Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

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Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

Katelyn Oranges: Hi everyone, good evening and welcome to our presentation tonight.

Faculty

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My name is Katie Oranges and I'm joined by Joe Sciasci. We're going to talk a little bit today about asparaginase hypersensitivity and silent inactivation.

Faculty Disclosures

- **Katelyn Oranges**, faculty for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.
- **Dr. Joseph Sciasci**, faculty for this educational activity, has no relevant financial relationship(s) with ineligible companies to disclose.

To start, we have no disclosures for today.

Asparaginase Therapy in Pediatric Cancers: An Overview

Now I'll hand it over to Joe, who's going to start to give us an overview about asparaginase therapy and treating pediatric cancers.

The History of Asparaginase

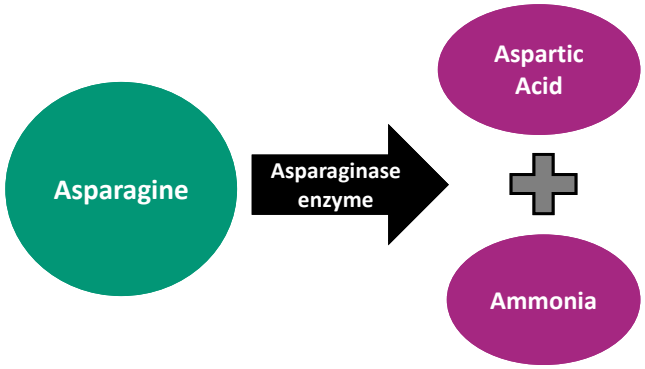
- Asparaginase was first identified as an anti-cancer agent in 1961
  - Identified as an anti-lymphoma agent in guinea pig serum
- Lymphoblastic leukemia cells are not able to appropriately synthesize asparagine, an amino acid required for protein production and cell replication
  - Leukemia cells depend on extracellular asparagine
  - When extracellular asparagine is not available, leukemia cells will not grow
- In modern times, asparaginase is typically derived from bacterial sources including *Escherichia coli* and *Erwinia chrysanthemi*

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

Joseph Sciasci: Thanks, Katie. To start going through the background of asparaginase therapy and why it's used so commonly in some pediatric leukemias. The history of asparaginase. It was first identified as an anti-cancer agent back in the 1960s. It was identified really in guinea pig serum and as an anti-lymphoma agent that existed in guinea pig serum. Lymphoblastic leukemia cells we know are not able to appropriately synthesize asparagine, which is an amino acid that's required for protein production and cell replication in all healthy cells, specifically in leukemia cells. These leukemia cells depend on that extracellular asparagine because they can't make it themselves. When extracellular asparagine is not available to the leukemia cells, leukemia cells cannot grow and will typically wither and die. In modern times, asparaginase that we will use is typically derived from bacterial sources, so including *E. coli* and *Erwinia chrysanthemi*.

Asparaginase Mechanism of Action

- Asparaginase is an enzyme that breaks apart asparagine into aspartic acid and ammonia
  - Asparagine is a vital amino acid that is required for protein synthesis in many types of cells
  - Reduced availability of asparagine leads to inhibition of leukemia cell growth



Talking about the specific mechanism of how asparaginase really works in leukemia is that asparaginase itself is an enzyme that breaks apart asparagine, that essential amino acid, into aspartic acid and ammonia. Asparagine, as I mentioned, is a vital amino acid that's really required for protein synthesis in multiple types of cells, but reduced availability of asparagine leads to inhibition of leukemia cell very specifically. And asparagine, when it's exposed to asparaginase, is going to be broken apart into aspartic acid and ammonia. Neither of those can be utilized by those leukemia cells.

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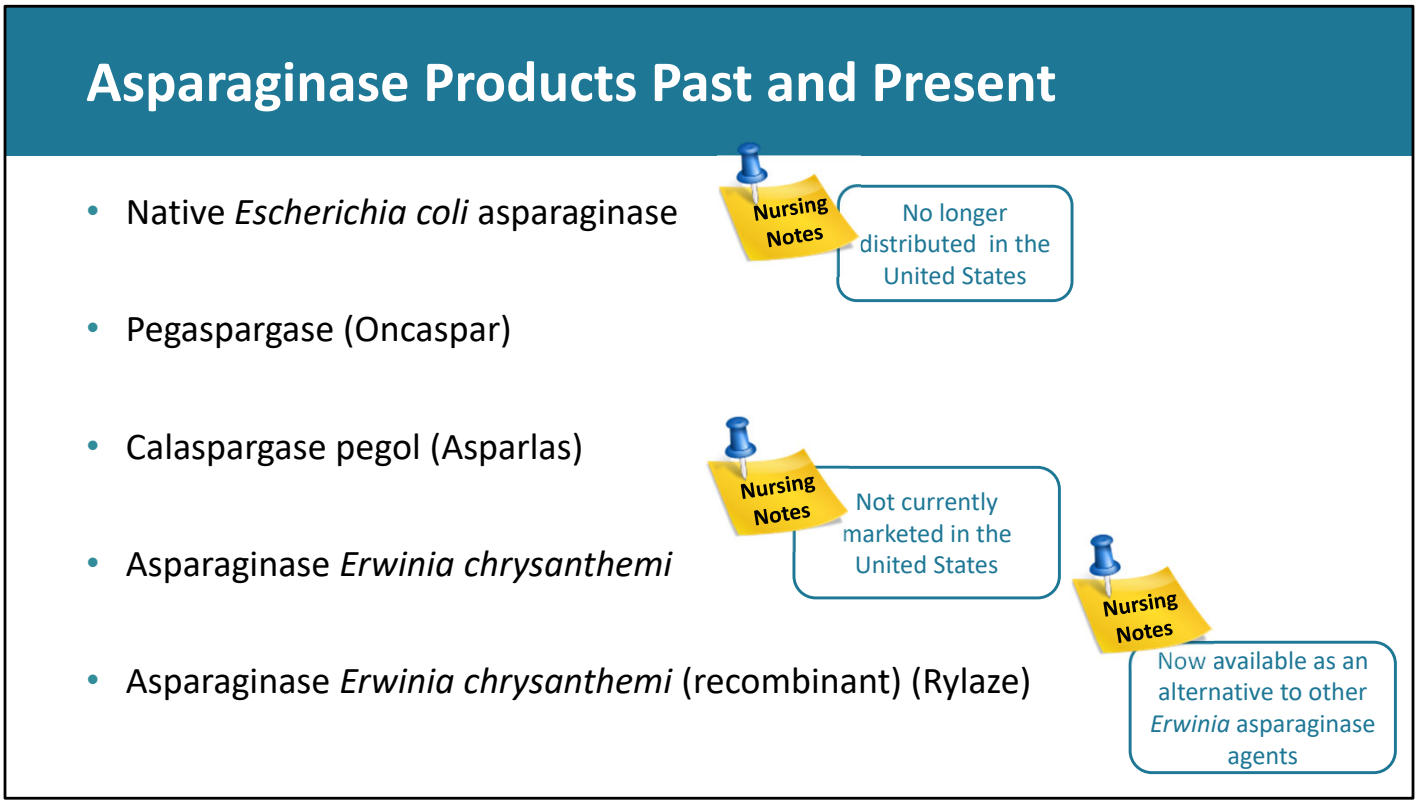

Looking at some asparaginase products that are available in the past and currently available, so native *E. coli* asparaginase is no longer distributed in the United States, it's not really used as often any longer. It's mostly replaced by pegaspargase or Oncaspar, which is a little bit longer-acting asparaginase formulation that we'll talk about. Calaspargase pegol or Asparlas, which is also a longer acting asparaginase product. Asparaginase *Erwinia chrysanthemi*, which is also not currently marketed in the United States. It was mostly replaced by asparaginase *Erwinia chrysanthemi* recombinant or Rylaze, which is now available on the US market recently as an alternative to asparaginase *Erwinia chrysanthemi*.

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Formulations of Asparaginase

Native *Escherichia coli* asparaginase	Pegylated asparaginase Calaspargase pegol-mknl (Asparlas)	Pegylated asparaginase Pegaspargase (Oncaspar)
• **No longer distributed in the United States**; but is available in some locations around the world • Administered as an intramuscular (IM) injection • Short half-life	• Dosage and Administration Schedule – The recommended dose is 2,500 units/m^2 given **intravenously** no more frequently than every 21 days	• Administration Schedule – The recommended dose of is 2,500 IU/m^2 **intramuscularly or intravenously** – Should be administered no more frequently than every 14 days

- Typically given as an intravenous infusion over 1-2 hours
- One infusion provides 2-3 weeks of asparagine depletion
- Addition of polyethylene glycol molecules extends the half-life by reducing clearance through the kidneys
- Typically used as first-line treatment option; ***calaspargase pegol-mknl is only approved for patients <22 years of age***

The treatment of ALL includes long-term use of multiagent chemotherapy, of which asparaginase is a cornerstone component

Heo YA, et al. *Drugs*. 2019;79(7):767-777.; NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia V.2.2021. ©National Comprehensive Cancer Network, Inc. 2020. To view the most recent and complete version of the guideline, go online to NCCN.org.; Lexicomp Online,® Pegaspargase, Hudson, Ohio: Lexi-Comp, Inc.; Sept 1, 2021.; Lexicomp Online,® Calaspargase Pegol, Hudson, Ohio: Lexi-Comp, Inc.; Sept 1, 2021.

