (UW Health very low quality evidence, weak/conditional recommendation)

3.3.3.2 If a patient is pre-medicated to decrease the risk of allergic reactions and possible hypersensitivity, it is recommended to draw an asparaginase enzyme activity level after seven days of the first administered dose of pegaspargase to assess drug activity and identify possible silent inactivation according to Table 2.1, 6, 7, 18, 22-25, 29 (UW Health very low quality evidence, weak/conditional recommendation)

3.4 Liver Function Tests

3.4.1 It is recommended to monitor liver function tests and total bilirubin prior to asparaginase administration in all patients.5-7, 9 (UW Health very low quality evidence, strong recommendation)

3.4.2 Adult patients

3.4.2.1 It is recommended to monitor liver function tests following pegaspargase administration once weekly for two weeks and prior to subsequent doses of chemotherapy that can cause an increased risk for hepatotoxicity.5, 9 (UW Health very low quality evidence, weak/conditional recommendation)

3.4.3 Pediatric patients

3.4.3.1 It is reasonable to consider monitoring liver function tests following pegaspargase administration for patients who have pre-existing hyperbilirubinemia or elevated baseline liver function tests.3, 6, 7 (UW Health very low quality evidence, weak/conditional recommendation)

3.5 Pancreatitis

3.5.1 Amylase, lipase, and triglycerides should be checked in all patients prior to administration of the first pegaspargase dose.5-7, 9 (UW Health very low quality evidence, strong recommendation)

3.5.2 Adult patients

3.5.2.1 During induction, amylase, lipase, and triglycerides should be checked weekly for two weeks following the first dose of pegaspargase.3, 5, 9 (UW Health very low quality evidence, strong recommendation)

3.5.2.2 For further doses of asparaginase products, amylase, lipase, and triglycerides should be checked prior to administration and once seven days post-asparaginase administration due to potential for development beyond induction of chemotherapy.25, 30 (UW Health low quality evidence, weak/conditional recommendation)
3.5.3.1 For further doses of asparaginase products, triglycerides should be checked prior to administration.\textsuperscript{25} (UW Health very low quality evidence, weak/conditional recommendation)

3.5.3.2 It is reasonable to consider checking amylase, lipase, and triglycerides seven days post-asparaginase administration if the patient has previously experienced grade 2 or 3 pancreatitis or grade 2-4 hypertriglyceridemia. \textsuperscript{3, 5-7, 9} (UW Health very low quality evidence, weak/conditional recommendation)

3.6 Glucose
3.6.1 It is recommended to monitor serum glucose in patients receiving asparaginase products periodically based on the specific treatment protocol being used to treat the patient. \textsuperscript{3, 5-7, 9} (UW Health very low quality evidence, weak/conditional recommendation)

3.7 Blood and coagulation
3.7.1 For all patients, it is recommended to monitor a complete blood count with differential and fibrinogen prior to administration of any asparaginase dose. \textsuperscript{3, 5-9, 16} (UW Health very low quality evidence, strong recommendation)

3.7.2 Adult patients
3.7.2.1 Platelets and fibrinogen should be monitored twice weekly for one week following each dose of asparaginase. \textsuperscript{3, 5-9} (UW Health very low quality evidence, strong recommendation)

3.7.2.2 It is reasonable to omit monitoring PT and PTT as part of the coagulation lab workup unless fibrinogen levels are below 100 mg/dL. (UW Health very low quality evidence, weak/conditional recommendation)

3.7.3 Pediatric patients
3.7.3.1 Platelets should be monitored at least weekly following each dose of asparaginase. \textsuperscript{3, 6, 7} (UW Health very low quality evidence, weak/conditional recommendation)

3.7.3.2 If patients develop a thrombosis while on asparaginase therapy, platelets and fibrinogen should be monitored with the same frequency as adult patients to help prevent thrombosis recurrence. \textsuperscript{3} (UW Health very low quality evidence, weak/conditional recommendation)

3.7.3.3 It is reasonable to omit monitoring PT and PTT as part of the coagulation lab workup. \textsuperscript{5, 7} (UW Health very low quality evidence, weak/conditional recommendation)

3.8 Ammonia
3.8.1 In patients that present with symptoms of altered mental status, unexplained fatigue, somnolence, or seizures, serum ammonia should be monitored weekly until symptom resolution. \textsuperscript{3, 9} (UW Health very low quality evidence, weak/conditional recommendation)

3.9 Patients that resume or retrial asparaginase therapy after experiencing an adverse event should be more closely monitored for recurrence of that event. \textsuperscript{3, 5-7, 9} (UW Health very low quality evidence, strong recommendation)

