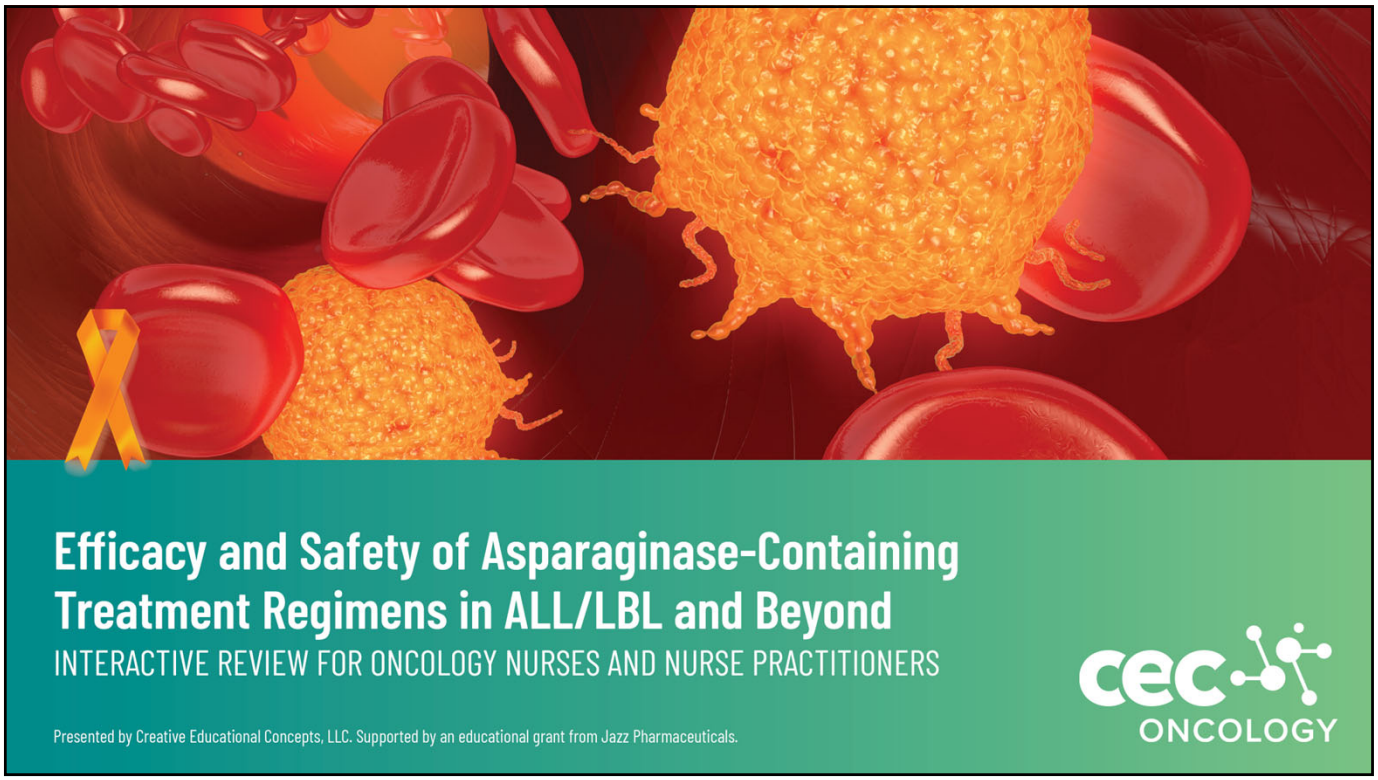

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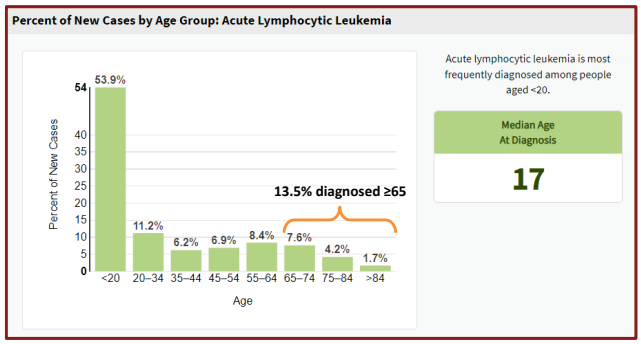
Learning Objectives

1. Examine the rationale for using asparaginase in the treatment of pediatric and adult/young adult acute lymphoblastic leukemia (ALL)/lymphoblastic lymphoma (LBL), as well as in other disease states.
2. Appraise key clinical trial data of different asparaginase-containing regimens in ALL/LBL and apply that knowledge to selection of optimal asparaginase-containing treatments, based on patient-specific factors as well as the latest data.
3. Identify the different asparaginase products available, and distinguish them based upon dose, route, formulation, proper monitoring, PK profiles, and unique safety concerns.
4. Recognize asparaginase-related toxicities that lead to poorer patient prognosis, identify the difference between asparaginase infusion reactions and clinical/subclinical hypersensitivity, develop monitoring/interpretation strategies for serum asparaginase levels to optimize treatment, and understand silent inactivation.
5. Use a case-based approach to formulate clinical strategies for asparaginase-containing regimens, focusing on efficacy and safety of different formulations, and practice approaches to monitor asparaginase levels while also preventing and mitigating asparaginase-related toxicities.

