Insights and Perspectives on Asparaginase Associated Adverse Events in Pediatric, AYA and Adult ALL and LBL:

A Discussion By and For Oncology Nurses

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Objectives

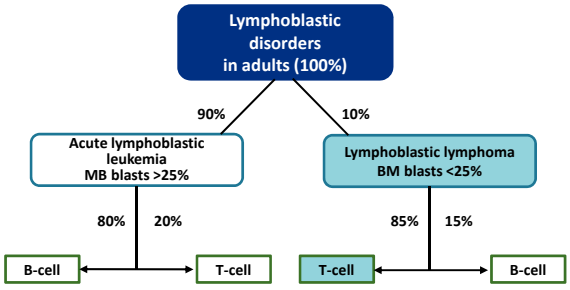
- Summarize current guidelines on the use of asparaginase-containing treatment regimens in adolescents, young adults, and adults with ALL/LBL
- Implement strategies for managing hypersensitivity reactions in patients with ALL/LBL including the use of serum asparaginase activity (SAA) levels
- Educate patients and families on the importance of prompt identification and management of hypersensitivity reactions

Faculty Disclosure

- Dr. Sandra Kurtin, faculty for this educational activity, has relevant financial relationships related to consulting from AbbVie Inc., Agios, Inc., Amgen Inc., AstraZeneca, Bristol Myers Squibb Company, GlaxoSmithKline plc, and Takeda Oncology.

All of the relevant financial relationships listed for this individual have been mitigated prior to this activity.

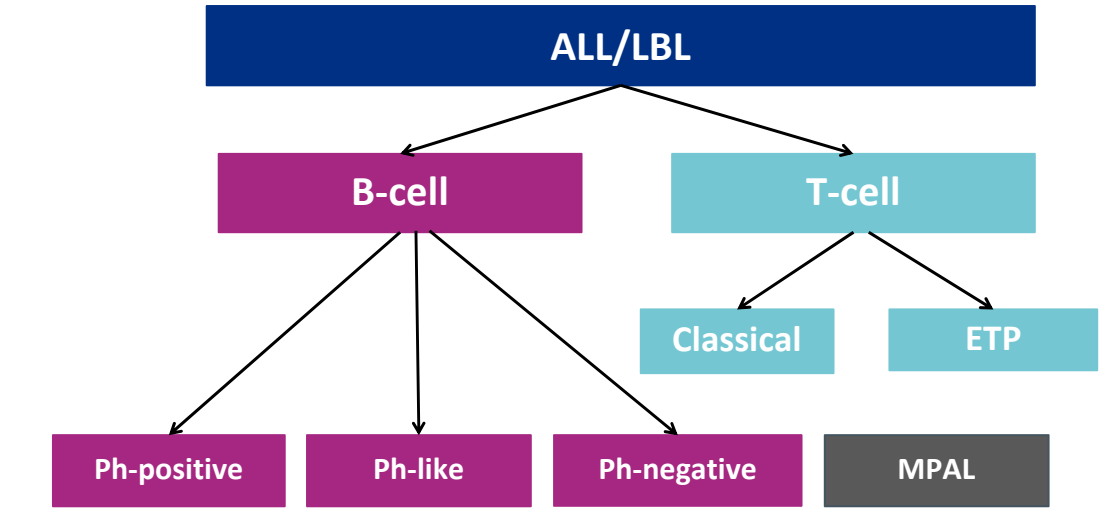
Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma: Disease Characteristics



- **B-cell ALL (75% of cases)**
  - Mature B-cell less favorable; treated with intense induction followed by allogeneic SCT
  - Pre-B-cell ALL in children and AYA is more common
  - Treatment based on risk
- **T-cell ALL**
  - More favorable in adults with initial diagnosis; relapse, however, is difficult to treat
  - More commonly involves extra-medullary site
- **Lymphoblastic lymphoma (LBL)**
  - Rare, highly aggressive lymphoma that shares biological and morphological features with ALL, T-cell most common
  - Distinguished from ALL by having <20-25% marrow infiltrating blasts
  - 2-4% of adult and <30% of children's non-Hodgkin lymphomas
  - Predominantly seen in young males (10-30 years)
  - Treated with ALL regimens

Jabbour E, et al. *JAMA Oncol*. 2018;4(10):1413-1420.; Kurtin S. *Semin Oncol Nurs*. 2019;35(6):150953.; Intermesoli T, et al. *Curr Oncol Rep*. 2022;24(1):1-12.

Classification of Acute Lymphoblastic Leukemia/ Lymphoblastic Leukemia



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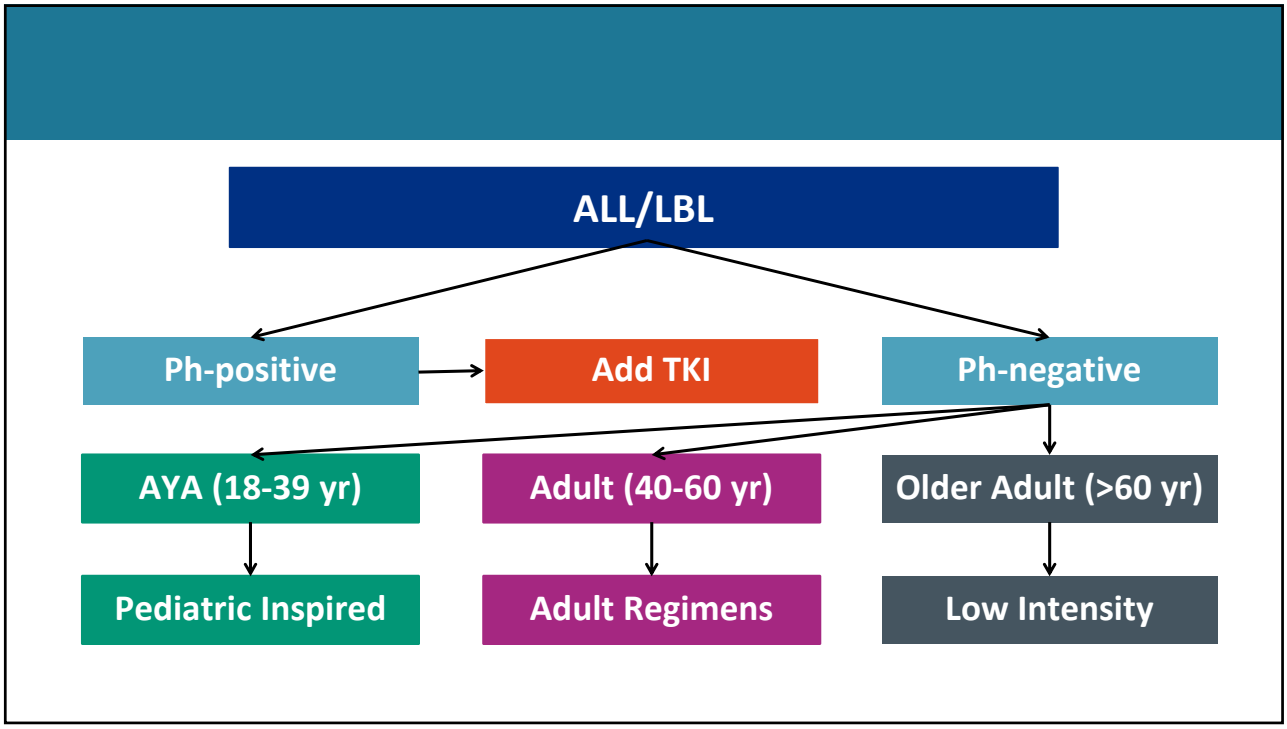


