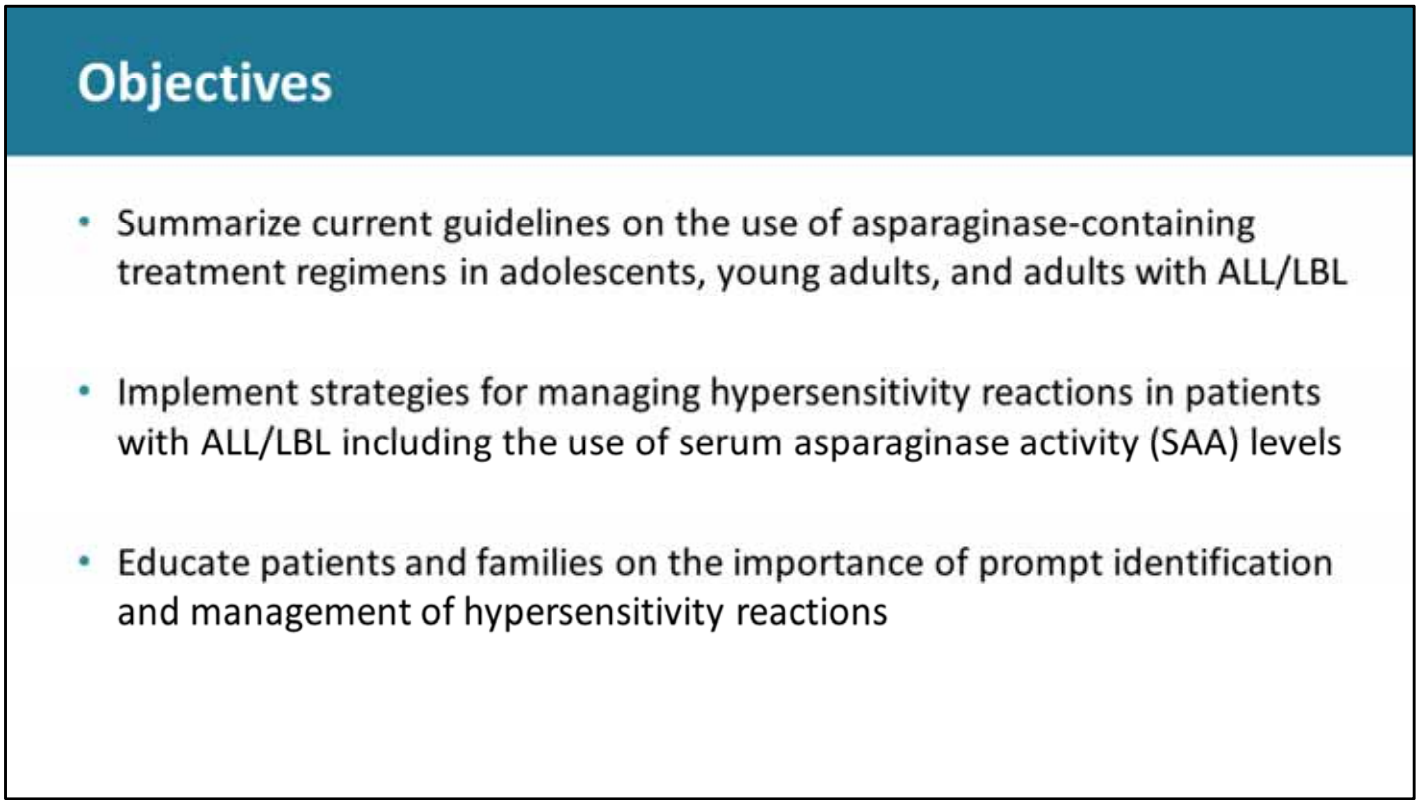
Moderator: Welcome to our CE presentation entitled *Nursing Insights on the Management of Patients with ALL/LBL Treated with Asparaginase Therapy*.

Today's program is provided by MediCom Worldwide and is supported by an independent medical education grant from Jazz Pharmaceuticals.

It's now my pleasure to turn the webcast over to Sandra Kurtin, PhD, ANPC, AOCN, FAPO, Assistant Professor of Clinical Medicine; Adjunct Clinical Professor of Nursing at the University of Arizona College of Medicine, Director of Advanced Practice Hematology/Oncology Nurse Practitioner at the University of Arizona Cancer Center in Tucson, Arizona. Dr. Kurtin, the floor is yours.

Sandra Kurtin: Thank you so much and welcome everyone. Good evening. I am Sandy Kurtin and I'm very pleased to be here tonight to talk to you about ALL and LBL. We'll get more into that and then very specifically, spend time talking about asparaginase therapies in these patients.



These are our objectives.