Acute Lymphoblastic Leukemia
Epidemiology and Etiology

- Estimated 6,660 new cases and 1,560 deaths in 2022
- 5-year relative survival of 70.8% (2012–2018)
  - Median age at death: 59 years
  - <20 years: 87.6%



Etiology

Exposure to ionizing radiation, benzene, selected chemotherapy

Prior history of hematologic malignancy

Viral infections (e.g., human T-cell leukemia virus, Epstein-Barr virus)

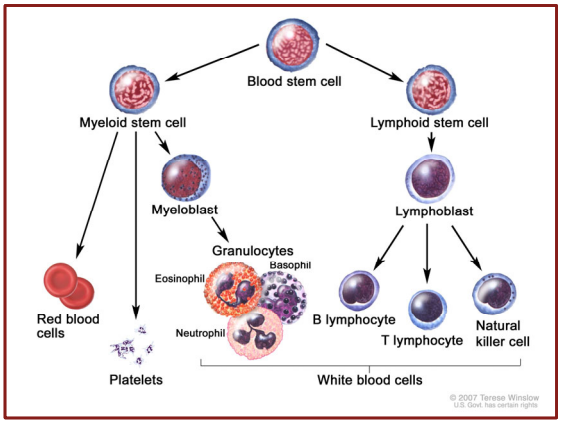
Genetic syndromes (e.g., Down syndrome, Fanconi anemia, Bloom syndrome, Li-Fraumeni syndrome) are associated with an increased risk of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)

Chronic autoimmune disease

https://seer.cancer.gov/statfacts/html/alyl.html; Bispo JAB, et al. *Cold Spring Harb Perspect Med*. 2020; Davis AS, et al. *Am Fam Physician*. 2014.

Acute Lymphoblastic Leukemia
Adult Disease Characteristics

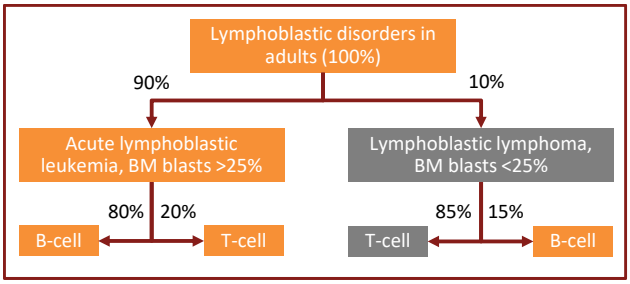
	B-Cell ALL	T-Cell ALL
Characteristics	75%–80%% of adult cases	More favorable in adults with initial diagnosis; however, relapse is difficult to treat
	Mature B-cell less favorable; treated with intense induction followed by allogeneic stem cell transplantation (SCT)	More commonly involves extra-medullary site
Immunophenotype	CD10, CD19, CD20, surface CD22, cytoplasmic CD22, cytoplasmic CD79a, cytoplasmic IgM, Pax5	CD1a, CD2, cytoplasmic CD3, surface CD3, CD4, CD5, CD7, CD8



Jabbour E, et al. *JAMA Oncol.* 2018; Kurtin S. *Semin Oncol Nurs*. 2019; Figure from https://nci-media.cancer.gov/pdq/media/images/526538.jpg.

Lymphoblastic Lymphoma
Disease Characteristics

- Lymphoblastic lymphoma (LBL) is a highly aggressive lymphoma that shares biological and morphological features with ALL
  - Originates in either B-cells or T-cells
  - Most common phenotype is T-cell
  - Distinguished from ALL by having <20%–25% marrow infiltrating blasts
- Considered a rare disease
  - 2%–4% of adult and <30% of children's non-Hodgkin lymphomas
  - Predominantly seen in young males (10–30 years)
- Treatment is similar to ALL
- Risk Factors
  - Ataxia-telangiectasia, Nijmegen breakage syndrome, constitutional mismatch repair deficiency
  - Human T-lymphotropic virus 1 (HTLV-1)
  - Trisomy 21
  - Other risk factors similar to ALL



Intermesoli T, et al. *Curr Oncol Rep*. 2022.

ALL/LBL
Diagnostic Evaluation

History and Physical Examination	Bone Marrow Analysis
Clinical presentation: fatigue, bleeding or bruising, infections, testicular pain *Attention to lymph nodes, skin, liver spleen, testicular exam in males	**Essential for confirmation of diagnosis and risk stratification,** including molecular and cytogenetic profile—comprehensive immunophenotyping with flow cytometry and molecular analysis to identify the leukemic clone **Largely drives prognosis and in some cases treatment selection**
Peripheral Blood	**Diagnostic Imaging**
Complete blood count (CBC), differential, chemistry profile, liver function tests (LFTs)	CT/MRI of head with contrast, if neurologic symptoms
Flow cytometry and review of peripheral smear (may quickly confirm the diagnosis while waiting on bone marrow analysis)	CT of neck/chest/abdomen/pelvis with IV contrast, as indicated for symptoms
Disseminated intravascular coagulation (DIC) panel: D-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)	Consider PET/CT if lymphomatous involvement is suspected and/or confirmed by CT imaging
Tumor lysis syndrome (TLS) panel: lactate dehydrogenase (LDH), uric acid, potassium, calcium, phosphorus	Scrotal ultrasound as indicated
Hepatitis B/C, HIV, CMV Ab testing	Echocardiogram or cardiac nuclear medicine scan
Lumbar puncture (LP), may give intrathecal (IT) chemotherapy if peripheral blood confirms lymphoblasts	
Pregnancy testing, fertility counseling, and preservation for female patients	

NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023.

International Consensus Classification
Integrating Morphologic, Clinical, and Genomic Data

B-ALL

- B-ALL with recurrent genetic abnormalities
- B-ALLwith t(9;22)(q34.1;q11.2)/*BCR::ABL1*
  - with lymphoid only involvement
  - with multilineage involvement
- B-ALLwith t(v;11q23.3)/*KMT2A* rearranged
- B-ALL with t(12;21)(p13.2;q22.1)/*ETV6::RUNX1*
- B-ALL, hyperdiploid
- B-ALL, low hypodiploid
- B-ALL, near haploid
- B-ALL with t(5;14)(q31.1;q32.3)/*IL3*::IGH
- B-ALL with t(1;19)(q23.3;p13.3)/*TCF3::PBX1*
- B-ALL, *BCR::ABL1*–like, ABL-1 class rearranged
- B-ALL, *BCR::ABL1*–like, JAK-STAT activated
- B-ALL, *BCR::ABL1*–like, NOS
- B-ALL with iAMP21
- B-ALL with *MYC* rearrangement
- B-ALL with *DUX4* rearrangement
- B-ALL with *MEF2D* rearrangement
- B-ALL with *ZNF384(362)* rearrangement
- B-ALL with *NUTM1* rearrangement
- B-ALL with *HLF* rearrangement
- B-ALL with *UBTF::ATXN7L3/PAN3,CDX2* ("CDX2/UBTF")
- B-ALL with mutated *IKZF1* N159Y
- B-ALLwith mutated *PAX5* P80R
  - Provisional entity: B-ALL, *ETV6::RUNX1*-like
  - Provisional entity: B-ALL, with *PAX5* alteration
  - Provisional entity: B-ALL, with mutated *ZEB2* (p.H1038R)/IGH::*CEBPE*
  - Provisional entity: B-ALL, *ZNF384* rearranged-like
  - Provisional entity: B-ALL, *KMT2A* rearranged-like
- B-ALL, NOS

T-ALL

- Early T-cell precursor ALLwith *BCL11B* rearrangement
- Early T-cell precursor ALL, NOS
- T-ALL, NOS

Arber DA, et al. *Blood.* 2022.