Common Multi-agent Multi-phase Drug Regimens Utilized in Pediatric, AYA and Adult ALL

- **Induction**
  - Most common: daunorubicin, vincristine, prednisone, **asparaginase**, methotrexate, dexamethasone, idarubicin
  - May include rituximab in adult patients (HyperCVAD regimen), may include nelarabine for T-cell ALL
  - Ph+ may add TKI: dasatinib, nilotinib, bosutinib, ponatinib (based on AE profile and mutational analyses)
  - CNS prophylaxis is regimen specific (methotrexate, cytarabine)
    - CNS treatment if positive at baseline – continued throughout induction, consolidation and in maintenance
- **Consolidation**
  - Cytarabine, etoposide**, asparaginase**, daunorubicin, vincristine, prednisone
  - CNS-prophylaxis continued
- **Maintenance**
  - 6-mercaptopurine, 6-thioguanine, methotrexate, vincristine, prednisone, **asparaginase**
- **Targeted therapies**
  - Blinatumomab*, inotuzumab**
- **Cellular therapies**
  - CAR-T, allogeneic stem cell transplant

*Blinatumomab is approved by the for the treatment of R/R CD19-positive B-cell precursor ALL in adults and children
**Inotuzumab is approved by the FDA for the treatment of adult patients with R/R ALL
NCCN Guidelines Version 1.2022, Acute Lymphoblastic Leukemia @https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

Asparaginase Therapy in Adolescents, Young Adults (AYA) and Adults: An Overview

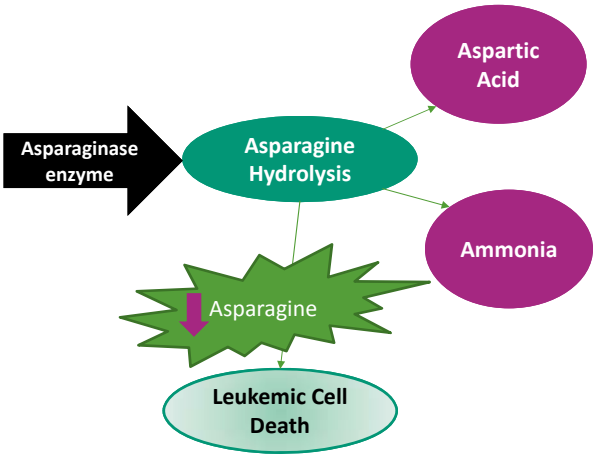
Evolution of Asparaginase Therapy for ALL/LBL

1978	1994	2000	2006	2018-2022
E coli-derived (native) L-asparaginase FDA approved as part of a multi-agent regimen	Peg-asparaginase (pegylated – E coli-derived) FDA approved for patients hypersensitive to native forms of L-asparaginase as part of a multi-agent regimen	Widened routine use of therapeutic drug monitoring (TDM)	Pegaspargase granted approval for frontline use with a multi-agent regimen	Novel asparaginase formulations FDA approved for 2nd-line therapy in case of hypersensitivity 2018: Calaspargase pegol-mknl (Erwinia-derived, pegylated) 2021: Erwinia chrysanthemi asparaginase-rywn (recombinant) Drug shortages for Erwinia-derived formulations

Riccardi R, et al. *Cancer Res*. 1981;41(11 Pt. 1):4554-4558. .

Asparaginase Mechanism of Action

- Asparaginase is an enzyme that:
  - **Hydrolyzes asparagine to aspartic acid and ammonia**
  - **Reduces availability of asparagine**
  - **Results in inhibition of leukemia cell growth**
  - **Higher levels of serum asparaginase activity (SAA) = lower amount of available asparagine**
- Continuous and prolonged asparagine depletion is necessary for apoptosis of the leukemic clone
  - 5-year, event-free survival (EFS) inferior in patients who receive 25 weeks or fewer weeks of therapy compared to at least 26 weeks (73% vs 90%)
- Measuring ammonia levels is critical to differentiating symptoms of asparaginase reactions vs hyperammonemia



Juluri KR, et al. *Blood Lymphat Cancer*. 2022;12:55-79, Silverman et al. *Blood*. 2001; 97: 1211-1218.

FDA-Approved Asparaginase Formulations

Formulation	Type/Species	Indications (All agents approved as a component of a multi-agent regimen)
Calaspargase pegol-mknl [Asparlas]	Pegylated E-Coli	Frontline Pediatric only (1 month ***up to age 21***) Only pegylated formulation available in pediatrics
Pegylated asparaginase (pegaspargase) [Oncaspar]	Pegylated E-Coli	Frontline Aged ≥ 22 years only given at 2000 IU/m2 no more frequently than every 14 days Only pegylated formulation available in adults
Erwinia chrysanthemi asparaginase-rywn (recombinant) [Ryalze]	Recombinant Erwinia chrysanthemi	Second-line – **E-Coli hypersensitivity** Pediatric, AYA, Adult
Erwinia asparaginase (asparaginase) (native) [Erwinase]	Native Erwinia chrysanthemi	Second-line – E-Coli hypersensitivity Pediatric, AYA, Adult **This product in not commercially available in the US – Global Shortage**

Juluri KR, et al. *Blood Lymphat Cancer*. 2022;12:55-79.; Prescribing information for pegasparaginase, calasparaginase, asparaginase erwinia chrysanthemi.