4. Management of asparaginase-related toxicities
4.1 Dosing based on asparaginase enzyme activity levels
4.1.1 Adult patients
4.1.1.1 For patients that experience severe non-hypersensitivity adverse effects and have asparaginase enzyme activity documented as therapeutic, it is reasonable to consider dose reduction of 20% as clinically indicated. With any dose reduction, re-check asparaginase enzyme activity weekly
for two weeks post-dose.\textsuperscript{1, 9, 18, 19, 22-25, 29} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.2 Hypersensitivity

4.2.1 Pegaspargase should be continued in patients that experience a grade 2 or lower hypersensitivity reaction.\textsuperscript{1, 3, 9, 15} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.2.2 Refer to Table 2 for grade 2 or lower hypersensitivity management for pediatric patients. (\textit{UW Health very low quality evidence, weak/conditional recommendation})

\begin{table}[h]
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\begin{tabular}{|c|p{4cm}|p{8cm}|}
\hline
\textbf{Hypersensitivity Grade} & \textbf{Symptoms} & \textbf{Management Strategy} \\
\hline
\textbf{Grade 1} & • Transient flushing/rash \  • Temperature < 38°C & • Acceptable to give diphenhydramine PO x 1 dose \  • Continue pegaspargase infusion \  • Draw an ammonia level to rule out hyperammonemia \\
\hline
\textbf{Grade 2 (non-severe)} & • Urticaria without respiratory symptoms \  • Hypotension \  • Edema & • Give medications to treat symptoms \  • Finish pegaspargase infusion if possible \  • Draw an ammonia level to rule out hyperammonemia \  • If at least \(1/4\) of the dose was given, draw asparaginase enzyme activity level 4-7 days post-dose to test for silent inactivation. If level is: \  o \textless{} 0.1 IU/mL – initiate Erwinia asparaginase as soon as possible \  > 0.1 IU/mL – re-draw at 14 days post-dose \  > 1 IU/mL – use pegaspargase with pre-medication for next cycle \  • If giving future doses of pegaspargase: consider pre-medication with diphenhydramine followed by asparaginase enzyme activity levels \\
\hline
\end{tabular}
\end{table}

4.2.3 Pegaspargase should be discontinued in patients that experience a severe grade 2 hypersensitivity reaction or a true grade 3 or 4 hypersensitivity reaction.\textsuperscript{1, 3-7, 9, 15} (\textit{UW Health low quality evidence, strong recommendation})

4.2.4 Patients should switch from pegaspargase to Erwinia asparaginase if the patient experienced hypersensitivity reactions that required parenteral intervention due to administration of pegaspargase.\textsuperscript{3, 5-7, 9-15} (\textit{UW Health very low quality evidence, strong recommendation})

4.2.5 For patients that have an asparaginase enzyme activity level of greater than 1 IU/mL while on pegaspargase, it is recommended that they continue pegaspargase therapy for their next scheduled dose as this represents an appropriate therapeutic level.\textsuperscript{1, 22-25} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.2.6 For patients that have an asparaginase enzyme activity between 0.1 – 1 IU/mL while on pegaspargase, it is recommended that a repeat level be redrawn at 14 days post-dose to detect silent inactivation and/or accelerated clearance.\textsuperscript{1, 22-25} (\textit{UW Health very low quality evidence, weak/conditional recommendation})
4.2.7 For patients that have an asparaginase enzyme activity level of less than 0.1 IU/mL while on pegaspargase, it is recommended that they switch to Erwinia asparaginase as this represents the presence of neutralizing antibodies causing silent inactivation.\(^1,22-25\) (UW Health very low quality evidence, weak/conditional recommendation)

4.2.8 Patients that are switched to Erwinia asparaginase should have an asparaginase enzyme activity level drawn within 24-48 hours after a dose of Erwinia administration to assess drug activity and detect silent inactivation if they experience a non-severe grade 2 or lower hypersensitivity reaction.\(^1\) (UW Health very low quality evidence, weak/conditional recommendation)

4.2.9 For patients that have an asparaginase enzyme activity level of less than < 0.1 IU/mL while on Erwinia asparaginase, asparaginase therapy should be discontinued permanently.\(^1,22-25\) (UW Health very low quality evidence, weak/conditional recommendation)

4.2.10 Erwinia asparaginase should be discontinued in patients that experience a severe grade 2 or a true grade 3 or 4 hypersensitivity reaction.\(^1,3-7,9\) (UW Health very low quality evidence, strong recommendation)