We're going to really talk about what the current guidelines are for asparaginase therapies in these populations including adolescents, young adults, and adults. We'll get more into all of that. Really looking at hypersensitivity, specifically with asparaginase, and then what the role of a serum asparaginase activity level is in determining the benefits and or barriers to effective therapy. Then how do we educate our patients and families about this therapy.

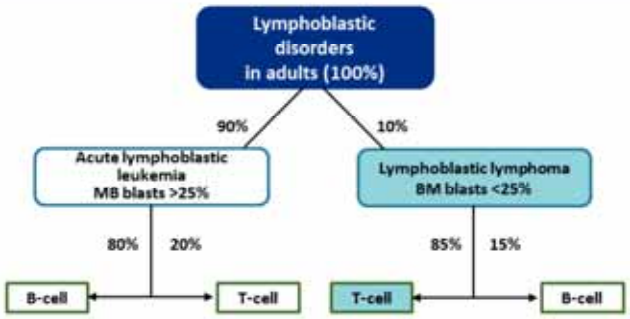
Faculty Disclosure

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

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

These are my disclosures.

Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma: Disease Characteristics



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

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

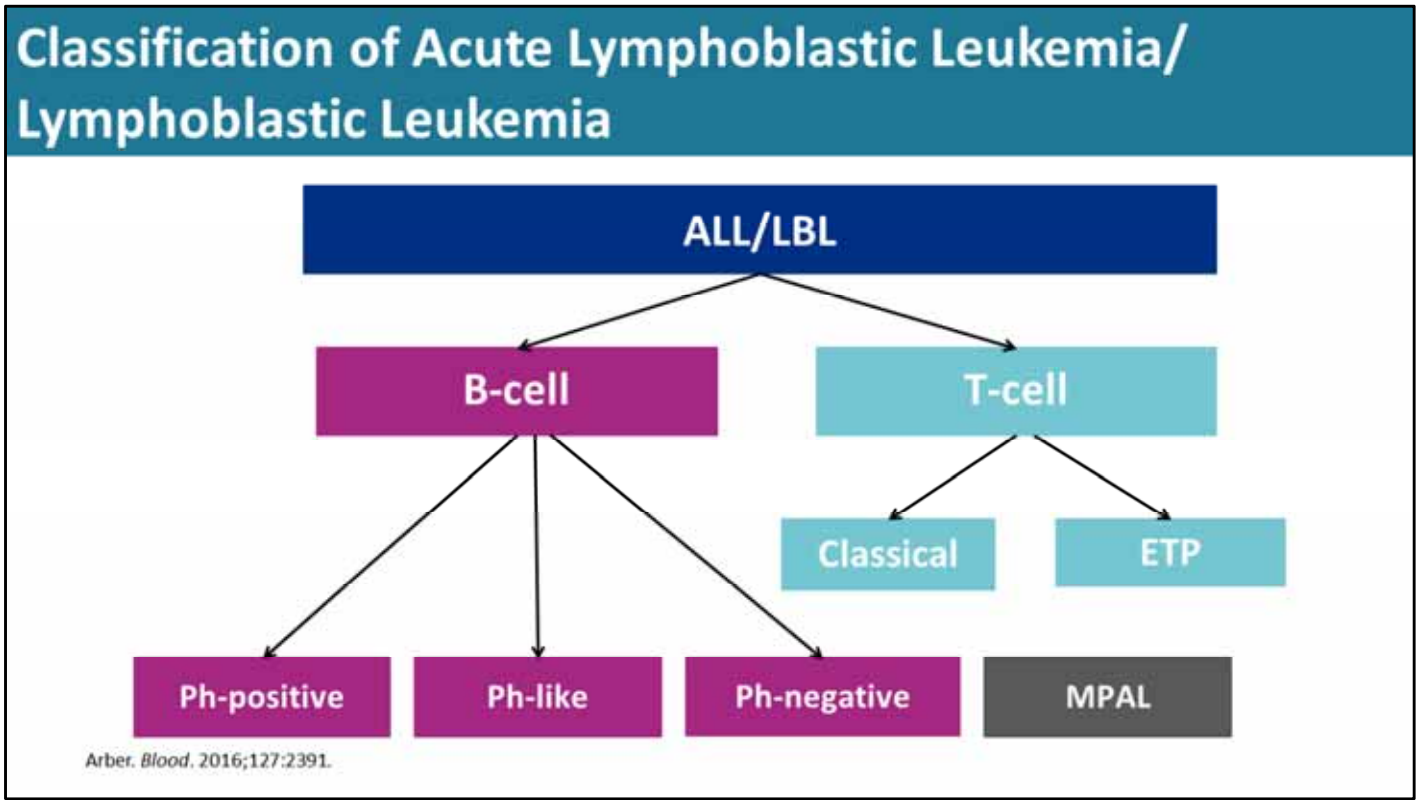
We'll get into the content now. We're going to talk tonight about acute lymphoblastic leukemia or ALL and lymphoblastic lymphoma or LBL. These are morphologically very much the same, they can be either B-cell or T-cell in origin.