New Updates: PEGylated Asparaginase Products

New Updates effective December 1, 2022 to ensure availability of PEGylated Asparaginase Products to Patients with ALL

- Calaspargase pegol-mknl (Asparlas) is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in pediatric and young adult patients aged 1 month to 21 years
  - Will be the only first-line PEGylated asparaginase option available for ALL regimens in patients **aged 1 month to 21 years**
  - IV formulation only
- Pegaspargase (Oncaspar) is indicated as a component of a multi-agent chemotherapeutic regimen and will continue to be available for ALL regimens in patients **aged ≥ 22 years only**

Bulletin to providers from manufacturer, 9/28/2022.

3 Currently Available Asparaginase Formulations

Formulation/ Species	Half-life based on route	Administration
Calaspargase pegol-mknl (E-coli) [Asparlas]	IV: 12.7-17.3 **days**	Age 1 month to 21 years Route: **IV only** Dose/Frequency: 2500 IU/m^2 no more frequently than every 21 days
Pegylated asparaginase (pegaspargase) (E-coli) [Oncaspar]	IM: 5.7 **days** IV: 4.9-5.3 **days**	Age: ≥*22 years only* Route: **IM or IV** Dose/Frequency: 2000 IU/m^2 no more frequently than every 14 days
Erwinia chrysanthemi asparaginase-rywn (recombinant) [Ryalze]	IM: 15.9 **hours**	Age: Pediatric, AYA, Adult Route: **IM only** Dose: 25 mg/***m²*** Every 48 hours *OR* 25/25/50 mg/***m²*** ***Monday morning, Wednesday morning and Friday afternoon***

Nursing Notes

Dosing of individual asparaginase therapies is not interchangeable and dosing conversions are required

Juluri KR, et al. *Blood Lymphat Cancer*. 2022;12:55-79.; Prescribing information for pegasparaginase, calasparaginase, asparaginase erwinia chrysanthemi.

Case Study 1: 24-year-old Female with T-cell ALL

*HIPAA-compliant, stock photo (not actual patient).

CJ*

- Presented to the emergency department with cervical adenopathy, bruising, headaches, bone pain and chest pressure
- FNA cervical node: TdT+
- Bone marrow biopsy shows 26.9% lymphoblasts

Diagnosed with **T-cell acute lymphoblastic leukemia (T-cell ALL)**

Case Study 1: 24-year-old Female with T-cell ALL

*HIPAA-compliant, stock photo (not actual patient).

CJ*

Patient Notes

- Starting induction regimen (AALL0434 with nelarabine – a pediatric-based regimen)

Induction

- Daunorubicin 25 mg/m^2 IV once per day on Days 1, 8, 15, 22
- **Pegaspargase 2000 units/m^2 IV once on Day 4**
- Vincristine 1.5 mg/m^2 (max dose of 2 mg/wk) IV once per day on Days 1, 8, 15, 22
- Prednisone 30 mg/m^2 PO twice per day on Days 1 to 28

The Rate and Risk Factors for Asparaginase Toxicities in Adults

Adverse Event	Risk Factors
Hypersensitivity	**Onset: Second dose and future doses** **Risk Factors: Y**ounger age, no premedication Genomics: HLA-DRB1*07:01 polymorphism
Thrombosis	**Onset: First cycle** **Risk Factors: O**lder age, obesity, mediastinal mass, cryoprecipitate replacement, central venous catheter or port, PICC line
Hypofibrinogenemia	**Onset: First cycle** **Risk Factors: S**evere obesity (BMI > 35)
Hyperbilirubinemia/↑LFTs	**Onset:** During the **induction cycle** **Risk Factors: O**lder age, obesity, higher dose of pegasparginase, low albumin, low platelet count **Genomics:** CC genotype of rs4880 polymorphism

Aldoss I, Douer D. *Blood.* 2020;135(13):987-995.

The Rate and Risk Factors for Asparaginase Toxicities in Adults

Adverse Event	Risk Factors
Hypertriglyceridemia	**Onset:** Beyond first cycle **Risk Factors:** **Hi**gh BMI, younger age
Hyperglycemia	**Onset:** Variable **Risk Factors:** Concomitant use of steroids, diabetes
Hyperammonemia	**Onset:** **A**fter any dose of asparaginase **Risk Factors:** Underlying liver disease
Pancreatitis	**Onset:** Variable **Risk Factors:** Older age, high-risk ALL stratification, **Genomics:** **G**ermline polymorphisms in ULK2 variant rs281366 and RGS6 variant rs17179470

Aldoss I, Douer D. *Blood.* 2020;135(13):987-995.

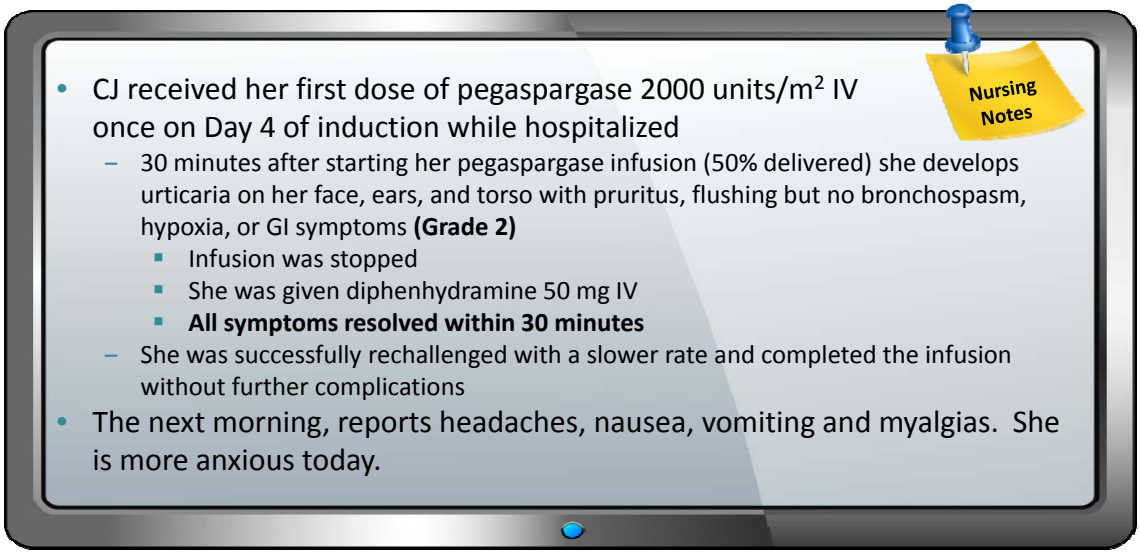
Obesity and Asparaginase-Associated Toxicities