Adolescent and Young Adult/Adult ALL
Risk-stratified Treatment

ALL treatments represent one of the most complex and intensive programs in cancer therapy.

Initial treatment selection largely driven by:

- Age: adult, AYA*/adult, pediatric
- Fit vs frail (physiologic age)
- Eligibility for allogeneic stem cell transplant
- Goals of care
- Characteristics of the ALL
  - T-cell vs B-cell
  - Degree of leukocytosis
- Cytogenetic-molecular abnormalities (adult vs pediatric)
  - Philadelphia chromosome (Ph)-positive ALL
    - Unfavorable; 25% vs 3%
  - Ph-like ALL
    - Unfavorable; 20% vs 8%
  - Hyperdiploidy
    - Favorable; 2% vs 25%
  - t(12;21)
    - Favorable; 2% vs 25%

AYA, adolescent and young adult.
*The ALL panel considers AYA to be within the age range of 15–39 years.

NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023.

Adolescent and Young Adult/Adult ALL
Risk-stratified Treatment

Risk Stratification

Workup →
- Ph+ ALL (AYA and adult): Ph+ AYA patients are grouped with fit, adult patients <65 years and relies on the addition of tyrosine kinase inhibitors that target BCR-ABL
- Ph-negative ALL (AYA)
- Ph-negative ALL (Adult)

Ph-negative ALL in AYA*/adult patients relies on multiagent pediatric regimens with a multiphase approach
- Induction
- Consolidation/intensification
- CNS treatment/prophylaxis
- Maintenance

Risk of relapse is related to:
- Achievement of minimal residual disease negativity following induction
- Incomplete therapy
- High-risk features

AYA, adolescent and young adult.
*The ALL panel considers AYA to be within the age range of 15–39 years.

NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023.

Patient Case 1
28-Year-old Female with Lymphadenopathy

A 28-year-old female presents with progressive cervical and clavicular adenopathy over a 5-month period. No precipitating factors are reported, nor are night sweats or weight loss. She is initially treated with antibiotics.

A fine needle aspiration (FNA) of right cervical level II/III nodes is performed. Flow cytometry expressed **TdT, cytoplasmic CD2, CD3, CD4, CD5.** Findings are consistent with T-cell lymphoblastic lymphoma.

A CT of the chest/abdomen/pelvis finds multistation lymphadenopathy involving the bilateral cervical chain, bilateral supraclavicular, prevascular mediastinal, and bilateral axillary lymph nodes

Patient Case 1
28-Year-old Female with Lymphadenopathy

Further testing finds:

- Bone marrow biopsy and aspirate
  - Normocellular with trilineage hematopoiesis and 6.2% lymphoblasts
  - Flow cytometry finds a small population of blasts with a T-cell phenotype is detected (CD2+, sCD3-, CD7+, CD5+, TDT+, cCD3+)
  - Collective findings indicate low-level involvement by T-cell lymphoblastic lymphoma
- Lumbar puncture (LP) with cytarabine 40 mg intrathecal (IT), flow cytometry negative
- ECHO shows ejection fraction of 64%; no left or right ventricular dysfunction
- HIV and hepatitis screens negative

Slide 14

NL0 Mg/mL?
Nichole Lainhart, 2022-12-09T18:18:31.676

KL0 0 Just mg
Katherine Lee, 2022-12-12T00:47:32.626

NL1 Intrathecal?
Nichole Lainhart, 2022-12-09T18:18:54.393

KL1 0 Yes
Katherine Lee, 2022-12-12T00:46:04.947

NL2 Liposomal?
Nichole Lainhart, 2022-12-09T18:19:39.204

KL2 0 Lumbar Puncture
Katherine Lee, 2022-12-12T00:45:59.829

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

Induction

- **Most common**: daunorubicin, vincristine, prednisone, **asparaginase**, methotrexate, dexamethasone, idarubicin
- May include rituximab in adult patients (hyper-CVAD regimen), may include nelarabine for T-cell ALL
- Ph+: add TKI—dasatinib, nilotinib, bosutinib, ponatinib (based on adverse event 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

Targeted Therapies

Blinatumomab, inotuzumab

Cellular Therapies

CAR-T, allogeneic stem-cell transplant

NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023.

NL2

Patient Case 1

28-Year-old Female with Lymphadenopathy

The patient is within the age range for AYA/adult-based treatment (age 15–39). She is started on the AALL0434 protocol (pediatric-based regimen).

Induction Regimen	
Daunorubicin 25 mg/m^2 IV	Once per day; Days 1, 8, 15, 22
Vincristine 1.5 mg/m^2 IV (maximum dose of 2 mg/week)	Once per day; Days 1, 8, 15, 22
Pegaspargase 2,500 units/m^2 IV	Once; Day 4
Prednisone 30 mg/m^2 PO	Twice per day; Days 1 to 28

Consolidation	
Nelarabine	Days 1–5
Cyclophosphamide	Day 8
Cytarabine	Days 8–11, 15–18
6MP	Days 8–21
PegasNL0**se**	Day 22
Vincristine	Days 22, 29
IT MTX	Days 18, 25

NL1

6MP, mercaptopurine; MTX, methotrexate.