4.3 Hepatotoxicity

4.3.1 It is recommended to continue scheduled administration of asparaginase products for patients who present with grade 1 or 2 hepatotoxicity.\(^3,9\) (UW Health very low quality evidence, weak/conditional recommendation)

4.3.2 For patients that present with grade 3 hepatotoxicity, either due to asparaginase, concomitant chemotherapy, or other hepatotoxic medications, it is reasonable to delay the next dose of asparaginase until the patient’s hepatotoxicity returns to below grade 2.\(^3,9\) (UW Health very low quality evidence, weak/conditional recommendation)

4.3.3 For patients that present with grade 4 hepatotoxicity, either due to asparaginase, concomitant chemotherapy, or other hepatotoxic medications, it is reasonable to discontinue asparaginase permanently or resume asparaginase therapy with close monitoring if the patient’s hepatotoxicity does not return to below grade 2 within one week.\(^3,9\) (UW Health very low quality evidence, weak/conditional recommendation)

4.3.4 A review of the patient’s medication list should be conducted to assess for hepatotoxic medications, which should be held until the patient’s liver function tests return to baseline values. (UW Health very low quality evidence, weak/conditional recommendation)

4.3.5 Patients that are re-trialed on asparaginase therapy after experiencing grade 3 or 4 hepatotoxicity should be monitored more closely.\(^3,9\) (UW Health very low quality evidence, strong recommendation)

4.3.6 It is recommended to continue asparaginase therapy in patients that present with grade 1 or 2 hyperbilirubinemia.\(^3,9\) (UW Health very low quality evidence, weak/conditional recommendation)

4.3.7 It is reasonable to hold asparaginase therapy if direct bilirubin is greater than 3.1 mg/dL and resume once direct bilirubin is below 2.0 mg/dL.\(^3,9\) (UW Health very low quality evidence, weak/conditional recommendation)

4.3.8 Adult patients

4.3.8.1 It is reasonable to consider the administration of levocarnitine 50 mg/kg IV daily and over the counter Vitamin B Complex 1 tab orally daily until liver function tests approach normal values patients who present with grade 3 or 4 hepatotoxicity.\(^1,31-34\) (UW Health very low quality evidence, weak/conditional recommendation)
4.4 Pancreatitis

4.4.1 It is recommended to continue asparaginase therapy with close monitoring for patients that experience grade 2 or lower pancreatitis.\(^3,9\) (UW Health very low quality evidence, weak/conditional recommendation)

4.4.2 It is recommended to permanently discontinue asparaginase therapy in patients that experience grade 4 pancreatitis (i.e. hemorrhagic pancreatitis, severe abdominal pain, intractable vomiting, grade 4 elevated amylase and/or lipase).\(^3,9\) (UW Health very low quality evidence, strong recommendation)

4.4.3 Adult Patients

4.4.3.1 It is reasonable to consider holding asparaginase if triglycerides are elevated beyond 1000 mg/dL and then resume the dose at the prior level once triglycerides return to the patient’s normal range.\(^3,9,35\) (UW Health very low quality evidence, weak/conditional recommendation)

4.4.3.2 It is reasonable to consider the use of micronized fenofibrate 67 mg daily (maximum dose 200 mg/day) in patients with grade 2 through grade 4 hypertriglyceridemia.\(^1,36\) (UW Health very low quality evidence, weak/conditional recommendation)

4.4.4 Pediatric Patients

4.4.4.1 It is reasonable to consider the use of intravenous octreotide either by continuous or intermittent infusion for patients who are admitted with grade 4 pancreatitis.\(^37\) (UW Health very low quality evidence, weak/conditional recommendation)

4.4.4.2 It is reasonable to continue asparaginase therapy without dose modifications for elevated triglycerides.\(^3,6,7,35\) (UW Health very low quality evidence, weak/conditional recommendation)

4.5 Hyperglycemia

4.5.1 Adult Patients

4.5.1.1 It is recommended to continue asparaginase therapy in patients that present with grade 2 or lower hyperglycemia.\(^3,9\) (UW Health very low quality evidence, strong recommendation)

4.5.1.2 For patients that require insulin therapy, it is reasonable to hold asparaginase and glucocorticoid therapy until the blood glucose is regulated.\(^3,9\) (UW Health very low quality evidence, weak/conditional recommendation)

4.5.1.3 For patients that present with grade 4 hyperglycemia and are restarted on asparaginase therapy, it is recommended to not make up for missed doses.\(^3,9\) (UW Health very low quality evidence, weak/conditional recommendation)