Select Grade 3/4 AEs, n (%)	BMI <30 kg/m^2 (n = 197)	BMI 30-40 kg/m^2 (n = 71)	BMI ≥40 kg/m^2 (n = 21)	P Value
Nonhematologic	152 (77.2)	57 (80.3)	18 (85.7)	.685
Hepatic toxicity	61 (31.0)	37 (52.1)	13 (61.9)	.001
Infection	43 (21.8)	19 (26.8)	9 (42.9)	.092
ALT increase	47 (23.9)	25 (35.2)	11 (52.4)	.009
AST increase	14 (7.1)	17 (23.9)	6 (28.6)	<.0001
Hyperbilirubinemia	23 (11.7)	22 (31.0)	10 (47.6)	<.0001
Pancreatitis	4 (2.0)	2 (2.8)	2 (9.5)	.123
Hyperglycemia	52 (26.4)	28 (39.4)	10 (47.6)	.030

- Grade 3/4 toxicities in CALGB 10403 study of pediatric ALL regimens in AYA patients aged ≤40 yr (N = 289)

Advani. *Blood Adv*. 2021;5:504.

Case Study 1: 24-year-old Female with T-cell ALL



- CJ received her first dose of pegaspargase 2000 units/m^2 IV once on Day 4 of induction while hospitalized
  - 30 minutes after starting her pegaspargase infusion (50% delivered) she develops urticaria on her face, ears, and torso with pruritus, flushing but no bronchospasm, hypoxia, or GI symptoms **(Grade 2)**
    - Infusion was stopped
    - She was given diphenhydramine 50 mg IV
    - **All symptoms resolved within 30 minutes**
  - She was successfully rechallenged with a slower rate and completed the infusion without further complications
- The next morning, reports headaches, nausea, vomiting and myalgias. She is more anxious today.

Adverse Event Profile for Asparaginase: Hyperammonemia

- Ammonia levels are critical in evaluating ***silent inactivation***
- Normal ranges for serum ammonia are age and gender dependent
- Risk factors for hyperammonemia:
  - Pre-existing liver disease; asparagine hydrolysis
- Signs and symptoms: anxiety, malaise, weakness, nausea, vomiting, and abdominal cramping
- Prevention and management: (not well studied)
  - Decreased protein intake
  - Limit strenuous exercise
  - Lactulose
  - Benzoic acid
  - Arginine or sodium phenylbutyrate

Age	Male (µ/dL)	Female (µ/dL)
1 to 6 m	42–137	42–137
7 m to 1 y	34–108	34–108
2 to 12 y	33–97	33–97
13 to 30 y	36–136	29–112
31 to 40 y	40–160	30–130
41 to 50 y	40–200	31–155
51 to 70 y	40–200	34–178
71 to 80 y	31–169	31–169
>80 y	28–135	28-135

Aldoss I, Douer D. *Blood.* 2020;135(13):987-995.; Pourhassan H, et al. *Curr Oncol Rep.* 2023;25(1):51-61.; NCCN Guidelines Version 1.2022, Acute Lymphoblastic Leukemia @https://www.nccn.org/professionals/physician_gls/pdf/all.pdf ; Glasgow AM. *Lab Med.* 1981; 12:151-157.

Silent Inactivation

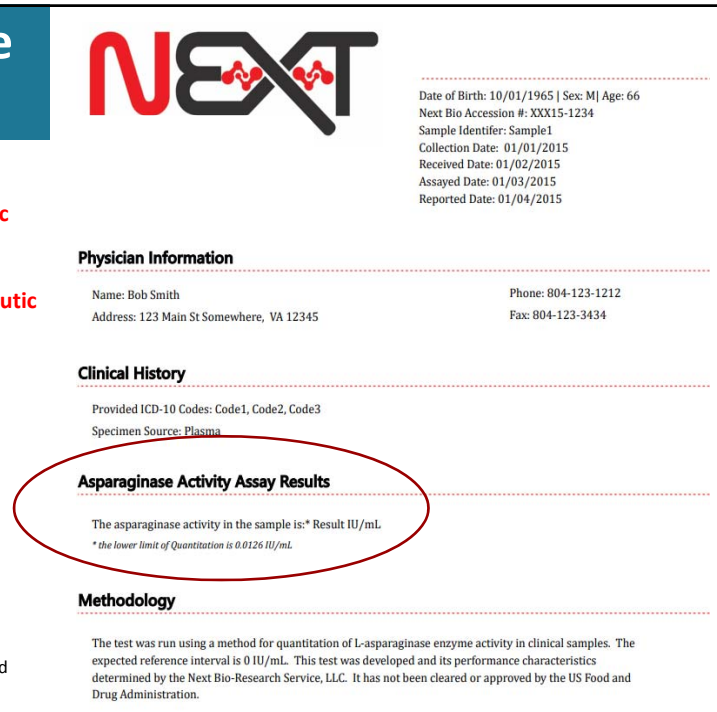
- Serum asparaginase activity (SAA) is a surrogate marker for asparagine levels
- Asparagine depletion is critical to effective suppression of the leukemic clone
- Goal for therapeutic SAA is > 0.1IU/mL
- Therapeutic drug monitoring and SAA driven therapy is an emerging trend
  - Included in NCCN guidelines
  - Early adoption in Europe
  - SAA is available as a CLIA-certified test
    - Turnaround time <1 week