Slide 16

NL0 Spell out? Mercaptopurine
Nichole Lainhart, 2022-12-12T16:07:23.512

KL0 0 Added footnote
Katherine Lee, 2022-12-13T18:48:08.626

NL1 Spell out methotrexate?
Nichole Lainhart, 2022-12-12T16:07:52.465

KL1 0 Added footnote
Katherine Lee, 2022-12-13T18:48:19.925

NL2 Add "FDA Prescribing Information" citation?
Nichole Lainhart, 2022-12-12T18:13:04.383

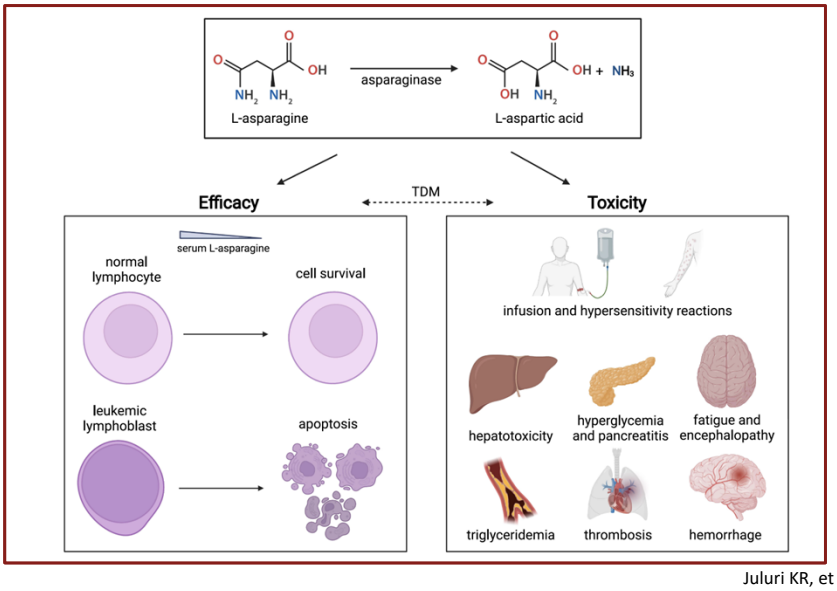
KL2 0 It is okay not to here because it’s an example from practice
Katherine Lee, 2022-12-13T18:46:06.945

Asparaginase in ALL/LBL

- Asparaginase is a critical component of multi-agent ALL regimens
  - Patients with lymphoblastic lymphoma benefit from multi-agent ALL regimens
- Asparagine is one of twenty amino acids necessary for cell function and survival
- Leukemic cells lack L-asparagine synthetase, required to make asparagine
- Leukemic cells require exogenous asparagine for survival
- Asparaginase lowers serum asparagine
  - Hydrolyzing asparagine to aspartic acid and ammonia
  - Leads to decreased protein synthesis in leukemic cells
  - Eventual leukemic cell death via apoptosis
- Continuous and prolonged asparagine depletion is associated with apoptosis of the leukemic clone
- Incomplete therapy (<26 consecutive weeks of asparaginase) is associated with inferior outcomes in pediatric patients
- Factors associated with suboptimal dosing of asparaginase
  - Resistance
  - Adverse events
  - Underdosing

Juluri KR, et al. *Blood Lymphat Cancer*. 2022.

Asparaginase in ALL/LBL



Juluri KR, et al. *Blood Lymphat Cancer*. 2022.

Asparaginase Formulations

Formulation	Derived from *E. coli*	FDA-approved Indication	Half-life	Administration
Pegylated asparaginase (pegaspargase)	Yes	As a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with: • First-line ALL • ALL and hypersensitivity to native forms of L-asparaginase	IM: 5.8 days IV: 5.3 days	Dose: 2,000–2,500 IU/m^2 Route: IM or IV Frequency: every 2 weeks
Erwinia asparaginase (asparaginase) (native)**	No	Treatment of patients with ALL as part of a multi-agent chemotherapeutic regimen	IM: 16 hours IV: 7.5 hours	Dose: 25,000 IU/m^2 Route: IM or IV Frequency: 3× a week
Calaspargase pegol-mknl	Yes	As a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in pediatric and young adult patients age 1 month to 21 years	IV: 16.2 days	Dose: 2,500 IU/m^2 Route: IV Frequency: every 3 weeks
Erwinia chrysanthemi asparaginase-rywn (recombinant)	No	As a component of a multi-agent chemotherapeutic regimen given by intramuscular injection for the treatment of ALL and LBL in adult and pediatric patients 1 month or older who have developed hypersensitivity to *E coli*-derived asparaginase	IM: 18.2 hours	Dose: 25 mg/m^2 Route: IM Frequency: every 48 hours

**Non-recombinant asparaginase Erwinia chrysanthemi no longer available in U.S.

Maese L, et al. *Blood*. 2022; Vrooman LM, et al. *J Clin Oncol. 2022;* Juluri KR, et al. *Blood Lymphat Cancer*. 2022; FDA Prescribing Information.

Incidence of Common Adverse Events for Asparaginase

Adverse Event	All Grades (%)	Grade ≥3 (%)
Hypersensitivity	7–22	4–10
Hyperbilirubinemia/↑LFTs	86	24–39
Pancreatitis	24	5–13
Hypertriglyceridemia	77	11–51
Thrombosis		11–27
Hypofibrinogenemia		48–51
Hyperglycemia	91	31–33

Aldoss I & Douer D. *Blood.* 2022; Maese L, et al. *Front Pediatr*. 2022.

Risk Factors for Hypersensitivity to Asparaginase

- Formulation of asparaginase
- Route of administration
- No premedication
- Schedule of administration: second dose and future doses
- *HLA-DRB1* polymorphism NL1
- Younger age
- Line of treatment
- Concurrent use of other therapeutic agents including corticosteroids
- Prior history of hypersensitivity to medications

Aldoss I, Douer D. *Blood*. 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia. V2.2023.

NL0

CTCAE 5.0 Grading of Infusion-related Reactions

- **Definition:** A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances

Grade	Signs/Symptoms
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
4	Life-threatening consequences; urgent intervention indicated

U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). 2017.