4.5.2 Pediatric Patients

4.5.2.1 It is reasonable to continue asparaginase therapy for hyperglycemia and treat with insulin if warranted.\(^6,7\) (UW Health very low quality evidence, weak/conditional recommendation)

4.6 Thrombosis

4.6.1 The goal fibrinogen level for patients on asparaginase therapy is greater than or equal to 100 mg/dL. (UW Health very low quality of evidence, weak/conditional recommendation) If clinically indicated it is reasonable to consider administration simultaneous administration of FFP and cryoprecipitate, as the FFP helps to balance the pro-coagulant effect of the cryoprecipitate and the asparagine present in FFP will immediately get cleaved by pre-existing asparaginase present in the body.\(^38,39\) (UW Health very low quality evidence, weak/conditional recommendation)
4.6.2 Patients administered cryoprecipitate and FFP should have their fibrinogen level checked the next day. *(UW Health very low quality of evidence, strong recommendation)*

4.6.3 FFP and cryoprecipitate should not be administered as prophylaxis against thrombosis due to a lack of clinical benefit shown in the current literature. *(UW Health low quality evidence, weak/conditional recommendation)*

4.6.4 LMWH as prophylaxis against potential thrombotic events in all patients on asparaginase therapy should be avoided due to a lack of mortality benefit. *(UW Health low quality evidence, weak/conditional recommendation)*

4.6.5 Non-central nervous system thrombosis

4.6.5.1 Patients with symptomatic grade 2-4 thrombosis should hold asparaginase therapy until clinically stable with appropriate antithrombotic therapy. *(UW Health very low quality evidence, weak/conditional recommendation)*

4.6.5.2 Once the thrombosis is clinically stable, it is reasonable to consider resuming asparaginase therapy with closer monitoring while on appropriate antithrombotic therapy or LMWH. *(UW Health very low quality evidence, weak/conditional recommendation)*

4.6.5.3 It is reasonable to consider continuation of asparaginase therapy in patients that present with abnormal coagulation laboratory findings without correlated clinical symptoms. *(UW Health very low quality evidence, weak/conditional recommendation)*

4.6.6 Central nervous system (CNS) thrombosis

4.6.6.1 Adult patients

4.6.6.1.1 Patients that present with grade 4 CNS thrombosis should discontinue all asparaginase products permanently. *(UW Health very low quality evidence, strong recommendation)*

4.6.6.1.2 Adult patients that present with grade 3 or less CNS thrombosis should discontinue therapy and treat with appropriate antithrombotic therapy. *(UW Health very low quality evidence, weak/conditional recommendation)*

4.6.6.1.3 For grade 3 or less CNS thrombosis, it is reasonable to consider resuming asparaginase at lower doses and/or longer intervals between doses. *(UW Health very low quality evidence, weak/conditional recommendation)*

4.6.6.2 Pediatric patients

4.6.6.2.1 Asparaginase should be held and treated with appropriate antithrombotic therapy. *(UW Health very low quality evidence, weak/conditional recommendation)*

4.6.6.2.2 It is reasonable to consider resuming asparaginase therapy at full dose when all symptoms have resolved and evidence of recanalization by CT or MRI imaging has been shown. *(UW Health very low quality evidence, weak/conditional recommendation)*

4.7 Bleeding

4.7.1 Non-CNS bleeding

4.7.1.1 Adult patients

4.7.1.1.1 For patients that present with grade 2-4 bleeding, it is recommended to withhold asparaginase therapy until the bleeding is < grade 1, until acute toxicity and clinical signs resolve, and coagulant replacement therapy is stable or
completed, then resume.\textsuperscript{3, 9} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.1.1.2 For patients that present with grade 2 bleeding based on abnormal lab findings without a clinical correlate, asparaginase therapy should not be withheld.\textsuperscript{3, 9} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.1.1.3 It is reasonable to consider the use of oral aminocaproic acid (1 gram four times a day) or tranexamic acid (1300 mg three times daily). (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.1.2 Pediatric patients

4.7.1.2.1 Symptomatic patients should be treated with appropriate factor or procoagulant replacement. Asparaginase dose should be held and resumed with the next scheduled dose.\textsuperscript{3, 6, 7, 45, 46} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.1.2.2 Asparaginase therapy should not be withheld in patients with abnormal laboratory findings without a clinical correlate.\textsuperscript{3, 6, 7, 45, 46} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.2 CNS bleeding