Looking a little more closely at these formulations of asparaginase, as I mentioned native *E. coli* asparaginase is not really distributed or not really used in the United States any longer, but it's still available in some locations around the world. Typically, when it was used it was administered as an intramuscular injection and has a really short half-life, so patients do require multiple injections to get the efficacy we would like. Pegylated formulations have replaced the native *E.coli* asparaginase, so pegylated asparaginase or calaspargase pegol is typically given at a dose of 2,500 units per meter squared. It's given IV and no more frequent than every 21 days, so again, a longer-acting formulation of that asparaginase product because it is pegylated. The pegylated asparaginase or pegaspargase, also called Oncospar, is recommended at a dose of 2,500 international units per meter squared IM or IV, and is typically not administered any more frequently than every 14 days. Typically, when it's given as an IV infusion these medications are given over one to two hours. One infusion does provide two to three weeks of asparagine depletion, so again these patients don't typically need multiple injections for that portion of therapy.

These agents became more long-acting because of addition of polyethylene glycol molecules to the product which extends the half-life though reducing clearance of the products through the kidneys. Typically, they're used as first-line treatment options. I would like to note that calaspargase is only approved for patients less than 22 years of age and the treatment of ALL includes long-term use of multiple agents of which asparaginase is a cornerstone or part of that therapy.

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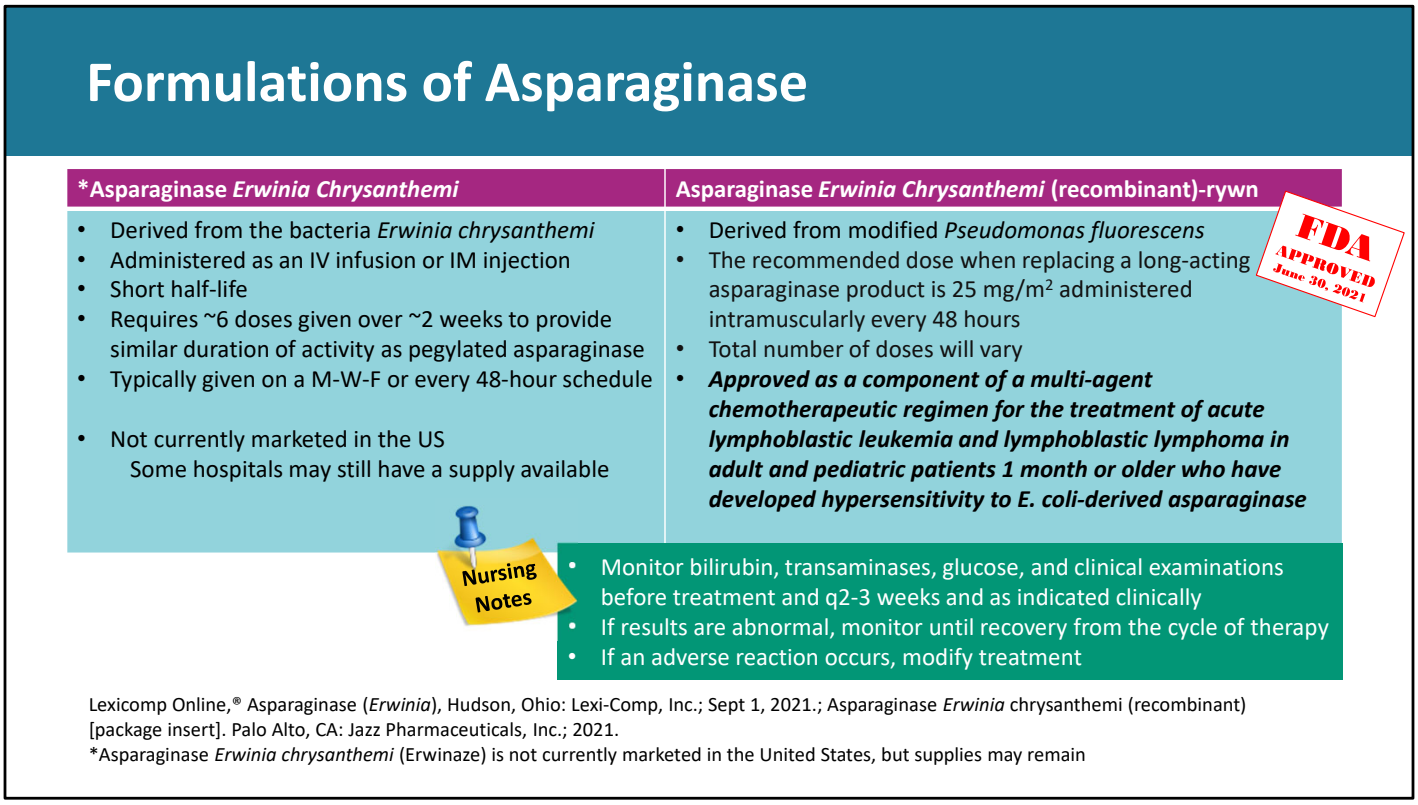

The other two agents we'd like to talk about tonight, asparaginase *Erwinia chrysanthemi*, which was derived from bacteria *Erwinia chrysanthemi* when it was used. Again, it's no longer currently available in the United States, it was given as either an IV infusion or an IM injection, but also has a shorter half-life because it's not pegylated. Typically, these patients will require about six doses given over two weeks to provide a similar duration of activity for a pegylated asparaginase product. Typically, it's given either on a Monday-Wednesday-Friday schedule or an every-48 hours schedule.

Asparaginase *Erwinia chrysanthemi* recombinant or Rylaze was derived from a modified pseudomonas bacteria. Recommended dose when this is used to replace a long-acting asparaginase product is 25 milligrams per meter squared, IM every 48 hours.

Total number of doses for this product is going to vary depending on what type of long-acting asparaginase product you're replacing, but again it's approved as a component of multi-agent chemotherapy for the treatment of ALL, an acute lymphoblastic lymphoma in both adults and pediatric patients one month or older who have developed a hypersensitivity to an *E. coli* derived asparaginase product. This was approved by the FDA back in the summer.

Just to note for both products, it is important to monitor bilirubin, transaminases, glucose, and of course exams before giving any of the doses and then at every two-to-three weeks or as clinically indicated part of the protocol. If any results are abnormal, patients are to be monitored during recovery in that cycle of chemotherapy, and if any adverse reactions do occur, therapy is typically modified.

Asparaginase *Erwinia Chrysanthemi* (Recombinant) Data

- Open-label, multicenter, dose confirmation, and PK study
- 102 patients (1-24 years old; median 10 years old)
- 93% patients with nadir serum asparaginase activity (NSAA) >0.1 IU/mL
- Serum asparaginase activity (SAA) is a surrogate marker for asparagine depletion
  - Higher levels of asparaginase activity = lower amount of available asparagine

Asparaginase *Erwinia chrysanthemi* (recombinant) [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2021.

Talking a little bit more about the newer product asparaginase *Erwinia chrysanthemi*, looking at one specific study that was done, it was an open-label multi-centered drug confirmation and PK study. Looking at the use of this agent in 102 patients between 1 and 24 years of age, the median patient age was 10 years of age. It makes sense when you think about the patient population with ALL. Ninety-three percent of patients had a nadir serum asparaginase activity or an SAA greater than 0.1.This serum asparaginase activity is used as a surrogate marker for asparagine depletion.

Going back to thinking about how asparaginase works. Higher levels of asparaginase activity will result in lower amounts of available asparagine, so leukemia cells can't find that asparagine outside their cells and therefore they can't grow.

Asparaginase Toxicities

- Common toxicities include:
  - Hypertriglyceridemia
  - Liver toxicity
  - Infusion related reactions
- Severe toxicities include:
  - Anaphylaxis
  - Thrombosis or increased bleeding risk
  - Pancreatitis

- Risk of infusion reactions and anaphylaxis are slightly higher with pegylated products
- Risk of other toxicities are similar across asparaginase products
  - Some patient populations will have higher rates of toxicities based on age and race
- **The ability to rapidly identify and manage asparaginase-associated toxicity will help ensure patients receive the maximal benefit from therapy**

Talking a little bit about common asparaginase toxicities, hypertriglyceridemia, liver toxicity is noted, and then infusion-related reactions, specifically with the pegylated products is a little bit more common than with the other products. Then severe toxicities include anaphylaxis, thrombosis, or an increased bleeding risk, and pancreatitis.