Burke MJ, Zalewska-Szewczyk B. *Future Oncol.* 2022;18(10):1285-1299.; van der Sluis, IM, et al. *Haematologica.* 2016;101(3):279-285.; NCCN Guidelines Version 1.2022, Acute Lymphoblastic Leukemia @https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

Sample Asparaginase Activity Report

- **SAA trough of > 0.1 IU/mL is the therapeutic target**
- **Levels < 0.1 are associated with subtherapeutic asparagine depletion**

https://7d2f7043-60da-494b-a021-170e20431584.filesusr.com/ugd/9b3624_f877290dfd124afda1097faaf8daa672.pdf



NEXT

Date of Birth: 10/01/1965 | Sex: M| Age: 66
Next Bio Accession #: XXX15-1234
Sample Identifer: Sample1
Collection Date: 01/01/2015
Received Date: 01/02/2015
Assayed Date: 01/03/2015
Reported Date: 01/04/2015

Physician Information

Name: Bob Smith
Address: 123 Main St Somewhere, VA 12345
Phone: 804-123-1212
Fax: 804-123-3434

Clinical History

Provided ICD-10 Codes: Code1, Code2, Code3
Specimen Source: Plasma

Asparaginase Activity Assay Results

The asparaginase activity in the sample is:* Result IU/mL
** the lower limit of Quantitation is 0.0126 IU/mL*

Methodology

The test was run using a method for quantitation of L-asparaginase enzyme activity in clinical samples. The expected reference interval is 0 IU/mL. This test was developed and its performance characteristics determined by the Next Bio-Research Service, LLC. It has not been cleared or approved by the US Food and Drug Administration.

Hypersensitivity or Inactivation?

Hypersensitivity Reactions	Silent Inactivation
• Develops during the infusion	• Antibody mediated
• Specific symptoms are commonly present	• Patients will not develop observable symptoms during infusion
• Antibody mediated	• Therapeutic drug monitoring required to assess

Nursing Notes

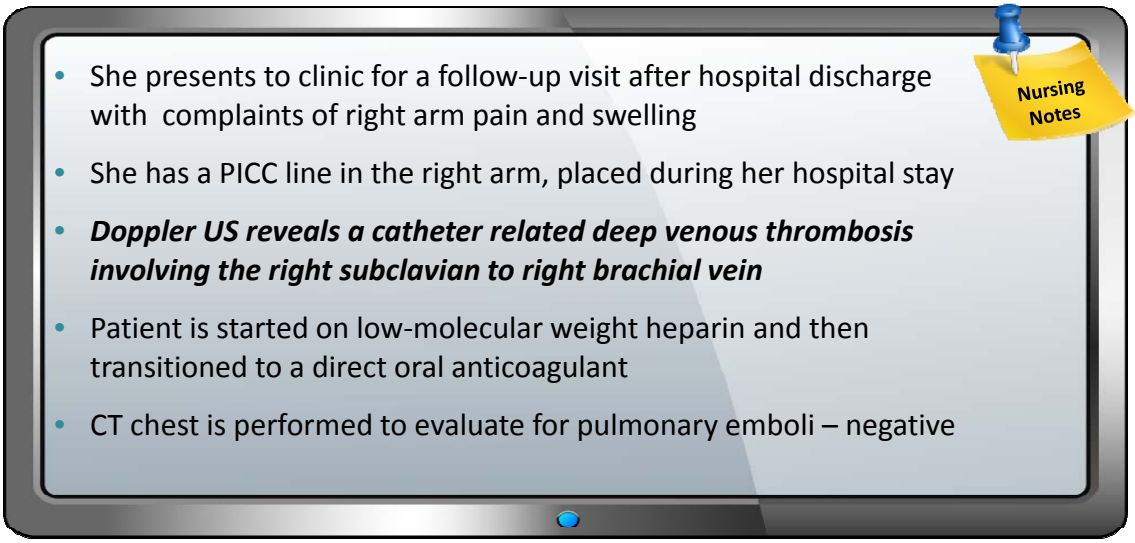
- **Whenever possible, therapeutic dose monitoring of asparaginase activity levels should be utilized to identify patients with suboptimal activity levels to adjust treatment accordingly**

Case Study 1: 24-year-old Female with T-cell ALL

Nursing Notes

- You draw serum ammonia and SAA levels after the first dose of pegaspargase
  - The SAA level is > 0.1 IU/mL
  - The serum ammonia level is 130 µ/dL (normal range 29–112 µ/dL)
- CJ is treated with fluids anti-emetics and symptoms improve

Case Study 1: 24-year-old Female with T-cell ALL



- She presents to clinic for a follow-up visit after hospital discharge with complaints of right arm pain and swelling
- She has a PICC line in the right arm, placed during her hospital stay
- ***Doppler US reveals a catheter related deep venous thrombosis involving the right subclavian to right brachial vein***
- Patient is started on low-molecular weight heparin and then transitioned to a direct oral anticoagulant
- CT chest is performed to evaluate for pulmonary emboli – negative

Adverse Event Profile for Asparaginase: Thromboembolism

Clinical Manifestations
- Grade 1: Medical intervention not indicated (e.g., superficial thrombosis)
- Grade 2: Medical intervention indicated
- Grade 3: Urgent medical intervention indicated (e.g., pulmonary embolism or intracardiac thrombus)
- Grade 4: Life-threatening consequences with hemodynamic or neurologic instability

Prevention and Management
- Evaluate history of thrombosis
- Monitor symptoms closely, particularly for implanted central catheters
- Avoid replacement with cryoprecipitate to correct laboratory abnormalities in the absence of clinical bleed
- Maintain adequate platelet counts while patient is receiving anticoagulation
- Consider antithrombotic therapy
- Prophylactic anticoagulation is controversial

Non-CNS Thrombosis
- Grade > 2 or thromboembolic event, hold asparaginase until resolved and treat with appropriate antithrombotic therapy
- Low molecular weight heparin or direct oral anticoagulant for 3 months (longer if still at risk)
- Upon resolution of symptoms and antithrombotic therapy stable or completed, consider resuming asparaginase
- Consider checking ATIII levels if administering heparin