Slide 21

NL0 Cannot access for free.

https://pubmed.ncbi.nlm.nih.gov/36449117/
Nichole Lainhart, 2022-12-06T16:07:37.800

NL1 Italicize?
Nichole Lainhart, 2022-12-12T18:50:54.339

Adverse Event Prevention and Mitigation
Hypersensitivity

- Prevention and management, general measures
  - Premedication with histamine 1 (diphenhydramine, cetirizine), histamine 2 (famotidine), corticosteroid (hydrocortisone), and acetaminophen
  - Slow the infusion for IV formulations for up to 2 hours
- Treatment based on grade of infusion-related reaction
  - **Grade 1 or 2** without bronchospasm, hypotension, edema, or need for parenteral intervention (rash, flushing, urticaria, and drug fever ≥38°C) the asparaginase that caused the reaction may be continued, with consideration for anti-allergy premedication (such as hydrocortisone, famotidine or ranitidine, diphenhydramine, cetirizine, and acetaminophen).
  - **Grade 2** or higher systemic allergic reactions, urticaria, or anaphylaxis can be (but are not necessarily) associated with neutralizing antibodies and lack of efficacy.
  - **Grade ≥3** merit permanent discontinuation of the type of asparaginase that caused the reaction
    - Erwinia formulations (erwinia, erwinia-rywn) may be used as a second-line agent in patients who have developed a systemic allergic reaction or anaphylaxis due to pegaspargase

Aldoss I, Douer D. *Blood.* 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023; U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). 2017.

Patient Case 2
35-Year-old Male with New Diagnosis of T-cell ALL

A 35-year-old male with newly diagnosed T-cell ALL has a history of hypertension, hyperlipidemia, and type 2 diabetes. He presented to the emergency department with chest pain and shortness of breath.

A chest CT shows a large mediastinal mass (15.5 × 9.4 × 10.7 cm), and biopsy confirms T-cell lymphoblastic leukemia/lymphoma. A US of the scrotum is negative for involvement.

A bone marrow biopsy finds T-lymphoblastic leukemia/lymphoma, with a blast count of 90%.

Started on Pediatric-based Regimen	
IT cytarabine 100 mg	Day 0
Prednisone 30 mg/m^2 BID	Days 1–28
Vincristine 1.5 mg/m^2	Days 1, 8, 15, 22
Daunorubicin 25 mg/m^2	Days 1, 8, 15, 22
Pegaspargase 2,500 IU/m^2 IM	Day 4
IT MTX 15 mg	Days 8, 29

MTX, methotrexate;

Patient Case 2
35-Year-old Male with New Diagnosis of T-cell ALL

On **Day 4** of a multi-agent regimen, the patient was given pegaspargase 2,500 IU/m^2 IV. He began having **flushing of skin, coughing, chest pain, and trouble breathing** when he was over halfway through the first administration of pegaspargase.

The pegaspargase infusion was discontinued, and his oxygen saturation decreased to 82%.

He was placed on oxygen and given IV diphenhydramine, hydrocortisone, and famotidine with incomplete resolution. Epinephrine 0.3 mg IM is given with gradual improvement.

In Case of "Hypersensitivity Reactions"

Option 1. Permanently discontinue ASNase therapy

Option 2. Switch to native *E. coli* ASNase, anticipating hypersensitivity toward PEG moiety

Option 3. Continue with PEG-ASNase with premedication (e.g., H1 and H2 blockers, steroids)

Option 4. Prescribe premedication at next PEG-ASNase dose and perform therapeutic drug monitoring (assuming it is available)

Option 5. Switch to IM ASNase, anticipating less hypersensitivity than with IV

Option 6. Switch to non-cross-reactive ASNase formulation (*Erwinia* ASNase)

Option 7. Continue ASNase therapy assuming "allergy-like" reaction

NCCN Guidelines. Acute lymphoblastic leukemia. v2.2022.

Patient Case 2
35-Year-old Male with New Diagnosis of T-cell ALL

On **Day 4** of multi-agent regimen, patient was given pegaspargase 2,500 IU/m^2 IV. He began having **flushing of skin, coughing, chest pain, and trouble breathing** when he was over halfway through the first administration of pegaspargase.

The pegaspargase infusion was discontinued, and his oxygen saturation decreased to 82%.

He was placed on oxygen and given IV diphenhydramine, hydrocortisone, and famotidine with incomplete resolution. Epinephrine 0.3 mg IM is given with gradual improvement.

Pegaspargase is discontinued permanently due to grade 3 infusion reaction/ hypersensitivity, and the patient is rechallenged with erwinia asparaginase without recurrent infusion-related reaction.