As I mentioned, the risk of infusion reactions, anaphylaxis is a little bit higher with the pegylated products due to the possible reaction to the pegylation itself, but the other toxicities are similar across all of your asparaginase products. However, some patient populations may have higher rates of toxicities based on their age and race, and so some providers across the country may see different rates of things like liver toxicity and other things like pancreatitis. The ability to rapidly identify and manage asparaginase associated toxicities helps to ensure patients receive the maximum benefit from therapy. It's really important to watch these patients and ensure that they can continue on these products and making sure that they're safely doing it.

Asparaginase Hypersensitivity and Silent Inactivation

Katelyn Oranges: Now that Joe has given us a background on how asparaginase works and the different ways we can give it, the next step is to understand what hypersensitivity and silent inactivation are and what it means for our patients.

Pathophysiology of Hypersensitivity/Inactivation

- Incidence: up to 30%
- Premedication may reduce the risk of grade 1/2 hypersensitivity reactions
- In the past, routine premedication was avoided due to concern for masking hypersensitivity reactions
  - With availability of therapeutic drug monitoring for asparaginase products, premedication is becoming a more common practice

Cooper SL, et al. *Pediatr Blood Cancer*. 2019;66:e27797.; Marini BL, et al. *Leuk Lymphoma*. 2019;60(12):2854-2868.; Swanson HD, et al. *Blood*. 2020;135(1):71-75.

We know that up to 30% of patients who receive asparaginase can either experience a hypersensitivity or a silent inactivation. It's clinically important to know that premedications could reduce the risk of mild allergic reactions. Historically, premedications were avoided in concern that we would be masking allergies.

However, now that we have therapeutic drug monitoring, we're able to make sure and confirm that patients do have true allergies, and if we are premedicating and masking any mild reaction we're able to confirm that they are truly allergic.

Why Does it Matter?

- Asparaginase is considered a cornerstone of ALL therapy
  - Is included in every pediatric ALL/Lly protocol
  - Is included in many adult ALL protocols as well
- The inability to receive asparaginase has prognostic implications for patients with ALL
  - This has been associated with significantly worse outcomes

Silverman LB, et al. *Blood.* 2001;97:1211-1218.; Gupta S, et al. *J Clin Oncol*. 2019;37[suppl]:Abstract 10005.

Like Joe said, it matters that we have these patients who are allergic or have silent inactivation to asparaginase because it's a cornerstone of acute lymphoblastic leukemia and lymphoma therapy. It's an important part of every pediatric protocol and is included in many adult ALL protocols as well. We know from the literature that the inability to get all of your planned doses of asparaginase actually has prognostic implications for patients with ALL, meaning that patients who don't get all of their asparaginase have significantly worse outcomes than those who do.

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

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

Then the question is, what are the differences? What does it mean if you have a patient with a hypersensitivity or a patient with silent inactivation? They are both antibody-mediated responses, but in hypersensitivity reactions, you actually see clinical symptoms during the infusion. In silent inactivation, patients won't have observable symptoms during the infusion and so the only way to detect it is by monitoring therapeutic drug levels.

Clinical Hypersensitivity Reactions

- Asparaginase is a protein of bacterial origin, which can cause an immune response when given to patients
- Anti-asparaginase antibodies are produced in response to the drug exposure
- Antibodies bind to the asparaginase molecule and reduce the enzymatic activity of the drug. This may or may not lead to low levels of serum asparaginase activity
- Patients can manifest symptoms of allergies, which are graded:
  - Bronchospasm
  - Angioedema
  - Urticaria
  - Anaphylaxis
- Low-grade clinical hypersensitivity reactions can also lead to formation of anti-asparaginase antibodies

Clinical hypersensitivity reactions happen because an anti-asparaginase antibody is produced. Asparaginase, like Joe said, is a protein that comes from bacterial origin and that can cause, when it's given to a patient, for the patient to develop an immune response. That immune response causes an anti-asparaginase antibody to be produced. Then the antibody actually binds to the asparaginase molecule and reduces the activity of the drug, which means that you most likely would have a low level of asparaginase activity. The hallmark of hypersensitivity is that the patient has an outward clinical change or an outward symptom. These can be in a variety of severity forms and can be in a bunch of different things. The most common things we think about are bronchospasm, urticaria, angioedema, anaphylaxis, rashes. I think it's commonly thought that the degree of reaction you have is related to the amount of anti-asparaginase antibodies, but we know that patients who have these lower-grade clinical hypersensitivities still have formation of anti-asparaginase antibodies and have lower drug levels.

Silent Inactivation

- Antibodies are produced in response to asparaginase, but there is no clinical hypersensitivity reaction
  - Patients do not have outward symptoms of an immune-mediated response
  - Historically, these patients were not easily identified to have treatment modifications made
  - It is more common to experience clinical hypersensitivity symptoms if antibodies have formed
  - Symptoms may be masked by pre-medications
- Patients experience rapid inactivation of the asparaginase from these antibodies, which means poor asparagine depletion

If silent inactivation goes unrecognized, patients could potentially be continued on the same asparaginase formulation with no therapeutic benefit

Compared to hypersensitivity, silent inactivation still results in an antibody formation, but patients can have one of two manifestations with this.

One is that you have no outward clinical symptoms of an immune-mediated response, or these patients would have had a mild Grade 1 or Grade 2 response but we're masking it by giving premedication. Because patients don't always have outward symptoms or may have mild symptoms, these patients are really hard to identify, and so treatment modifications are sometimes not made. It's way more common to experience clinical hypersensitivity symptoms if you have antibodies. If silent inactivation goes unrecognized, patients could potentially be continued on the same form of their asparaginase with no therapeutic benefit because again, with the formation of an antibody you have a rapid inactivation of the asparaginase and you have poor asparagine depletion, meaning the leukemia cells potentially have more access to asparagine.

Risk Factors for Silent Inactivation

- Premedication with steroids may increase the risk of silent inactivation through reducing observed grade 1/grade 2 reactions
- Inconsistent dosing of asparaginase
  - Extended intervals between asparaginase doses may increase the risk of the development of neutralizing antibodies

Cooper SL, et al. *Pediatr Blood Cancer*. 2019;66:e27797.; Woo MH, et al. *J Clin Oncol*. 2000;18(7):1525-1532.

There are some risk factors for silent inactivation. Premedication, especially with steroids, could increase observed Grade 1 or Grade 2 mild reactions. There's a theory that inconsistent dosing of asparagine, so increased intervals between doses, could increase your risk for the development of neutralizing antibodies, meaning that the antibodies actually have time to develop because of those extended breaks in between.

Grading Hypersensitivity Reactions: Immune System Disorders

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; IV intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen. **Navigational Note:** If related to infusion, use injury, poisoning and procedural complications: Infusion related reaction. Do not report both.					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anaphylaxis	_	_	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					

US Dept. of Health and Human Services. NIH. NCI. CTCAE. V 5.0. 2017.
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

I've alluded to this Grade 1/Grade 2 are mild reactions, but what does that mean? The CTCAE is a common adverse reaction chart that you can use for any type of adverse event. This chart is for immune system disorders or for allergic reactions and anaphylaxis and you can see that it goes from a Grade 1, which is very mild, meaning no intervention is indicated, all the way to a Grade 5 which is very severe and death. Typically, we think of a Grade 1 or Grade 2 as a more mild reaction, and then a Grade 3/Grade 4 would be a more severe reaction.

Defining Reactions: Grading Scale Example

Modified Pegasparaginase Reaction Grading Scale Modified from Common Terminology Criteria for Adverse Events (CTCAE) V5.0 Consider use of below definitions when classifying pegasparaginase infusion reactions	
Grade 1	– Transient flushing or rash during the infusion that resolves without intervention – Fever <38.4°C
Grade 2	– Persistent symptoms that require interruption of infusion – Flushing – Rash with urticaria – Dyspnea – Fever ≥38.5°C
Grade 3	– Persistent symptoms that require discontinuation of infusion – Cough, shortness of breath, bronchospasm, or other significant respiratory symptoms – Edema or angioedema – Hypotension
Grade 4	– Life-threatening reaction necessitating urgent intervention
Grade 5	– Death

This is just an example of a modified grading scale that was made specifically for pegasparaginase reactions based off the CTCAE but just putting it in some of the more common things that people expect to see with a pegasparaginase reaction. Again, going from Grade 1 which is very mild, doesn't need intervention, all the way to a Grade 4 which would require urgent intervention.

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 pegasparaginase hypersensitivity – Hyperammonemia from asparaginase metabolism can cause anxiety, malaise, weakness, nausea, vomiting, and abdominal cramping

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

The other thing that we have to think about when a patient has an allergic-like response during an asparaginase infusion, is it or is it not a true allergy?