CNS Thrombosis, Ischemia or Stroke
- For Grade < 3 or less, if symptoms/signs fully resolve, consider resuming asparaginase at lower doses and/or longer intervals between doses
- Grade $\geq$ 3 permanently discontinue asparaginase

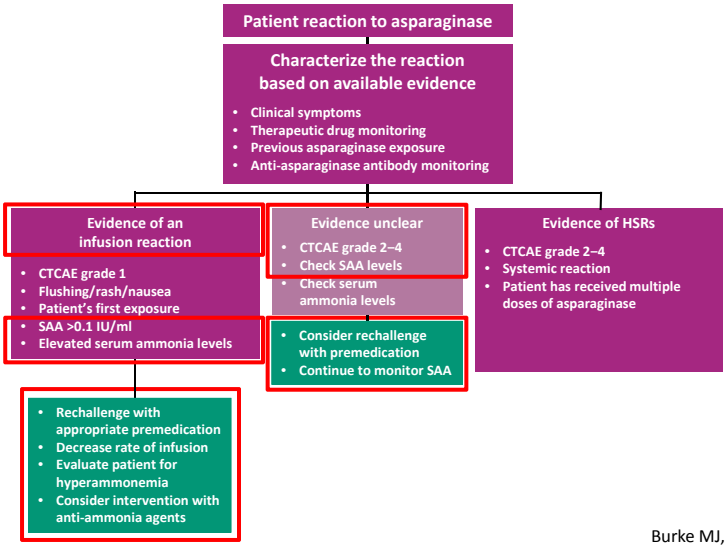
Aldoss I, Douer D. *Blood.* 2020;135(13):987-995.; Pourhassan H, et al. *Curr Oncol Rep.* 2023;25(1):51-61.; NCCN Guidelines Version 1.2022, Acute Lymphoblastic Leukemia @https://www.nccn.org/professionals/physician_gls/pdf/all.pdf.

Case Study 1: 24-year-old Female with T-cell ALL

- Swelling and pain improve
- Patient is restarted on asparaginase with continued anticoagulation using DOAC and low-molecular weight heparin based on platelet counts
- Continue monitoring CBC, CMP, fibrinogen, triglycerides, LDH, amylase, lipase

Nursing Notes

Treatment Algorithm and Therapeutic Drug Monitoring (TDM) Following a Reaction to Asparaginase Therapy

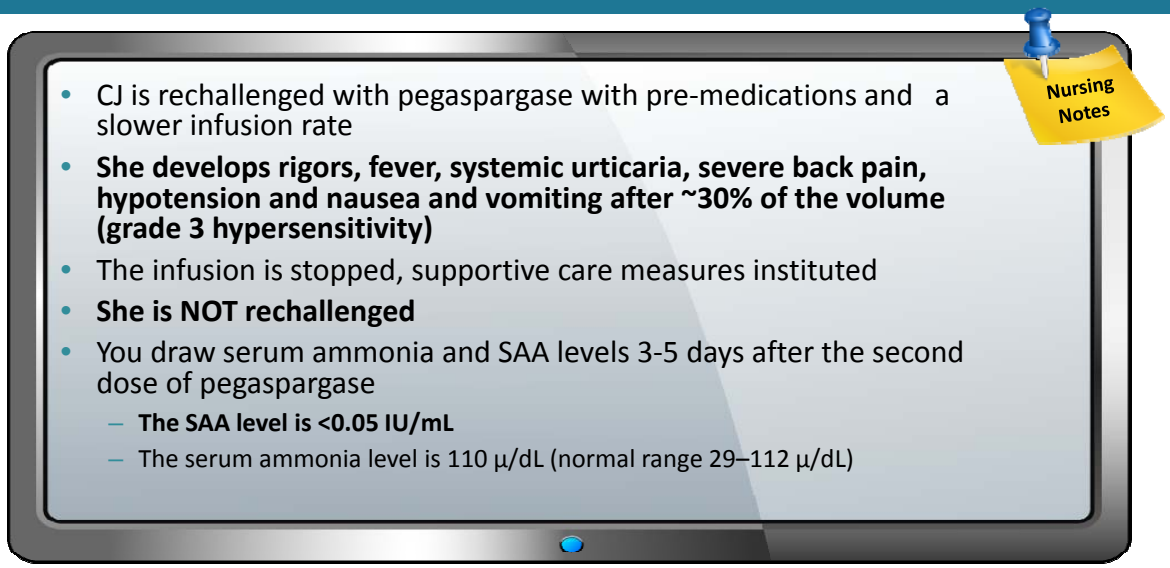


Nursing Notes

- **SAA trough of ≥ 0.1 IU/mL is the therapeutic target**
- **Levels < 0.1 are associated with subtherapeutic asparagine depletion**

Burke MJ, Zalewska-Szewczyk B. *Future Oncol.* 2022;18(10):1285-1299.

Case Study 1: 24-year-old Female with T-cell ALL



Asparaginase Hypersensitivity Reactions

Differentiating Infusion Reactions and Hypersensitivity

Infusion Reaction (Nonallergic reaction)	**Allergic Reaction** (Hypersensitivity)	**Silent Inactivation** (Subclinical Hypersensitivity)	**Hyperammonemia**
Non-antibody mediated	Antibody mediated; antibodies inactivate asparaginase, reducing asparaginase activity	Patients develop anti-asparaginase antibodies without clinical signs of hypersensitivity	Non-antibody mediated, results from spikes in serum ammonia levels
When misdiagnosed as allergic reaction, can lead to unnecessary contraindication to and switching or discontinuation of asparaginase treatment	Nonallergic reactions cannot be distinguished from allergic reactions based on clinical symptoms or grade	If unrecognized, patients are often continued on the same asparaginase formulation with no therapeutic benefit	If misdiagnosed as an allergic reaction, can lead to unnecessary contraindication to and switching or discontinuation of asparaginase treatment
Premedication can reduce the risk of nonallergic reactions	**TDM can help distinguish between allergic and nonallergic reactions**	**TDM will help to establish whether a patient has silent activation**	**TDM can help distinguish between allergic reactions and hyperammonemia**

TDM = Therapeutic Drug Monitoring

Burke MJ, et al. *Leuk Lymphoma*. 2017;58(3):540-551.; Asselin B, et al. *Future Oncol*. 2016;12(13):1609-1621.; Demoly P, et al. *Allergy.* 2014;69(4):420-437.; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia V.1.2022. © National Comprehensive Cancer Network, Inc.; Tong WH, et al. *Blood*. 2014;123(13):2026-2033.; Kloos RQ, et al. *Pediatr Blood Cancer.* 2016;63(11):1928-1934.