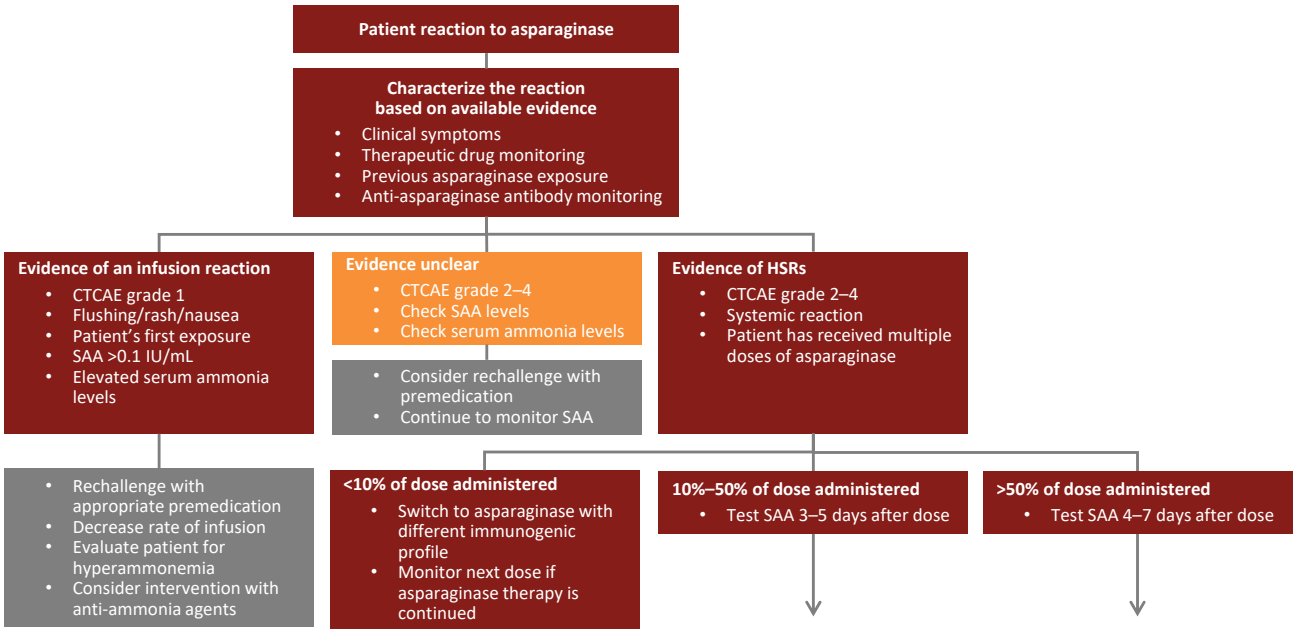
Resistance to Asparaginase

Resistance to asparaginase may occur due to several factors:

- Upregulation of asparagine synthetase
- Production of neutralizing antibodies
  - Results in removal of the protein
  - Decreased therapeutic efficacy (often a result of hypersensitivity)
  - Silent inactivation (not a result of hypersensitivity)
- Measuring serum asparaginase activity (SAA) may be warranted when there are gaps in asparaginase therapy or in the setting of relapse
- SAA-driven therapy is an emerging trend
  - Included in NCCN guidelines
  - Early adoption in Europe
  - SAA is available as a CLIA-certified test with a turnaround time of less than 1 week
  - Generally accepted SAA assay targets include a minimum trough of ≥0.1 IU/mL
  - Data indicate that when SAA levels fall below 0.4 IU/mL, asparagine is no longer depleted and begins to rebound, suggesting an optimal trough of ≥0.4 IU/mL

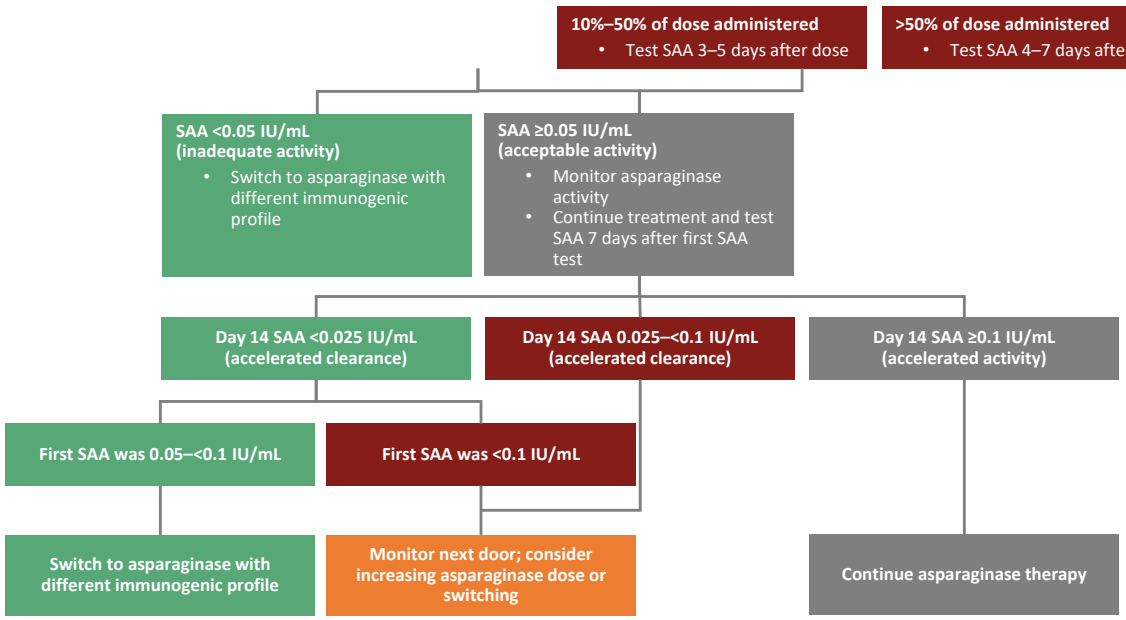
van der Sluis IM, et al. *Haematologica*. 2016; NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023.

Treatment Decisions following Reaction to Asparaginase-based Therapy



Burke MJ, Zalewska-Szewczyk B. *Future Oncol*. 2022.

Treatment Decisions following Reaction to Asparaginase-based Therapy



Burke MJ, Zalewska-Szewczyk B. *Future Oncol*. 2022.

Adverse Event Profile for Asparaginase
Thromboembolism

Risk Factors
• Increasing age • Obesity • Mediastinal mass at diagnosis • Low white blood cell count at diagnosis

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

Aldoss I, Douer D. *Blood.* 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023; U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). 2017.

Patient Case 1
28-Year-old Female with Lymphadenopathy

The patient is within the age range for AYA/adult-based treatment (age 15–39). She is started on AALL0434 protocol (pediatric-based regimen).

Induction Regimen	
Daunorubicin 25 mg/m^2 IV	Once per day; Days 1, 8, 15, 22
Vincristine 1.5 mg/m^2 IV (maximum dose of 2 mg/week)	Once per day; Days 1, 8, 15, 22
Pegaspargase 2,500 units/m^2 IV	Once; Day 4
Prednisone 30 mg/m^2 PO	Twice per day; Days 1 to 28

Consolidation	
Nelarabine	Days 1–5
Cyclophosphamide	Day 8
Cytarabine	Days 8–11, 15–18
6MP	Days 8–21
Pegaspargase	Day 22
Vincristine	Days 22, 29
IT MTX	Days 18, 25

She presents to clinic for a follow-up visit with complaints of right arm pain and swelling. She has a PICC line in the right arm that was placed during her hospital stay. A doppler US reveals a catheter-related deep venous thrombosis involving the right subclavian to right brachial vein.