4.7.2.1 Adult patients

4.7.2.1.1 For patients that present with grade 3 or lower hemorrhage, it is recommended to discontinue asparaginase therapy until symptoms/signs have fully resolved.\textsuperscript{3, 9} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.2.1.2 For patients that present with grade 4 hemorrhage, it is recommended that asparaginase therapy be permanently discontinued.\textsuperscript{3, 9} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.2.1.3 It is reasonable to consider coagulation factor replacement in patients with grade 3 or lower hemorrhage.\textsuperscript{3, 9} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.2.1.4 It is reasonable to consider resuming asparaginase at lower doses and/or longer intervals between doses.\textsuperscript{3, 9} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.2.2 Pediatric patients

4.7.2.2.1 Symptomatic patients should be treated with appropriate factor or procoagulant replacement and have their asparaginase dose held and resumed with the next scheduled dose.\textsuperscript{3, 6, 7, 45, 46} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.7.2.2.2 Asparaginase therapy should not be withheld in patients with abnormal laboratory findings without a clinical correlate.\textsuperscript{3, 6, 7, 45, 46} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.8 Hyperammonemia

4.8.1 It is recommended to administer lactulose in patients who present with symptomatic hyperammonemia (altered mental status, unexplained fatigue, somnolence, or seizures) starting at 20g by mouth three times daily with further titration to produce 2 to 3 soft stools daily.\textsuperscript{3, 9} (\textit{UW Health very low quality evidence, weak/conditional recommendation})
4.8.2 Adult patients
4.8.2.1 Patients should continue therapy as normal for grade 2 hyperammonemia.\textsuperscript{3, 9} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.8.2.2 Full doses can be resumed in patients with grade 3 and 4 hyperammonemia once the toxicity becomes grade 2 or lower.\textsuperscript{3, 9} (\textit{UW Health very low quality evidence, weak/conditional recommendation})

4.8.3 Pediatric Patients
4.8.3.1 Pediatric patients \( \leq 20 \text{ kg} \): start dosing at 10g by mouth three times daily. (\textit{UW Health very low quality evidence, weak/conditional recommendation})

\textbf{Disclaimer}
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
Methodology

Development Process
Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:
The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:
- PubMed
- American Society of Hematology Annual Meeting Abstracts
- Children’s Oncology Group Protocols

Time Period: All published literature through December 2017

Search Terms:
- Pegasparagase OR pegasparaginase OR asparaginase OR Erwinia
- Hypersensitivity OR allergic reaction
- Hepatotoxicity OR liver toxicity
- Pancreatitis
- Dyslipidemia OR hypertriglyceridemia
- Thrombosis
- Hyperammonemia
- Hyperglycemia
- Pediatric
- Adult
- Acute lymphoblastic leukemia

Methods to Select the Evidence:
Electronic database searches (PubMed, abstracts from the American Society of Hematology Annual Meeting, and Children Oncology’s Group protocols) were conducted by the guideline author(s) and workgroup members to collect evidence for review. External practices from other institutions, expert opinion, and clinical experience were also considered during discussions of the evidence.

Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1).

**Figure 1. GRADE Methodology adapted by UW Health**

### Rating Scheme for the Strength of the Evidence/Recommendations:

**GRADE Ranking of Evidence**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

**GRADE Ratings for Recommendations For or Against Practice**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.</td>
</tr>
<tr>
<td>Weak/conditional</td>
<td>Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.</td>
</tr>
</tbody>
</table>

**Cost Analysis:**

A cost analysis was done by Tong et al in 2013 on a set of patients enrolled in the Dutch Childhood Oncology Group ALL-10 medium-risk group intensification protocol. Treatment costs were calculated based on 84 patients and compared patients who had no allergies to pegaspargase to those that did have allergies to pegaspargase and required a switch to Erwinia...
asparaginase. From their analysis, they found that the total costs of the intensification course of 30 weeks were $57,893 (n=64) in patients without a pegaspargase allergy, while patients that required a switch to Erwinia asparaginase incurred costs of $113,558 (n=20). Decision tree analyses and simulations of part of the treatment were required in order to calculate these values.¹⁴

Table 3. UW Health Acquisition Cost Table

<table>
<thead>
<tr>
<th></th>
<th>Pegaspargase (3750 unit vial)</th>
<th>Erwinia asparaginase (10000 unit vial)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost per Cycle</strong></td>
<td>2500 units/m² x 1 dose</td>
<td>25000 units/m² x 6 doses</td>
</tr>
<tr>
<td><strong>Cost per Vial</strong></td>
<td>$14,399.09*</td>
<td>$3,799.46*</td>
</tr>
<tr>
<td><strong>Cost per Cycle</strong></td>
<td>$28,798.18</td>
<td>$113,983.80*</td>
</tr>
<tr>
<td><strong>(1.7 m² patient)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on acquisition cost in December 2017