Is it or is it not a "True" Allergic Response?

Immune Mediated	**Non-Immune Mediated**
• Allergic manifestations typically occur within a few minutes of starting the infusion and can range from urticarial rashes, flushing, nausea and vomiting to bronchospasm, hypotension, and respiratory distress syndrome	• Non-immune mediated reactions are either due to the infusion itself or from hyperammonemia • These may present very similarly and be mistaken for pegaspargase hypersensitivity

Woods D, et al. *J Pediatr Oncol Nurs*. 2017;34(6):387-396.

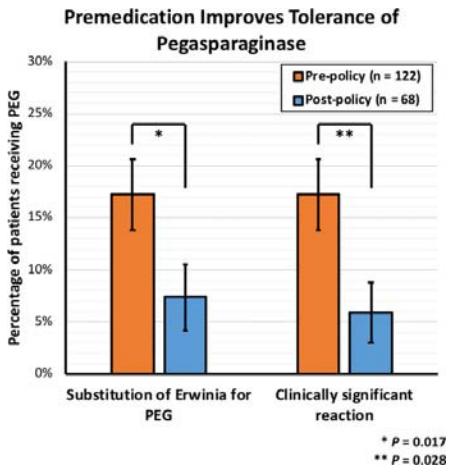
Hypersensitivity (HSR) vs Infusion-related Reactions (IRR) Related to Asparaginase

- HSRs are indicative of the development of **neutralizing anti-asparaginase antibodies (IgG complexes)** even when mild (Grade 1/2)
- Re-exposure to the same formulation of asparaginase may lead to:
  - Phagocytosis of asparaginase through the liver and spleen
  - Shortened t1/2
  - Reduced serum asparaginase activity (SAA)
  - Reduced asparagine depletion
  - Increased severity of hypersensitivity reactions

Burke MJ, Zalewska-Szewczyk B. *Future Oncol.* 2022;18(10):1285-1299.; Aldoss I, Douer D. *Blood.* 2020;135(13):987-995.; Pourhassan H, et al. *Curr Oncol Rep.* 2023;25(1):51-61.

Hypersensitivity (HSR) vs Infusion-related Reactions (IRR) Related to Asparaginase

- Premedication can reduce the risk of hypersensitivity reactions but does not prevent silent inactivation
- Requires therapeutic drug monitoring (TDM)
- Important to check serum asparaginase activity (SAA) levels
  - In patients who are premedicated
  - In patients with any grade infusion reaction or hypersensitivity reaction



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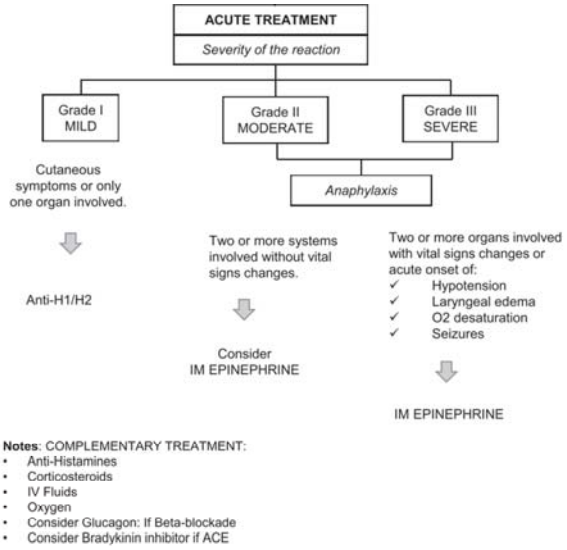
Practical Consideration in Prevention and Management of Infusion-related or Hypersensitivity Reactions

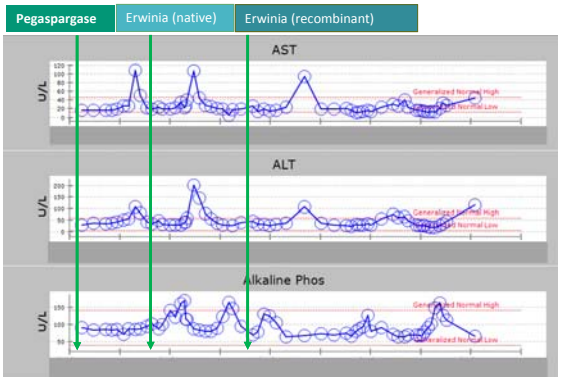
- All patients receiving drugs with a high risk of hypersensitivity should be scheduled early in the day and earlier in the week
- Prior to infusion for ALL PATIENTS:
  - Review treatment plan
  - Review pre-medications
  - Review cycle of therapy
- Ensure patient has active standing orders for infusion reaction intervention (institutional variations may exist)
- Institute monitoring appropriate for risk

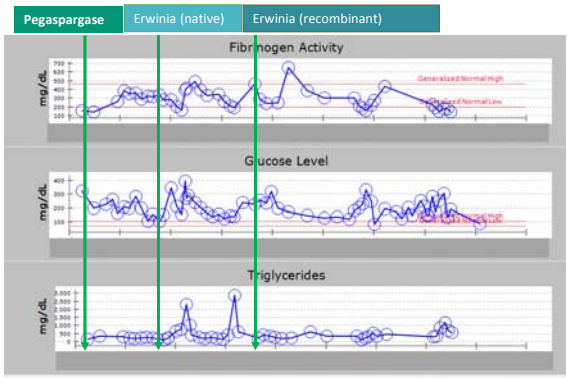
Labella M, et al. *Curr Opin Allergy Clin Immunol.* 2018;18:190-197.