As you can see here in adults, 90% of these patients have ALL and that is characterized by greater than 25% bone marrow blasts. In lymphoblastic lymphoma, they tend to have more nodal disease and fewer blasts in the bone marrow, so less than 25% bone marrow blasts. Then in each category, you can see they are either categorized to B-cell or T-cell.

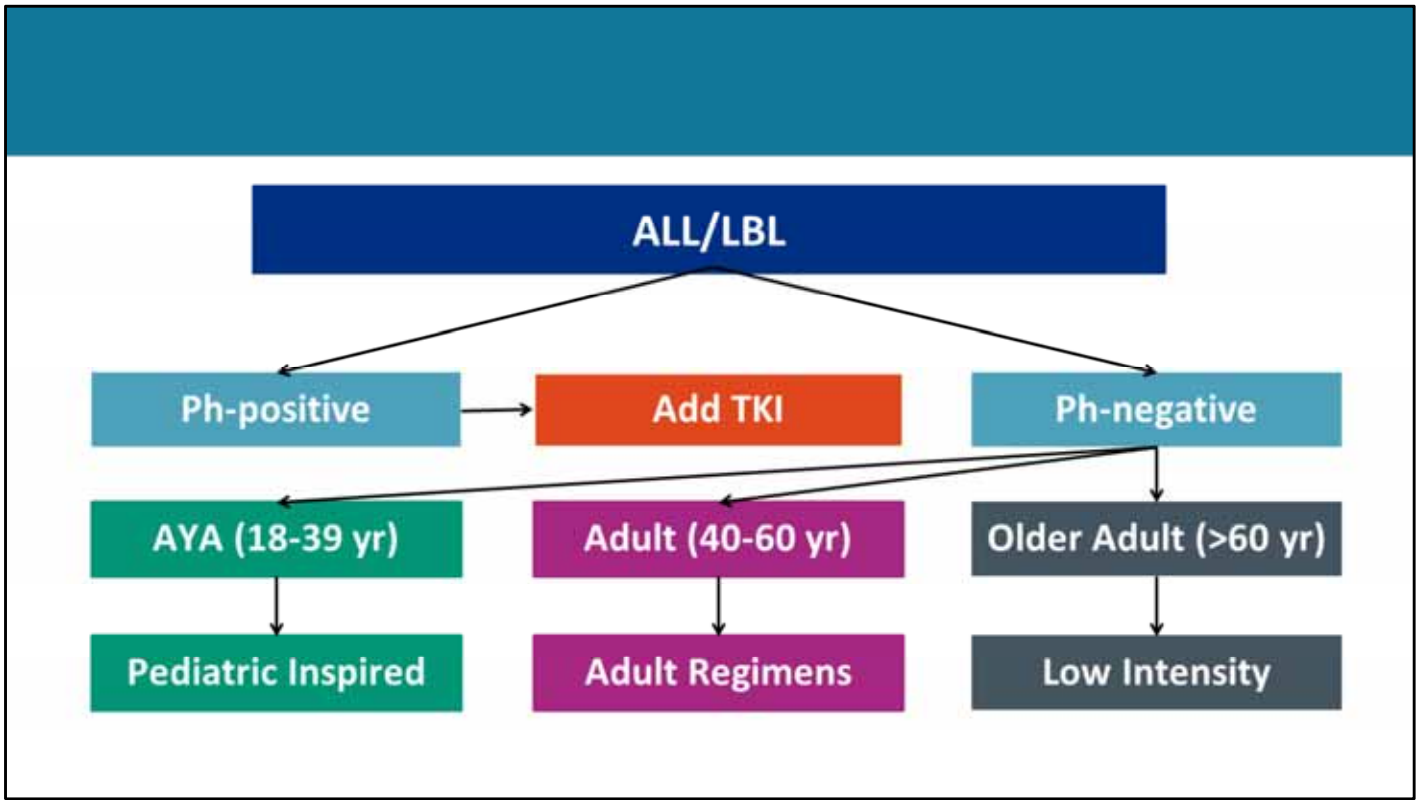
In adults, B-cell ALL is more common than T-cell. T-cell is more common in younger patients. LBL or lymphoblastic lymphoma is more commonly T-cell and less commonly B-cell. Most of the B-cell patients, or 75% of those, have mature B-cell disease. This is less favorable, and it requires intensive therapy moving into allogeneic stem cell transplant.

Then in the pre-B-cell ALL, this is more common in children and adolescents, and young adults or AYA. T-cell ALL is more favorable in adults at initial diagnosis. However, if they have incomplete treatment, they don't do well and then need to definitely go to an allogeneic stem cell transplant. These patients more commonly, as I mentioned, have nodal disease, so large mediastinal masses or other nodal regions.