In immune-mediated responses, so those like hypersensitivity or silent inactivation, the antibodies are actually being formed in response to the drug exposure. For an immune-mediated response, you typically see these allergic manifestations happen within a few minutes of starting the infusion, and it can range again from those very mild flushing, rashes, to nausea, vomiting, bronchospasm, hypotension and even respiratory distress. In non-immune mediated reactions, you have very similar symptoms, but the reaction is either due to the actual infusion or from a transient hyperammonemia from asparaginase metabolism. It's really challenging to tell the difference because they present very similarly, and so without therapeutic drug monitoring, there's no way to tell whether or not the patient is truly having an allergic reaction or just a non-immune mediated reaction.

Pre-medications

- Pre-medications are administered to minimize risk for non-inactivating reactions to pegasparaginase
- Pre-medication is not seen to have affect on pegasparaginase activity

- Common pre-medications:
  - Diphenhydramine
  - Acetaminophen
  - Methylprednisolone or hydrocortisone
  - Famotidine

Losasso M, et al. *F1000Res*. 2019;8:1007.

With the idea that there are patients who could have just an infusion reaction or a non-immune mediated reaction, knowing that pegasparaginase and asparaginase products are so important to chemotherapy regimens, premedications have become more widely used as a way to minimize risk for patients having non-inactivated reactions to pegasparaginase. We know that giving these premedications does not have an effect on the actual activity of the drug. Commonly you may see drugs like diphenhydramine, acetaminophen, steroids like methylprednisolone or hydrocortisone and famotidine given to patients.

Grading Infusion Reactions

Injury, poisoning, and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reactions to the infusion of pharmacological or biological substances					

Again, just because infusion reactions are non-immune mediated reactions are so similar to those immune-mediated responses, this is just the CTCAE guidelines on what an infusion-related reaction looks like. Again, you can see that they are almost identical. Grade 1 being very mild, meaning you don't need to do anything, all the way to a Grade 4 which is life-threatening or a Grade 5 which is death.

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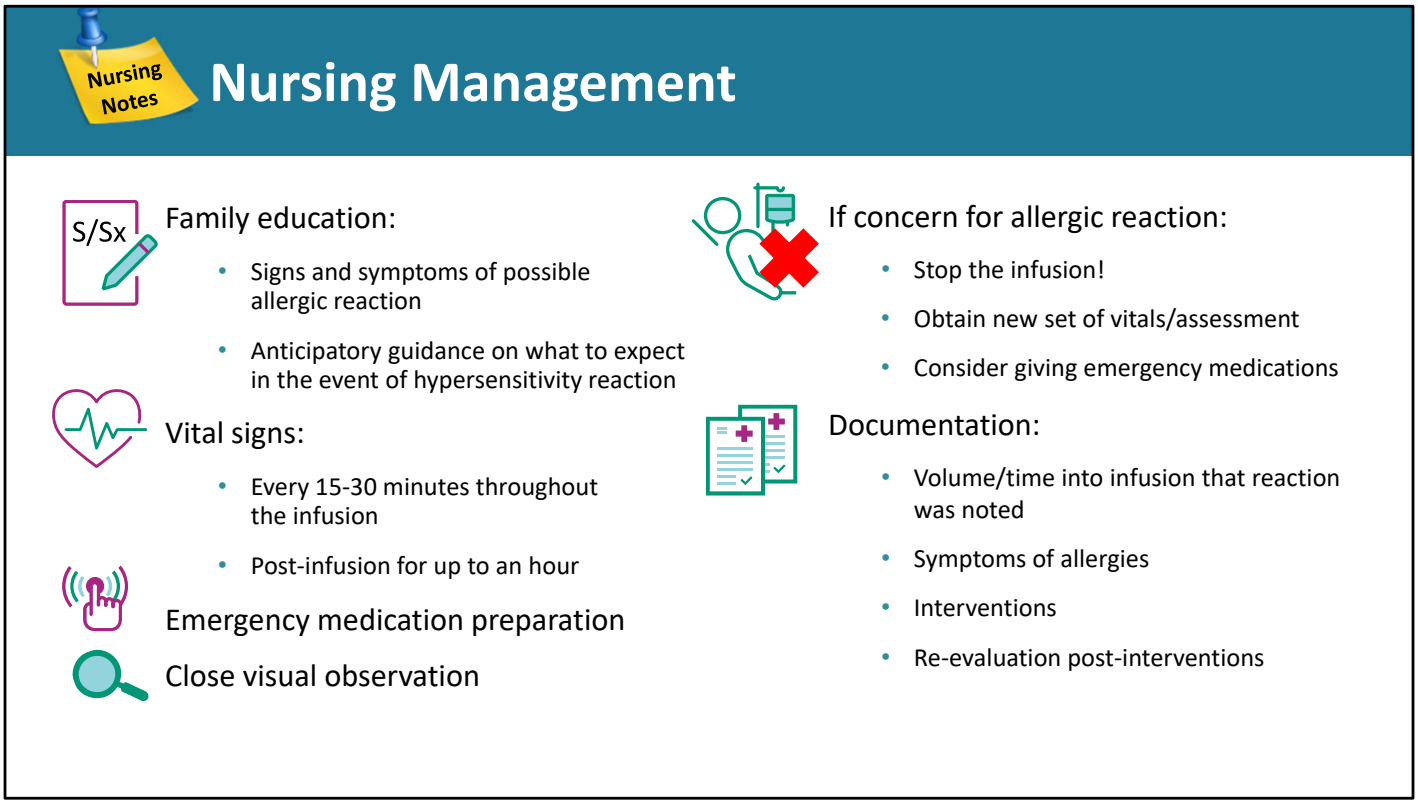

Nursing-wise, the management is going to be the same whether you have an infusion or a non-immune mediated response or a hypersensitivity. Going into the infusion, educating families on what the signs and symptoms of possible allergies may be and providing anticipatory guidance on what to expect in the event that their child were to have an allergic response. You're monitoring the patient, their vitals and their assessment. It may vary between institutions but typically we expect vital signs every 15 to 30 minutes throughout the infusion and then even post infusion up to an hour.

You're watching the patients to see are their skin colors changing? Are they having changes in breathing? Are they having changes in their nausea/vomiting and their mental status? And having emergency medications prepared and readily available in case you need them. If there is concern for an allergic reaction, the most important thing is to first stop the infusion and then get a new set of vitals and an assessment of the patient. Then simultaneously you'll be considering giving emergency medications.

After all of this, then it's time to think about documenting, and so things that are important to make sure that you're documenting include how much of the drug or how long into the infusion the patient was before the reaction was noted, what their symptoms were, what the interventions were, and any reevaluation done post the interventions.

Emergency Medication Management

- IV diphenhydramine (1 mg/kg/dose, max dose of 50 mg)
- IV methylprednisolone (2 mg/kg)
- IM epinephrine
- IV famotidine (0.5 mg/kg/dose, max dose of 20 mg)

Please check with your institutional protocols as dosages for each medication may vary depending on standard of care protocols across institutions

Emergency medication-wise, you may see some variation between hospitals, but common drugs that you will see given include IV diphenhydramine, IV methylprednisolone, IM epinephrine, or IV famotidine.

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Asparaginase Systemic Allergic Reactions/Anaphylaxis

- For severe allergic reaction
  - Discontinue pegylated asparaginase formulations and substitute with an asparaginase *Erwinia*-based formulation. Asparaginase *Erwinia*-based therapy should begin within 72 hours of the reaction or earlier if possible
- For mild-moderate reversible reaction
  - If the infusion (given by IM route or IV administration) was completed, consider sending an asparaginase activity level. Note that an asparaginase level of at least 0.1 IU/mL, 14 days after administration is considered therapeutic. There are several reports that suggest different thresholds for switching to asparaginase *Erwinia*-based formulation. The following guideline can be considered, but decisions are ultimately up to the treating clinician
  - If the infusion was discontinued early, consider re-challenging with pegaspargase after premedication and send asparaginase levels as above

Timepoint after completion of pegaspargase infusion	Asparaginase activity level	Action
1 hour-1 day**	<0.5 IU/mL	Substitute with asparaginase *Erwinia*-based formulation
7 days	<0.3 IU/mL	Substitute with asparaginase *Erwinia*-based formulation
14 days	<0.1 IU/mL	Substitute with asparaginase *Erwinia*-based formulation

**Note that waiting at least 18 hours to check asparaginase levels after IM administration is optimal but not required. Children's Oncology Group.

Because we know asparaginase is so important in treating children with leukemia and lymphoma, we also have wording built into protocols and standards of care as to what to do in cases of severe allergic reactions, or mild to moderate reactions that are reversible. Considering sending levels to look at asparaginase activity, or should we be switching the formulation that we're giving to the patient? These are all things that go into, based off of the documentation, the reactions of the patients, their responses to medicines, what the clinicians will do to make the next decisions for the patients.

Case Study

Instructions on Interactive Replies

With that, we're going to get into our first case study.