**Recognition of Potential Health Care Disparities:**
Health care disparities exist in cancer care. Patients that are uninsured are less likely to receive proper cancer screening and express lower rates of delayed follow-up after any abnormal test results, which lead to diagnosis at more advanced stages. Furthermore, institutions most likely to serve minorities may not have as much access to state of the art diagnostic and therapeutic measures and the ability to participate in cancer clinical trials, affecting the overall quality of care. Additional factors that may influence outcomes of minorities include distrust of the health care system, stigmas related to cancer and death, literacy and language barriers, and poor expectations regarding the outcome from cancer care.⁴⁷
Collateral Tools & Resources
The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics
- Adherence to the clinical practice guideline
- Number of doses of pegasparagase used at UW Health
- Number of doses of asparaginase (Erwinia) used at UW Health
- Incidence and severity of asparaginase toxicities as identified through voluntary reporting and retrospective chart review

Beacon Protocols
1. AFCH ONC RSCH/SOC AALL1231 ARM A and B INTERIM MAINTENANCE (CMTX – AL PATIENTS) (56D) – T-ALL AND T-NHL [5584]
2. AFCH ONC SOC PHILADELPHIA CHROMOSOME POSITIVE LEUKEMIA INDUCTION [6149]
3. CSC HEM ALL CALGB 10403 CONSOLIDATION (56D) [5815]
4. CSC HEM ALL CALGB 10403 EXTENDED REMISSION (15D) [5802]
5. CSC HEM INPT/OP DEXAMETHASONE/ETOPOSIDE/IFOSFAMIDE/METHOTREXATE/PEGASPARGASE [4390]
6. CSC HEM INPT/OUTPT CALGB 10403 INDUCTION (29D) [5751]
7. CSC-R AALL1231 (ADULT) ARM A AND B INTERIM MAINTENANCE (CMTX – ALL PATIENTS) (56D) – T-ALL AND T-NHL [6126]
8. PATIENT SPECIFIC TEMPLATE AFCH AALL0631 REINDUCTION (ARM A)) [5999]
9. PATIENT SPECIFIC TEMPLATE CSC HEM INPT/OP DEXAMETHASONE/ETOPOSIDE/IFOSFAMIDE/IT CHEMO/ METHOTREXATE/PEGASPARGASE/VINCRISTINE (CCG-1941) [5760]
10. AFCH ONC SC ERWINIA ASPARAGINASE [4728]
11. AFCH SOC AALL0631 INDUCTION (PT GREATER THAN OR EQUAL TO 6 MO OLD AT DX) (35D) [5848]
12. AFCH SOC AALL0631 INDUCTION (PT GREATER THAN OR EQUAL TO 7 D AND LESS THAN 6 MO OLD AT DX) (35D) [5094]

Clinical Practice Guidelines
1. Perioperative Medication Management - Adult/Pediatric - Inpatient/Ambulatory
2. Intravenous Administration of Formulary Medications – Adult – Inpatient/Ambulatory
3. Intravenous Administration of Formulary Medications – Pediatric/Neonatal – Inpatient/Ambulatory

Patient Resources
1. Health and Nutrition Facts for You #6079: What to Do for an Allergic Reaction to Asparaginase Chemotherapy
2. Medication Fact Sheet: Asparaginase
3. Lexicomp: Pegaspargase
4. Lexicomp: Asparaginase (Erwinia)

Policies
1. UWHC Policy 6.1.1: Chemotherapy Processes: Informed Consent, Ordering, Verification, Administration, Documentation, and Patient/Family Education
2. UWHC Policy 6.1.14: Approval of Core and Patient-Specific Chemotherapy Regimens for the Treatment of Adult Malignancy
## Appendix A. Grading of Common Asparaginase Toxicities