Adverse Event Profile for Asparaginase
Thromboembolism

- 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

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 if antithrombotic therapy is stable or completed, consider resuming asparaginase
- Consider checking antithrombin III 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 4, permanently discontinue asparaginase
- Consider antithrombotic therapy

Aldoss I, Douer D. *Blood.* 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023.

Patient Case 1
28-Year-old Female with Lymphadenopathy

She is started on low–molecular weight heparin and then transitioned to a direct oral anticoagulant. A chest CT is negative for pulmonary emboli.

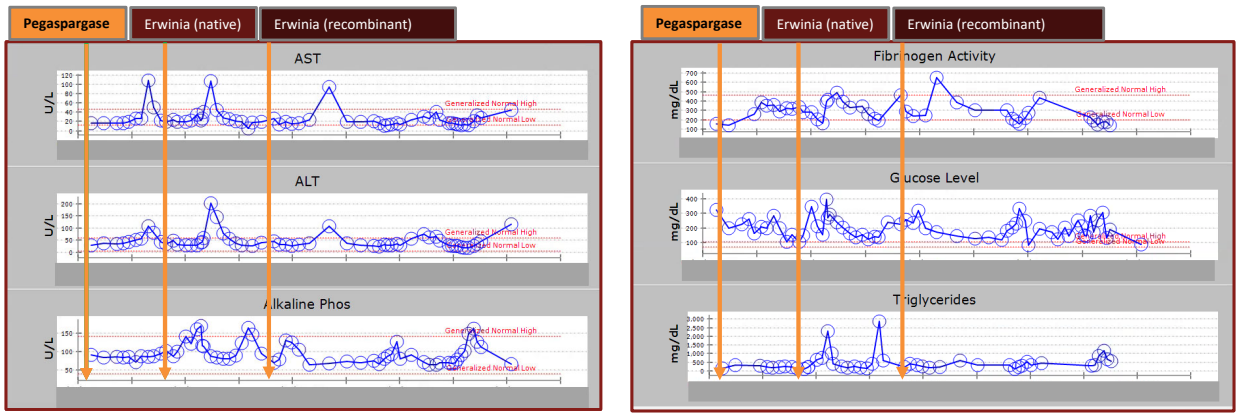
The PICC line is removed, and her swelling and pain improve.

She is restarted on asparaginase with continued anticoagulation using DOAC and low–molecular weight heparin based on platelet counts.

Labs Tuesday/Friday (CBC, CMP, fibrinogen, triglycerides, LDH, and amylase, lipase) with possible transfusion.

Patient Case 2
35-Year-old Male with New Diagnosis of T-cell ALL

Pegaspargase is discontinued permanently due to grade 3 infusion reaction/hypersensitivity. The patient is rechallenged with an erwinia asparaginase formulation (asparaginase Erwinia chrysanthemi-rywn) as a part of a multi-agent-regimen-drug shortage.



Adverse Event Profile for Asparaginase
Hyperbilirubinemia and Transaminitis

- Hepatotoxicity is the most common adverse effect of pegaspargase in adults (reported in **24%–39%** of adults treated with pediatric regimens)

Grade ≥3 Hyperbilirubinemia
>3.0–10.0 × ULN if baseline was normal
>3.0–10.0 × baseline if baseline was abnormal

- Transaminitis in adults is common (all grade at 93%; grade ≥3 at 50%)

Grade 3 Transaminitis
AST, ALT, or ALP >5.0–20.0 × ULN if baseline was normal
>5.0–20.0 × 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; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia.. V2.2023; U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). 2017.

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**

Aldoss I, Douer D. *Blood.* 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023.

Adverse Event Profile for Asparaginase
Pancreatitis

- Risk factors
  - Older age
  - Native American ancestry
  - High cumulative doses of asparaginase (≥240,000 U/m^2)
  - 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

Aldoss I, Douer D. *Blood.* 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023; U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). 2017.

Adverse Event Profile for Asparaginase
Hypofibrinogenemia/Hemorrhage

- Risk factors
  - Unknown
- Prevention and management
  - Not an indication to discontinue pegasparagase
  - 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 anticoagulation, monitor patients closely when anticoagulation is necessary
  - Monitor for concurrent thrombocytopenia

Aldoss I, Douer D. *Blood.* 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023.

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

Aldoss I, Douer D. *Blood.* 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023.

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 (>1,000 mg/dL)

	Triglyceride Levels	Management
Grade ≤3	>500–1,000 mg/dL; >5.7–11.4 mmol/L	Continue asparaginase without interruption or dose adjustment
Grade 4	>1,000 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 antidiabetic 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
  - Insulin therapy should be initiated to achieve glycemic control
  - Asparaginase can be continued if normal glucose levels are achieved with insulin (<200 mg/dL or 11 mmol/L)

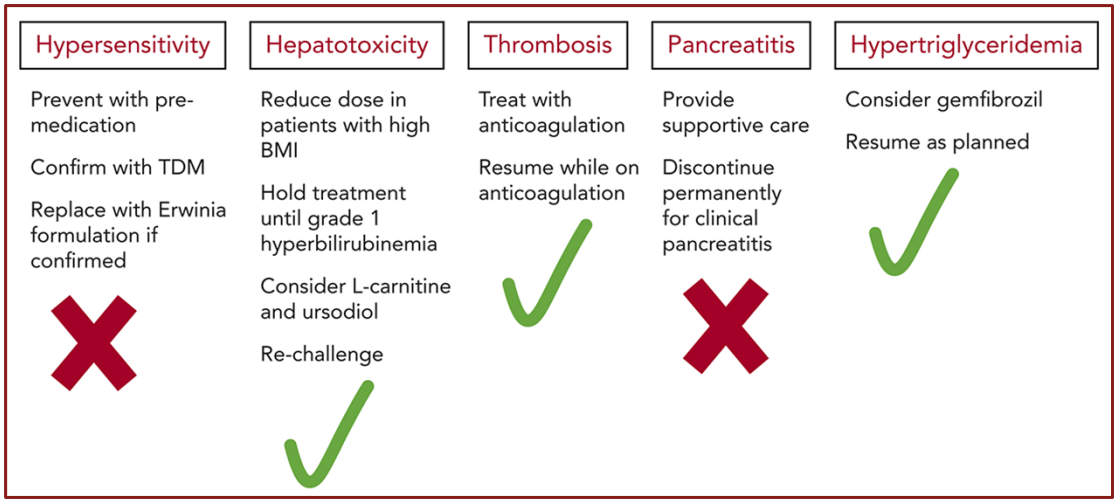
Aldoss I, Douer D. *Blood.* 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023; U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). 2017.