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Meet James

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

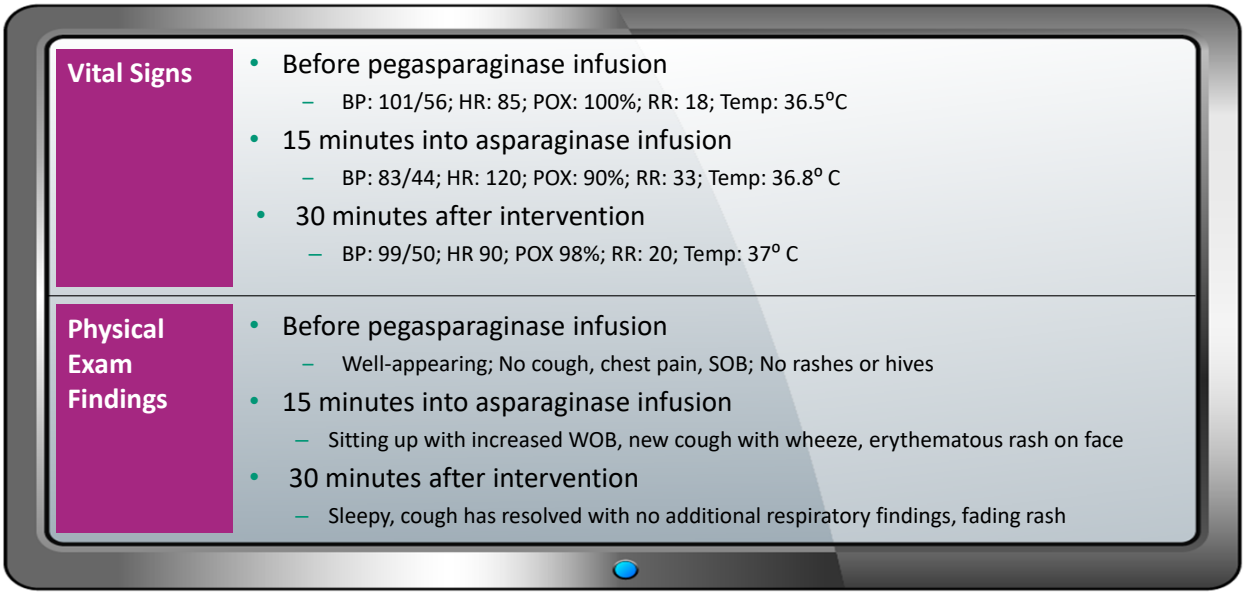
James

Patient Notes	• 5-year-old male • Diagnosed with T-cell lymphoblastic leukemia • No reported drug allergies • Has tolerated all of his chemotherapy thus far without complications
Current Visit	• He is day 2 of his interim maintenance chemotherapy • In clinic today for pegasparaginase infusion; received methotrexate and vincristine yesterday

We're going to meet James, who is a five-5-old with T-cell lymphoblastic leukemia with no reported drug allergies, and he has done really great with his chemotherapy thus far. He is coming to clinic today for day 2 of his interim maintenance chemotherapy, which means he's due for his next dose of pegasparaginase. He received his methotrexate and vincristine yesterday and did just fine with it.

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

James' Clinic Day



Before the asparaginase infusion was started, James had vital signs that seemed at his baseline. He was well-appearing. He didn't have any cough, chest pain, shortness of breath, rashes, or hives, but 15 minutes into the infusion, he was noted to have a decrease in his pulse ox with an increase in his respiratory rate. His heart rate increased. His blood pressure went down. He was sitting up with just noticeable increased work of breathing, a new cough with wheeze, and had an erythematous rash on his face.

The infusion was stopped, and James received some emergency medications. He got famotidine, Benadryl, and methylpred. Thirty minutes after the interventions were done, he was sleepy, but his cough had resolved and he had no new respiratory findings, and the rash on his face was fading. His vital signs returned back more towards his baseline.

Question

Based on the vital signs and reported physical exam findings, are you concerned that James is having allergic reaction to his pegasparaginase?

A. Yes

B. No

C. I'm not sure

Please select your response below the video window and click the submit button to poll.

The question is, based on these vital signs and the reported physical exam findings, are you concerned that James is having an allergic reaction to his pegasparaginase?

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

Nursing Notes

Yes

James is having clinical symptoms of an allergic reaction.

Yes, James is having clinical symptoms of an allergic reaction. Based on the CTCAE grading, I would probably put that at a Grade 3 to a Grade 4, because he required IV medications, but didn't have severe respiratory instability that required epinephrine, or further respiratory support.

Question

Based on James' case, is there a way to help evaluate if he has a true allergy to pegasparaginase or if his reaction was infusion related?

A. Yes

B. No

C. I'm not sure

Please select your response below the video window and click the submit button to poll.

Then based on this, is there a way to help evaluate if James truly has an allergy to pegasparaginase, or if his reaction was just an infusion-related response?

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

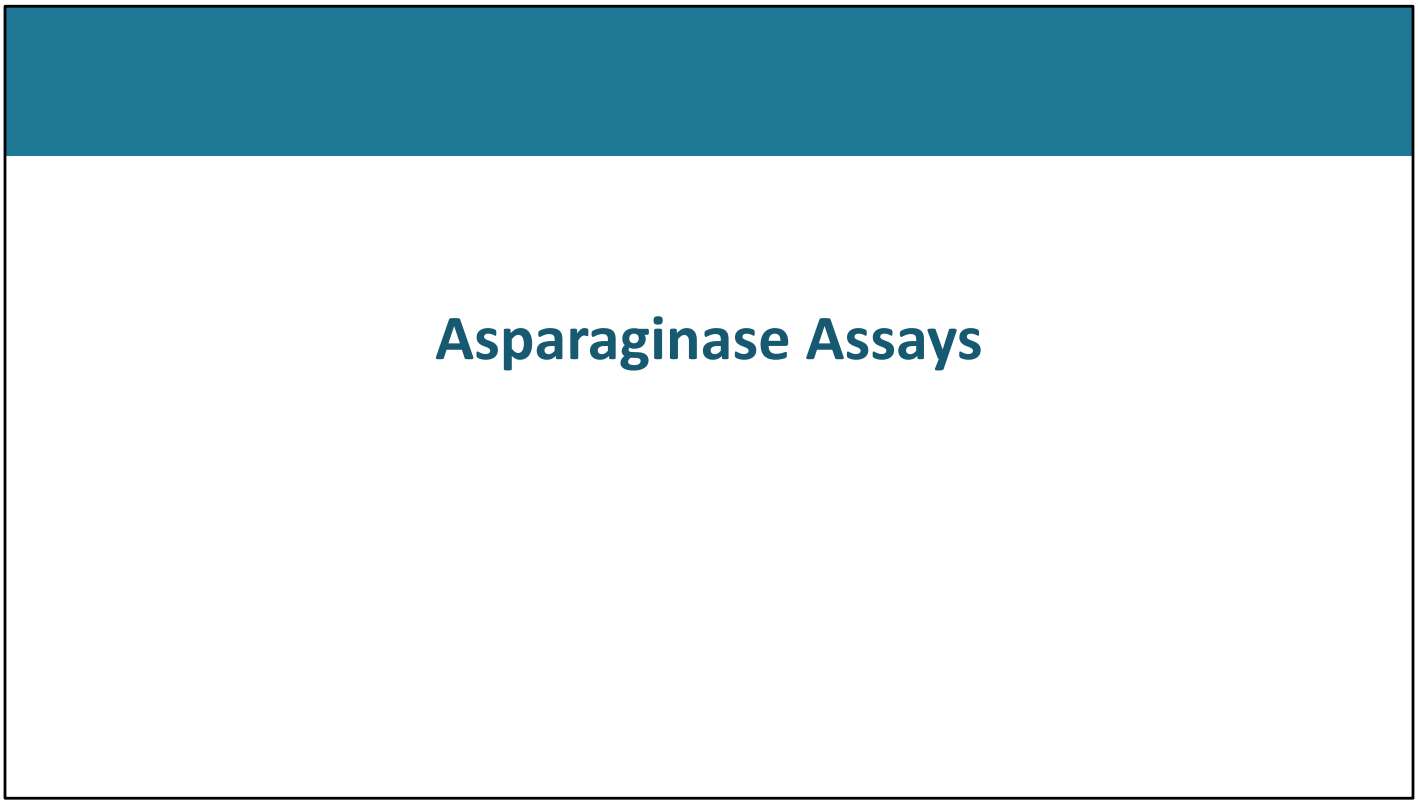
Nursing Notes

Yes

Asparaginase activity testing can help to differentiate between a true drug allergy and an infusion reaction.

James should have an asparaginase activity assay sent, assuming he received over 10% of his planned dose.

The answer is yes. We know that we can use asparaginase activity testing to help differentiate if he had a true drug allergy, or an immune-mediated response, or if he had a non-immune-mediated response or infusion reaction. We would recommend that James should have an asparaginase activity assay sent, assuming that he was able to get over 10% of his planned dose.



With that, that'll bring us back into, what are these assays, what do they mean, and how do we interpret them?