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity (Allergic reaction / Anaphylaxis)</td>
<td>Transient flush or rash, drug fever &lt; 38 degrees C (&lt; 100.4 degrees F); intervention not indicated</td>
<td>Urticaria without bronchospasm, hypotension, edema, or need for parenteral intervention</td>
<td>Symptomatic bronchospasm with or without urticaria, indicated parenteral intervention, angioedema, or hypotension</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>&gt; ULN – 3.0 x ULN</td>
<td>&gt; 3.0 – 5.0 x ULN</td>
<td>&gt; 5.0 – 20.0 x ULN</td>
<td>&gt; 20.0 x ULN</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>-</td>
<td>Enzyme elevation or radiologic findings only</td>
<td>Severe pain; vomiting; medical intervention indicated (e.g. analgesia, nutritional support)</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Elevated Serum Amylase</td>
<td>&gt; ULN – 1.5 x ULN</td>
<td>&gt; 1.5 – 2.0 x ULN</td>
<td>&gt; 2.0 – 5.0 x ULN</td>
<td>&gt; 5.0 x ULN</td>
</tr>
<tr>
<td>Elevated Serum Lipase</td>
<td>&gt; ULN – 1.5 x ULN</td>
<td>&gt; 1.5 – 2.0 x ULN</td>
<td>&gt; 2.0 – 5.0 x ULN</td>
<td>&gt; 5.0 x ULN</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>&gt; ULN – 1.5 x ULN</td>
<td>&gt; 1.5 – 3.0 x ULN</td>
<td>&gt; 3.0 – 10.0 x ULN</td>
<td>&gt; 10.0 x ULN</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>150 mg/dL – 300 mg/dL</td>
<td>&gt; 300 mg/dL – 500 mg/dL</td>
<td>&gt; 500 mg/dL – 1000 mg/dL</td>
<td>&gt; 1000 mg/dL; life threatening consequences</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Fasting glucose value &gt; ULN – 160 mg/dL</td>
<td>Fasting glucose value &gt; 160 – 250 mg/dL</td>
<td>&gt; 250 – 500 mg/dL; hospitalization indicated</td>
<td>&gt; 500 mg/dL; life-threatening consequences</td>
</tr>
<tr>
<td>Thromboembolic Event</td>
<td>Venous thrombosis (e.g. superficial thrombosis)</td>
<td>Venous thrombosis (e.g. uncomplicated deep vein thrombosis), medical intervention indicated</td>
<td>Thrombosis (e.g. uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated</td>
<td>Life-threatening (e.g. pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Mild; intervention not indicated</td>
<td>Moderate symptoms; medical intervention or minor cauterization indicated</td>
<td>Transfusion, radiologic, endoscopic, or operative intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Hyperammonemia / Encephalopathy</td>
<td>Mild Symptoms</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>
APPENDIX B. Asparaginase Toxicity Monitoring Strategy Summary

<table>
<thead>
<tr>
<th>Hypersensitivity</th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Draw asparaginase enzyme activity level after seven days of first administered dose</td>
<td>• Only draw asparaginase enzyme level if patient is pre-medicated or if patient receives at least ¼ of dose prior to development of hypersensitivity reaction (see Table 2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver Function Tests</th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Monitor alkaline phosphatase, AST, ALT, and total bilirubin prior to administration</td>
<td>• Monitor alkaline phosphatase, AST, ALT, and total bilirubin prior to administration</td>
<td></td>
</tr>
<tr>
<td>• Monitor following administration weekly for two weeks and prior to doses of chemotherapy with increased risks for hepatotoxicity</td>
<td>• Consider monitoring following administration if patient has pre-existing hyperbilirubinemia or elevated baseline liver function tests</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pancreatitis</th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amylase, lipase, and triglycerides prior to first dose</td>
<td>• Amylase, lipase, and triglycerides prior to first dose</td>
<td></td>
</tr>
<tr>
<td>• First dose: check labs weekly for two weeks following first pegaspargase dose</td>
<td>• Further doses: check triglycerides prior to administration</td>
<td></td>
</tr>
<tr>
<td>• Subsequent doses: Check labs prior to administration and once seven days after dose</td>
<td>• Consider checking all labs seven days post-administration if patient has previously experienced grade 2-3 pancreatitis or grade 2-4 hypertriglyceridemia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Monitor periodically</td>
<td>• Monitor periodically</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood and Coagulation</th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complete blood count with differential and fibrinogen prior to any dose</td>
<td>• Complete blood count with differential and fibrinogen prior to any dose</td>
<td></td>
</tr>
<tr>
<td>• Platelets and fibrinogen twice weekly for one week post-dose</td>
<td>• Platelets weekly post-dose</td>
<td></td>
</tr>
<tr>
<td>• If thrombosis occurs, platelets and fibrinogen twice weekly for one week post-dose</td>
<td>• If thrombosis occurs, platelets and fibrinogen twice weekly for one week post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Omit PT and PTT</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ammonia</th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weekly if patient is symptomatic (i.e. altered mental status, somnolence) until symptom resolution</td>
<td>• Weekly if patient is symptomatic (i.e. altered mental status, somnolence) until symptom resolution</td>
<td></td>
</tr>
</tbody>
</table>