Case Study 1: 24-year-old Female with T-cell ALL

- Patient is converted to asparaginase erwinia chrysanthemi-rywn (recombinant) to complete her multi-agent therapy
- Monitoring of labs over the course of treatment shows transaminitis, hypofibrinogemia, hyperglycemia and hypertriglyceridemia emphasizing the need to monitor





Adverse Event Profile for Asparaginase: Hyperbilirubinemia and Transaminitis

- Hepatotoxicity is the most common adverse event for pegaspargase in adults
  - Grade ≥3 hyperbilirubinemia
    - ✓ Grade 3 hyperbilirubinemia: >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal
    - ✓ Reported in 24% to 39% of adults treated with pediatric regimens
- Transaminitis in adults is common (all grade = 93%, grade ≥3 =50%)
  - Grade 3 transaminitis: AST, ALT or ALP >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
- Risk Factors
  - Induction cycle
  - Older age
  - Obesity,
  - Higher dose of asparaginase
  - Low albumin
  - Low platelet count
  - CC genotype of rs4880 polymorphism

Aldoss I, Douer D. *Blood.* 2020;135(13):987-995.; Pourhassan H, et al. *Curr Oncol Rep.* 2023;25(1):51-61.; NCCN Guidelines Version 1.2022, Acute Lymphoblastic Leukemia @https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. U.S. Department of Health and Human Services. (2017). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Adverse Event Profile for Asparaginase: Hyperbilirubinemia and Transaminitis

- Incidence and Duration
  - Almost always reversible
  - Most common after initial dose
  - Time to onset after administration of pegaspargase to grade ≥3 hyperbilirubinemia is ~ 2 weeks
  - Median to resolution to grade 1 may be up to 4 weeks after administration of pegaspargase
  - Generally, resolves and does not recur after initial dosing
  - Grade ≥3 hepatotoxicity is low with Erwinia-derived asparaginase but no data support switching to Erwinia-derived asparaginase for hepatotoxicity
- Prevention and Management
  - Hold drugs with known hepatotoxicity/primary liver metabolism
  - Delay the next chemotherapy cycle until hyperbilirubinemia resolves to grade 1 and transaminitis is grade ≤2

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Adverse Event Profile for Asparaginase: Pancreatitis

- Risk Factors
  - Older age
  - Native American ancestry
  - High cumulative doses of asparaginase (≥ 240,000 U/m2)
  - Asparaginase formulation
- Prevention and Management
  - Treatment of pancreatitis
  - Grade 2: Enzyme elevation; radiologic findings only
    - Hold asparaginase until enzyme levels or radiologic findings resolve
  - Grade ≥ 3: Severe pain; vomiting; medical intervention indicated; grade 4 = Life-threatening consequences; urgent intervention indicated
    - ***Permanently discontinue asparaginase***

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Adverse Event Profile for Asparaginase: Hypofibrinogenemia/Hemorrhage

- Risk Factors
  - Unknown
- Prevention and Management
  - Not an indication to discontinue pegaspargase
  - Monitor PT/PTT, fibrinogen levels prior to each dose of treatment
  - Prophylactic replacement for fibrinogen levels below 50 mg/dL or during active bleeding or before procedures
  - Avoid concurrent anti-coagulation, monitor patients closely when anticoagulation is necessary
  - Monitor for concurrent thrombocytopenia

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Adverse Event Profile for Asparaginase: Hypertriglyceridemia

- Risk Factors
  - Hypertriglyceridemia is a common laboratory abnormality during asparaginase therapy
  - Generally, resolves spontaneously and quickly
  - More frequent during consolidation cycles
  - Increased body mass index
  - Younger age inverse association with increased age
  - Pre-existing hypertriglyceridemia

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Adverse Event Profile for Asparaginase: Hypertriglyceridemia

- Prevention and Management
  - Evaluate and treat other causes of underlying hypertriglyceridemia
  - Because hypertriglyceridemia is a risk factor for pancreatitis and because both toxicities can occur post-asparaginase, clinicians may wish to treat hypertriglyceridemia to avoid pancreatitis
  - Treatment/prevention with gemfibrozil or other fibrates, particularly for high-grade triglyceridemia (>1000 mg/dL)
  - Grade $\leq$3:
    - >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L
    - Continue asparaginase without interruption or dose adjustment
  - Grade 4:
    - >1000 mg/dL; >11.4 mmol/L; life-threatening consequences
    - Hold asparaginase and resume when normalized

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Adverse Event Profile for Asparaginase: Hyperglycemia

- Risk Factors
  - Pre-existing diabetes or hyperglycemia
  - Concurrent use of corticosteroids
- Prevention and Management
  - Dietary restriction of simple sugars
  - Adjustment of anti-diabetic medications
  - Continue asparaginase for grade ≤ 2 toxicity
  - Hold asparaginase and glucocorticoids for grade ≥ 3 toxicity :
    - Grade 3:Insulin therapy initiated; hospitalization indicated
    - Grade 4: Life-threatening consequences; urgent intervention indicated
  - Asparaginase can be continued if normal glucose levels are achieved with insulin (<200 mg/dL or 11 mmol/L)
  - Insulin therapy should be initiated to achieve glycemic control

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Patient and Family Considerations

Inform Patients and Family → Change in asparaginase formulation will change the number and frequency of visits required

Content to review:

- Importance of dose intensity relative to treatment outcomes
- Frequency and duration of visits may vary across formulation of asparaginase
- Education about the importance of therapeutic drug monitoring
- Infusion reactions or hypersensitivity to one formulation does not exclude the ability to safely use an alternative formulation
- Familiarity with required post infusion/injection monitoring is essential

Key Take-aways

- ✓ Asparaginase is an essential chemotherapeutic agent for the treatment of pediatric, AYA, and adult ALL and LBL
- ✓ Subtherapeutic dosing of asparaginase is associated with inferior outcomes
- ✓ IgG complex neutralizing antibodies to asparaginase may develop with or without overt symptoms of hypersensitivity
- ✓ Therapeutic drug monitoring using SAA
  - ✓ Allows for clinicians to monitor for silent inactivation
  - ✓ Indicates the need to switch to an alternative formulation of asparaginase
- ✓ In the future
  - ✓ Asparaginase therapy may include individualized dosing based on SAA levels
  - ✓ Incorporation of pharmacogenomics to predict risk of toxicities
  - ✓ Development of additional strategies to mitigate toxicities