Asparaginase Assays

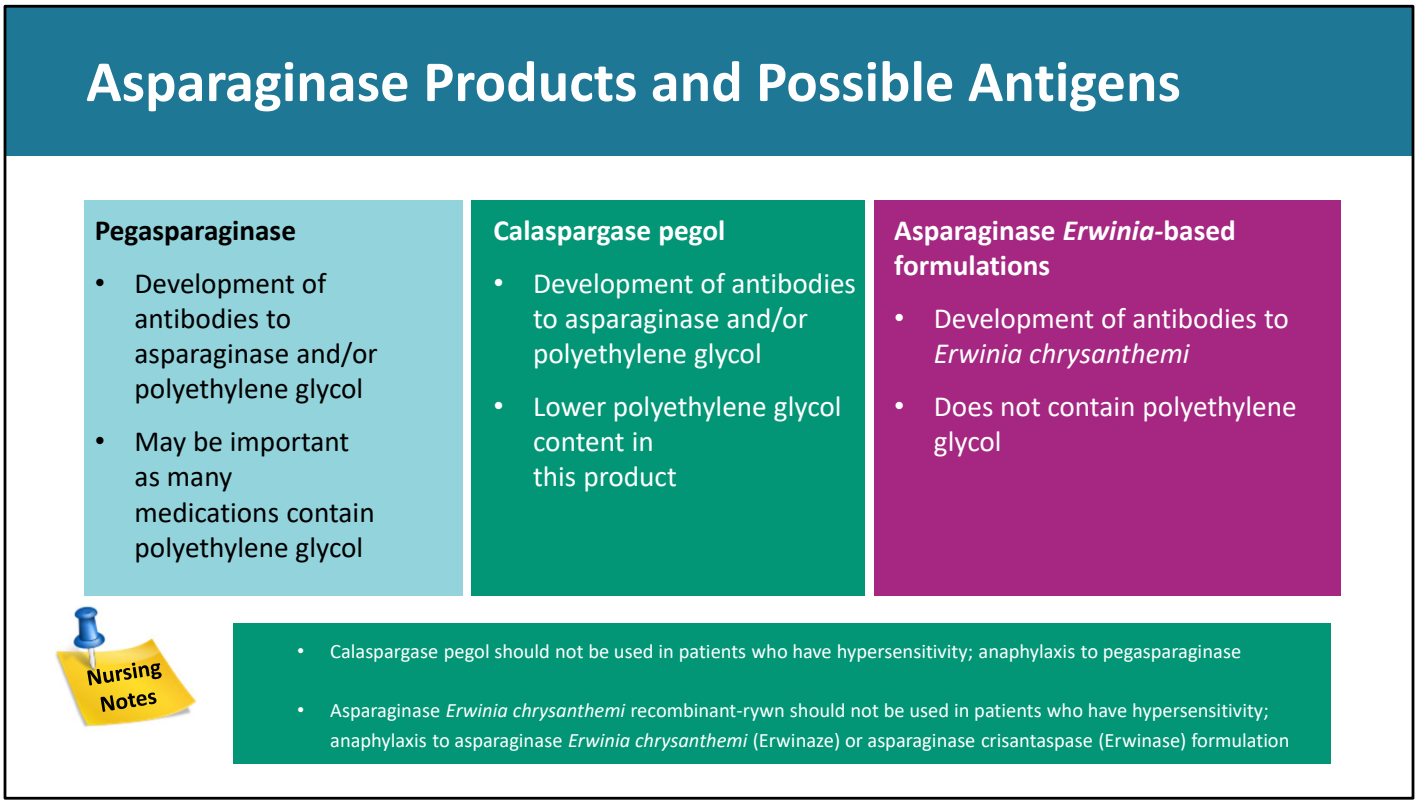
Two Common Assays Are Readily Available	
Asparaginase activity	**Asparaginase antibodies**
• Measures serum asparaginase activity – regardless of type of asparaginase given • Higher levels of serum asparaginase activity = lower available asparagine	• Identifies antibodies to asparaginase that may have developed • Antibodies may inactivate asparaginase products • Only commercially available test evaluates *E. coli* derived asparaginase

Joseph Sciasci: Talking a little bit about the asparaginase assays that can be used, two common assays are readily available. There's an asparaginase activity assay that measures serum asparaginase activity, regardless of the type of asparaginase that's given. Again, going back to higher levels of serum asparaginase activity means there's lower available amounts of asparagine available for those leukemia cells to take up and use.

There's also an assay that looks at asparaginase antibodies. That identifies antibodies to asparaginase that may have developed. Again, those patients who are developing that antibody reaction that then reduces the amount of asparaginase that's available and produce antibodies that inactivate that asparaginase.

The commercial products that are currently used, really only looks at *E. coli*-derived asparaginase products. That's really what they're tested against at this time.

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation



Thinking about what asparaginase products are and the possible antigens. Thinking about, what are patients reacting to if they are developing a true hypersensitivity to one of your products? With pegasparaginase, patients can develop antibodies due to the asparaginase, or the polyethylene glycol. We know that polyethylene glycol is involved in other medications as well, both IV medications, and even some oral medications and food products as a stabilizer. It might be important to think about, does that patient already have exposure to polyethylene glycol and that's why they're reacting.

Calaspargase pegol, patients can develop antibodies to asparaginase or the polyethylene glycol, but I do want to mention that this product does have a lower amount of polyethylene glycol used in the product. Patients may have a lower rate of reactions with this product. Asparaginase

Erwinia-based formulations do not contain any polyethylene glycol. Patients are reacting to the polyethylene glycol, it's unlikely that they'll react to the asparaginase *Erwinia*-based formulations.

Patients can develop antibodies to *Erwinia chrysanthemi*. Talking about the differences in when patients should be rechallenged. If patients develop a hypersensitivity to pegasparaginase, they should not be rechallenged with calaspargase pegol. Again, going back to the idea that they may be reacting to the polyethylene glycol content. In asparaginase *Erwinia chrysanthemi*, recombinant should not be used in patients who have a hypersensitivity or anaphylaxis to other asparaginase Erwinia products or formulations. Either *Erwinia chrysanthemi* Erwinaze, or crisantaspase formulations that may have been used in the past.

When to Draw Activity or Antibodies

- If no concern for hypersensitivity reaction
  - Consider obtaining serum asparaginase activity when premedication is used
- If patients develop infusion-related reaction concerning for hypersensitivity
  - Obtain serum asparaginase activity after infusion stops and once patient is clinically stable
  - Repeat asparaginase activity samples should be sent 3-7 days after dose, and again immediately prior to next dose
- Anti-asparaginase antibody sample may also be sent in patients with concern for hypersensitivity reactions

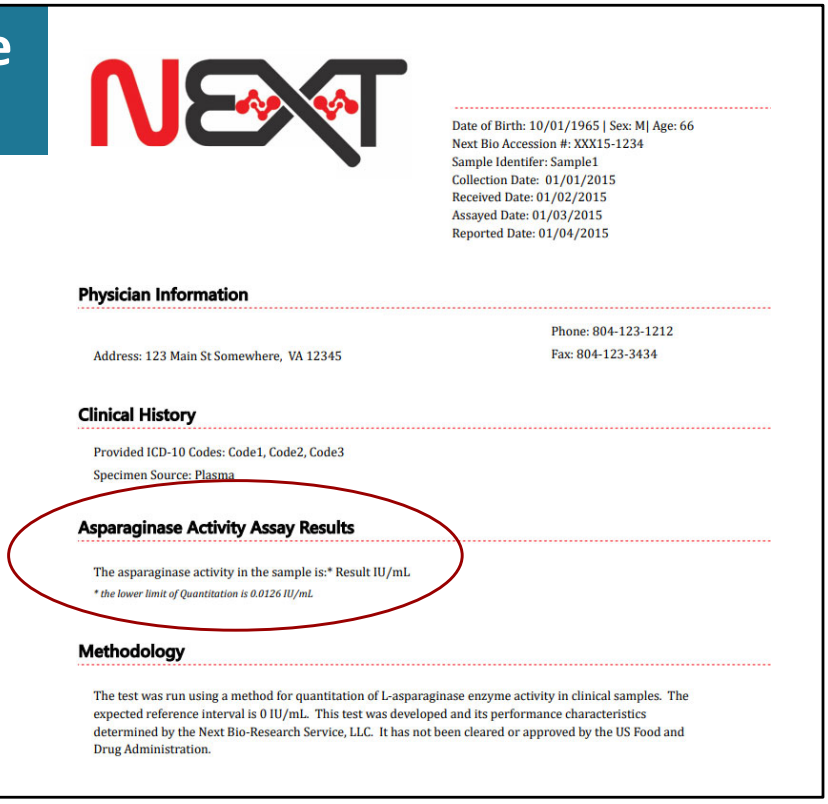
Thinking about when you should draw these activity or antibody levels in patients, obviously, patients don't have a concern for hypersensitivity reaction if they tolerated the infusion. Some centers may still consider obtaining serum asparaginase activity levels when those patients receive premedication before they receive their asparaginase product. It goes back to the concern that if you premedicate these patients, you may mask some of those Grade 1/ Grade 2 low-level symptoms the patients would have maybe presented with before, and mask that reaction.