Effective 4/19/2018. Contact CCKM@uwhealth.org for previous versions
### APPENDIX C. Asparaginase Toxicity Management Summary

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
</table>
| **Hypersensitivity**     | • Always pre-medicate  
  • Grade 1-2: continue therapy  
  • Grade 3-4: switch therapy or discontinue if on Erwinia asparaginase | • Pre-medication not recommended by COG, but can do so if an asparaginase enzyme activity level is checked  
  • Grade 1-2 (non-severe): refer to Table 2  
  • Grade 2 (severe) or higher: switch therapy or discontinue if on Erwinia asparaginase |
| **Hepatotoxicity**       | • Grade 1-2: continue  
  • Grade 3: delay until grade ≤2  
  • Grade 4: discontinue permanently or resume with close follow up if grade ≤2 not achieved within one week  
  • Can consider IV levocarnitine + PO vitamin B complex | • Grade 1-2: continue  
  • Grade 3-4: delay until grade ≤2 within one week |
| **Hyperbilirubinemia**   | • Grade 1-2: continue  
  • Hold if > 3.1 mg/dL and resume when below 2.0 mg/dL | • Grade 1-2: continue  
  • Hold if > 3.1 mg/dL and resume when below 2.0 mg/dL |
| **Pancreatitis**         | • Grade 1-2: continue  
  • Discontinue permanently if grade 4 | • Grade 1-2: continue  
  • Discontinue permanently if grade 4  
  • Can consider IV octreotide via continuous or intermittent infusion if admitted inpatient with grade 4 |
| **Hypertriglyceridemia** | • Hold therapy if triglycerides > 1000 mg/dL and resume at same dose when triglycerides normalize  
  • Can consider micronized fenofibrate for grade 2-4 | • Continue without dose modifications for elevated triglycerides |
| **Hyperglycemia**        | • Grade 1-2: continue  
  • Reasonable to hold therapy if insulin therapy is required until levels are regulated | • Treat with insulin if warranted and continue therapy |
| **Non-CNS Thrombosis**  | • Hold therapy if symptomatic grade 2-4 until stable on antithrombotic therapy  
  • Can consider resuming therapy with closer monitoring while on antithrombotic therapy or LMWH  
  • Continue treatment in patients with abnormal lab findings without correlated clinical symptoms | • Hold therapy if symptomatic grade 2-4 until stable on antithrombotic therapy  
  • Can consider resuming therapy with closer monitoring while on antithrombotic therapy or LMWH  
  • Continue treatment in patients with abnormal lab findings without correlated clinical symptoms |
| **CNS Thrombosis**      | • Grade 1-3: discontinue and treat with antithrombotic therapy  
  • Can consider resuming therapy in lower doses and/or longer intervals  
  • Grade 4 – discontinue all asparaginase products permanently | • Hold therapy and treat with antithrombotic therapy  
  • Can consider resuming therapy at full dose when symptomatically resolved and imaging shows recanalization |
| **Non-CNS Bleeding**     | • Grade 2 via lab findings: Do not withheld therapy without a clinical correlate  
  • Grade 2-4: hold therapy until bleeding is lower than grade 1 | • Treat with appropriate factor or pro-coagulant blood product replacement  
  • Hold dose and resume with next scheduled dose  
  • Do not withhold dose without clinical correlate |
| **CNS Bleeding**         | • Grade 1-3: discontinue therapy until full symptomatic resolution  
  • Grade 1-3: Can consider coagulation factor replacement and resuming at lower doses and/or longer intervals  
  • Grade 4: permanently discontinue therapy | • Treat symptomatic patients with appropriate factor or procoagulant replacement  
  • Hold dose and resume with next scheduled dose  
  • Do not withhold dose without clinical correlate |
| **Hyperammonemia**       | • Lactulose if symptomatic  
  • Do not withhold dose without clinical correlate  
  • Grade 1-2: continue therapy as normal  
  • Grade 3-4: dose reduce per protocol, resume full dose once grade 2 or lower | • Lactulose if symptomatic |
References


5. Cancer and Leukemia Group B. CALGB 10403/ECOG C10403/SWOG C10403: An Intergroup Phase II Clinical Trial for Adolescents and Young Adults with Untreated Acute Lymphoblastic Leukemia (ALL). 2011.