Adverse Event Profile for Asparaginase
Hyperammonemia

- Risk factors
  - Already existing liver disease
- Prevention and management (not well studied)
  - Decreased protein intake
  - Lactulose treatment
  - Benzoic acid
  - Arginine
  - Sodium phenylbutyrate

Aldoss I, Douer D. *Blood.* 2020; Pourhassan H, et al. *Curr Oncol Rep*. 2022; NCCN Guidelines. Acute Lymphoblastic Leukemia.v2.2023.

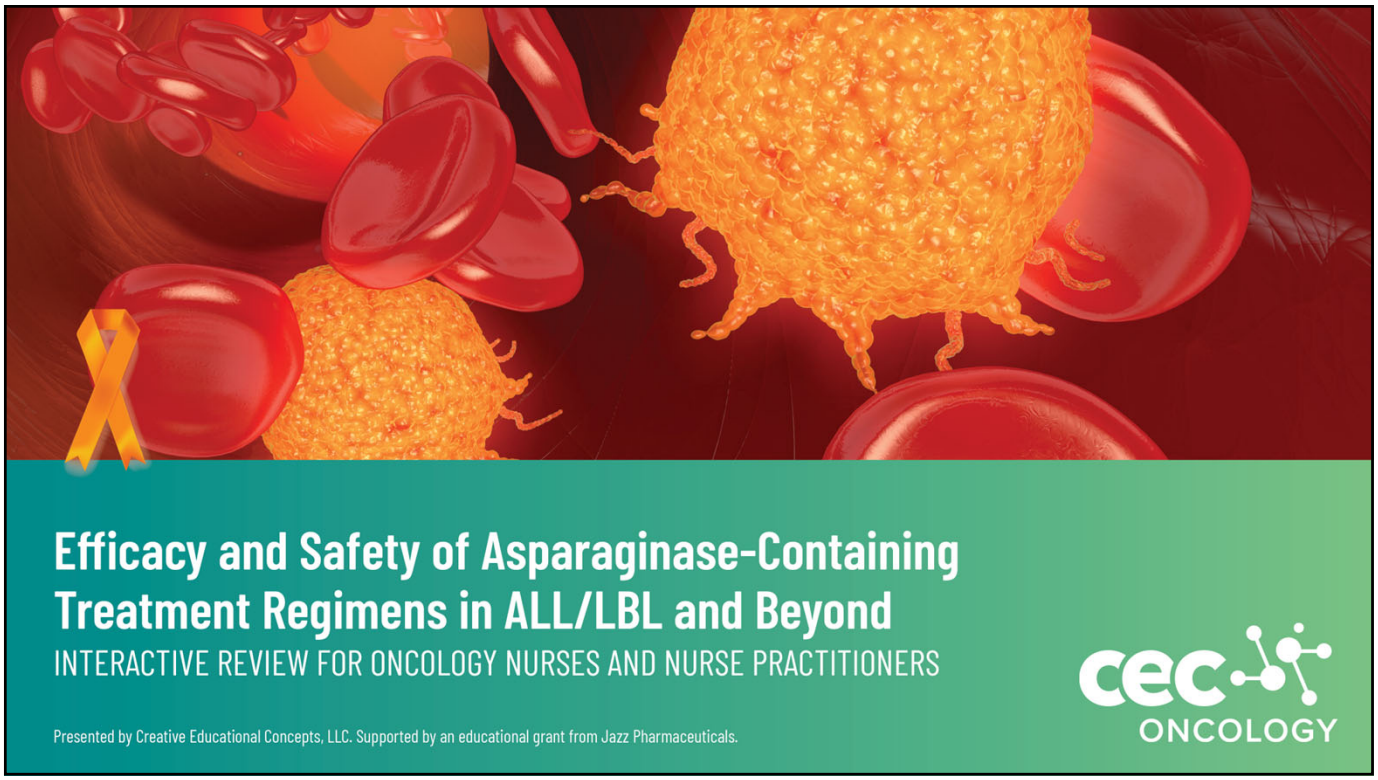
Pegaspariginase Toxicity in Adults



Aldoss I, Douer D. *Blood.* 2020.

Key Takeaways

- Asparaginase plays a critical role in pediatric-inspired multi-agent regimens used to treat ALL and LBL
- Although associated with unique toxicities, the majority are nonfatal, manageable, and reversible
- Newer formulations of asparaginase offer alternatives to continuing asparaginase treatment
- Familiarity with each formulation and consideration of prevention and management strategies is essential to optimizing therapy



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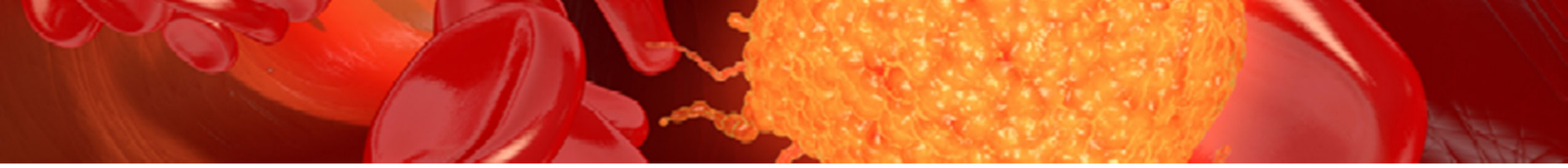

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