Thinking about ensuring that patients are still responding and getting appropriate activity levels you want, even if they don't have a concern for hypersensitivity reaction when you premedicate. Obviously, if patients develop an infusion-related reaction that's concerning for hypersensitivity, most centers will obtain serum asparaginase activity levels after the infusion stops, and once patients are clinically stable. Stop the infusion, give the medications to help manage that reaction, and then go ahead and draw an activity level basically the same day they're in clinic.

Repeat asparaginase activity levels are typically sent three to seven days after that initial dose was started, and again immediately prior to the next dose. Thinking through that, if they received a long-acting asparaginase product, for example, you want to ensure that they’re having an appropriate level of asparaginase activity throughout the duration of expected therapy. Anti-asparaginase antibody samples may also be sent in some patients that have a concern for these hypersensitivity reactions. Really, again, to think about, is there a true antibody, can you identify an antibody that these patients are developing a reaction to?

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

Sample Asparaginase Activity Report



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

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.

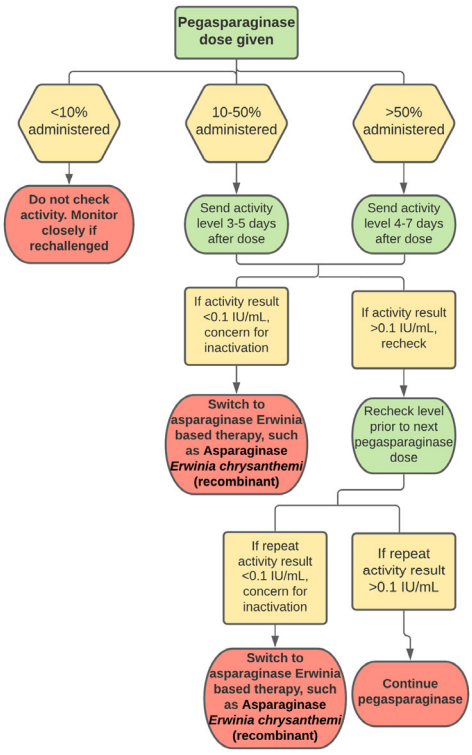
https://7d2f7043-60da-494b-a021-170e20431584.filesusr.com/ugd/9b3624_f877290dfd124afda1097faaf8daa672.pdf

This is just an example of an asparaginase activity report that is sometimes received after you send these activity levels. As you can see circled, there's an asparaginase activity assay result. This is where most centers will use this to see how much activity is around, how much benefit is that patient still deriving from that dose of asparaginase.

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

Interpreting Serum Asparaginase Activity

Click
Download Algorithm
below video to see an enlarged chart



Adapted from: Bleyer A, et al. *Pediat Blood Cancer*. 2015;62:1102-1105.

Looking at an algorithm that's sometimes used to interpret that serum asparaginase activity. It goes back to thinking about, as Katie mentioned, documentation during and right after the infusion stops is really important because we're going to look to see how much of that asparaginase dose those patients received to help interpret this level. If patients received less than 10% of their intended pegasparaginase dose, you don't typically have an activity level done because we know that those patients may just have very low activity levels because they didn't have enough exposure to the medication. If they had 10-50% of the dose administered, the activity level is typically sent after the dose and then three to five days after the dose was given. If patients received 50% of the expected administered dose, activity levels are usually sent four to seven days after that dose.

That result is going to dictate what you do in the future. If those first sets of activity results, when they're available, if they show that their activity result is less than 0.1, there's clearly a concern for inactivation. Typically, at that point, patients are switched to an asparaginase *Erwinia*-based therapy, such as asparaginase *Erwinia chrysanthemi* recombinant. If there's activity levels at first check are greater than 0.1, typically we will recheck, again, to ensure that patients are having the appropriate exposure that we expect.

That recheck level is typically done either prior to the next pegasparaginase dose, or five to seven days after that first level was sent. If at repeat activity level is less than 0.1, again, there's concern for activation. Patients are going to have more asparagine available to the leukemia cells than you'd want. We'll typically recommend switching those patients to an asparaginase *Erwinia*-based therapy such as asparaginase *Erwinia chrysanthemi* recombinant. If those repeat activity levels are greater than 0.1, however, it's telling us that these patients will probably derive expected benefit from that pegasparaginase infusion they received, even if they didn't get the full dose. Typically, those patients are continued on pegasparaginase, but they may have continued monitoring or more close monitoring with future infusions.

Interpreting Asparaginase Assays

Immune Mediated	Non-Immune Mediated
• Immune responses are characterized by the formation of anti-asparaginase antibodies • Anti-asparaginase antibodies neutralize the drug, so patients will have a lower or non-detectable asparaginase level	• Non-immune mediated responses do not result in the formation of anti-asparaginase antibodies – It is possible to experience an infusion-related reaction with a first dose • Because there are no antibodies, patients will have a normal asparaginase level

Interpreting these asparagine assays, again goes back to thinking about is this an immune-mediated or non-immune mediated reaction? Since immune-mediated responses are characterized by the formation of anti-asparaginase antibodies, we expect the anti-asparaginase antibodies neutralize the drugs. These patients are going to have lower or non-detectable asparaginase levels because those immune cells are recognizing this as something that shouldn't be there, it's helping clear it more quickly, so patients are not going to get the benefit you'd expect.

In non-immune mediated reactions, they're not going to have the development of formation of anti-asparaginase antibodies. It is still possible to experience an infusion-related reaction, even with the first dose, for example, but it's unlikely that it's immune-mediated, and therefore there are not antibodies around, patients should have normal asparaginase activity levels. Again, using the asparaginase activity level, monitoring will help to determine what you should do.

Case Study

Instructions on Interactive Replies

Katelyn Oranges: We'll go into our next case study.

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

Meet Amy

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

AMY*

Patient Notes	• 15-year-old female • Diagnosed with high-risk pre-B cell lymphoblastic leukemia • No reported drug allergies • Tolerated day 4 of induction asparaginase without issue
Current Visit	• She is day 15 of her consolidation chemotherapy • In clinic today for vincristine and pegasparaginase infusion

Amy is a 15-year-old who was diagnosed with high-risk pre B-cell lymphoblastic leukemia, and again, no reported drug allergies. Received her day four of induction pegasparaginase dose without any issues, and comes to clinic today for day 15 of her consolidation chemotherapy. She is due for vincristine and her next pegasparaginase infusion.

What would be some nursing considerations for Amy given her planned chemotherapy for the day?

Just thinking about Amy and where she is in therapy, what would be some nursing considerations for her given the planned chemotherapy for the day?

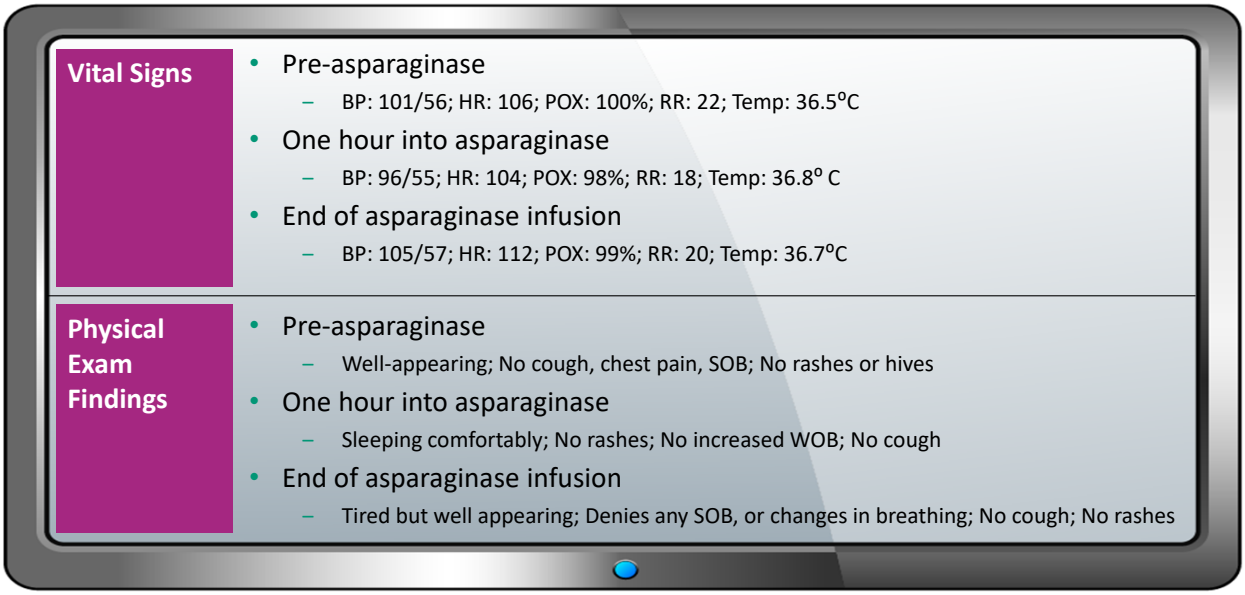
Key Considerations

- Pre-medication for asparaginase infusion
- Timing of asparaginase around potential blood products
- Emergency medication preparation
- Patient/family education
  - Signs of allergic reaction
  - Expected monitoring
  - Pre-medication regimen

Some of the key considerations would be, does Amy need pre-medications for her asparaginase infusion? If she needs blood products, do we need to think about timing the asparaginase around those blood products, either giving the blood products first or separating both by some time to make sure that it's clear if she were to react, what she was reacting to. You want to make sure that the emergency medications are prepared and nearby, and you're also going to educate Amy and her family about the day.

This is only the second time she's gotten pegasparagine. The first time she got it, she had just been diagnosed with leukemia four days before. Oftentimes, families don't really remember the pegasparaginase part of their induction and what those reactions could be, what we're monitoring, and what we're getting pre-medications for. It's really important today in clinic that Amy and her family are re-educated on what are some of the symptoms of allergic reactions, what monitoring are we going to be doing, and what pre-medications are we giving her and why.

Amy's Clinic Day



Amy's pre-asparaginase looks great. She doesn't have any cough, chest pain, shortness of breath. Her skin exam is normal, and her vital signs look pretty good.

One hour into her two-hour infusion, her vitals are stable, and she's sleeping comfortably after her Benadryl premedication. She doesn't have any rashes, no increased work of breathing, and no cough. At the end of her infusion, her vitals are again pretty stable. She's tired, but well appearing, is not complaining of any shortness of breath or changes in her breathing, she doesn't have a cough, and she doesn't have any rashes.

Question

Based on the vital signs and reported physical exam findings, are you concerned that Amy has had an allergic reaction to her pegasparaginase?

A. Yes

B. No

C. I'm not sure

Please select your response below the video window and click the submit button to poll.

Based on those vital signs and the exam findings, are you concerned that Amy has had an allergic reaction to her pegasparaginase?

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

Nursing Notes

No

Amy had no outward clinical signs or vital sign changes that would suggest an allergic reaction to her pegasparaginase infusion

Amy hasn't had any outward clinical signs or vital sign changes that would suggest that she had an allergic reaction to her pegasparaginase.

Amy's Serum Asparaginase Activity

Post-Dose #1

Dose	Level #1	Level #2
1	0.945	0.444

Post-Dose #2

Dose	Level #1	Level #2
2	<0.014	Pending

Amy comes back to clinic a week later and gets her asparaginase activity level set. The first dose levels are the ones after her day 4 of induction asparaginase and post dose #2 are post her day 15 of consolidation. You can see that her first level was less than .014, and her second level is pending.

Question

Based on Amy's most recent asparaginase assay, would you want to alter any of her chemotherapy?

A. Yes

B. No

C. I'm not sure

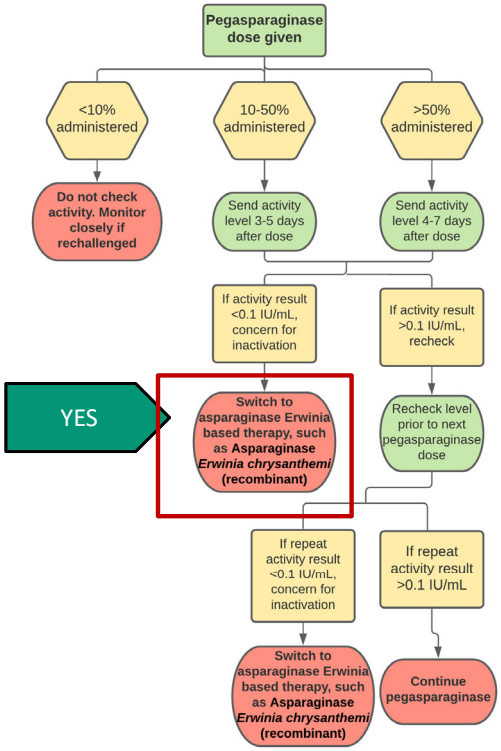
Please select your response below the video window and click the submit button to poll.

Based on these assays, would you want to alter any of Amy's chemotherapy?

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

Nursing Notes

- Based on the level from Amy's last lab, it is concerning that she did not have an appropriate level of serum asparaginase activity detected. This means that asparagine is likely still available to any remaining leukemia cells



Adapted from: Bleyer A, et al. *Pediat Blood Cancer*. 2015;62:1102-1105.

Using the chart that Joe went over with us, based on that level from Amy's last lab, it is concerning that she didn't have an appropriate level of serum asparaginase activity, which means that we're not having that asparagine depletion that we need and so asparagine would be available to any remaining leukemia cells. Looking at the chart, if you follow it down, she received all of her doses. Then we checked her level and her level was less than the detectable range of 0.1. There's concern that she would be a silent inactivator.

Question

Would you change the formulation of asparaginase that Amy is getting?

A. Yes

B. No

C. I'm not sure

Please select your response below the video window and click the submit button to poll.

If you follow along, this will bring us into our next question. Would you want to change the formulation of asparaginase that Amy is getting?

Acute Lymphoblastic Leukemia:
Nursing Notes on Asparaginase Hypersensitivity & Silent Inactivation

Treatment Decision

Would you change the formulation of asparaginase that Amy is getting?

Yes

Would discuss with family need to switch to another formulation of asparaginase in order to deliver appropriate chemotherapy

Amy would be switched to an asparaginase *Erwinia*-based formulation:

- Asparaginase *Erwinia chrysanthemi* (recombinant)-rywn

*Asparaginase *Erwinia chrysanthemi* (Erwinaze) is not currently marketed in the United States, but supplies may remain

Yes, we would want to change the type of asparaginase that we're giving Amy. The concern is that she had a true silent inactivation, so had those anti-asparaginase antibodies, neutralizing the drug, and so didn't get the asparagine depletion that we need from her. If we did not switch her asparaginase, the risk would be that we're giving her suboptimal therapy. We would want to discuss with the family the need to switch to another form of asparaginase to ensure that we're giving her the best therapy available.

Since Amy received pegasparaginase, we would switch her to an asparaginase *Erwinia*-based formulation, which the current is the asparaginase *Erwinia chrysanthemi* recombinant.

Family/Patient Considerations

Inform Patients and Family

Change in asparaginase formulation will change the number and frequency of visits required

- Patients will require additional visits and injections when switching products
  - For example, to replace one dose of pegasparaginase, patients will need to receive at least six doses of an asparaginase *Erwinia*-based product
- Timing:
  - Asparaginase *Erwinia chrysanthemi* (recombinant)-rywn is currently FDA approved for every 48 hours only
- Administration:
  - Asparaginase *Erwinia chrysanthemi* (recombinant)-rywn currently approved for IM administration only
  - Require monitoring during and post-administration to monitor for allergic reactions; may vary between institutions, but typical is every 30 minutes until 60 minutes post-injection

Just some considerations when we're making the switch for Amy, is that the change in formulation of asparaginase means that we have to change the number and the frequency of visits that she needs. In general, to replace one dose of a pegylated asparaginase product, we expect patients would need to receive at least six doses of an asparaginase *Erwinia*-based product.

Rylaze or the asparaginase *Erwinia chrysanthemi* recombinant, is FDA-approved for every 48 hours as an IM injection. Typically monitoring during and post the injection is still required to monitor for any further allergic reactions, and typically is about every 30 minutes until 60 minutes post the injection.

Key Take-aways From Today's Talk

- ✓ Asparaginase is an essential chemotherapeutic agent for the treatment of pediatric leukemia and lymphoma
- ✓ The inability to administer asparaginase to a patient has been associated with worse outcomes
- ✓ Patients can experience clinical hypersensitivity to asparaginase products, but can also develop anti-asparaginase antibodies in the absence of clinical symptoms
- ✓ Asparaginase assays can help to differentiate between infusion reactions and true drug allergies
- ✓ Monitoring of asparaginase assays allows for clinicians to monitor for silent inactivation and make adjustments in a patient's treatment regimen if necessary

To wrap up our key takeaways from today, asparaginase is an essential chemotherapy for the treatment of pediatric leukemias and lymphomas. Because of this, the inability to give asparaginase to patients has been associated with worse outcomes. Patients can experience either clinical hypersensitivities to asparaginase products or can develop anti-asparaginase antibodies in the absence of clinical symptoms, or have silent inactivation. Using asparaginase assays, we can differentiate between patients who have true drug allergies or immune-mediated responses, or patients who are having non-immune mediated or infusion reactions. Monitoring asparaginase assays allows for a clinician to monitor for silent inactivation and make adjustments in patient treatment regimens if necessary.