Lymphoblastic lymphoma similarly has more nodal disease. Again, less than 20% to 25% blasts. This is more common in children and particularly young males. Collectively, these patients are all treated with ALL-like regimens.

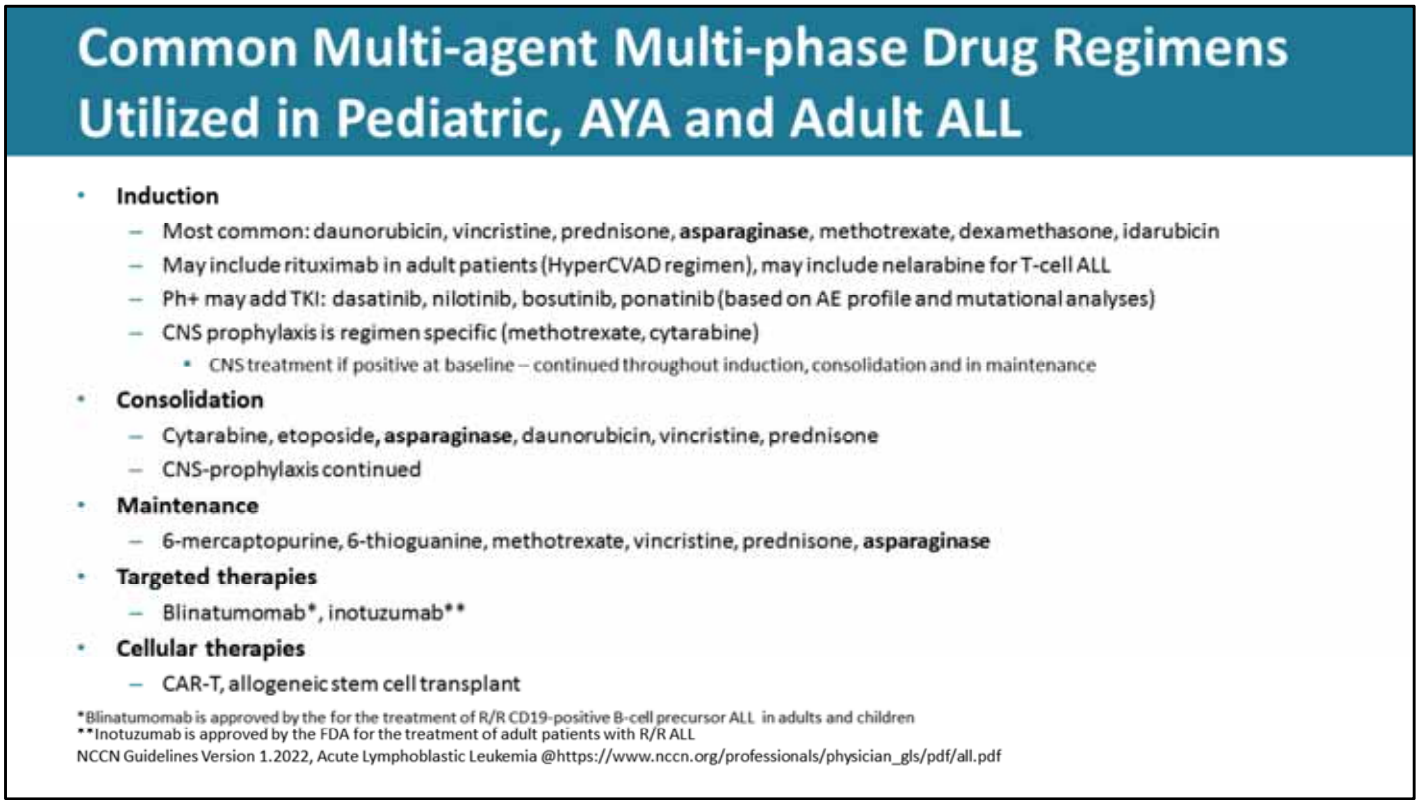


This is just a different way of looking at that. I think the last layer here is that we look at whether or not they carry the Philadelphia chromosome. In patients with B-cell ALL, we test for BCR-ABL, which is the molecular abnormality or mutation that we see in CML, chronic myelogenous leukemia, but can also be present in these B-cell ALL patients. For those patients, then we talk about adding a tyrosine kinase inhibitor like we would use for CML.



Then this is just another way of looking at risk of stratifying that based on Philadelphia chromosome positive or negative. We'll add a TKI, tyrosine kinase inhibitor. These are drugs like dasatinib is the most common one, or Sprycel, and less commonly nilotinib or some of the other TKIs.

If they're pH negative, regardless of group, it's going to really depend on fitness and/or frailty and what can they tolerate. The largest group is going to get pediatric-inspired ALL regimens. We're going to talk more about that.

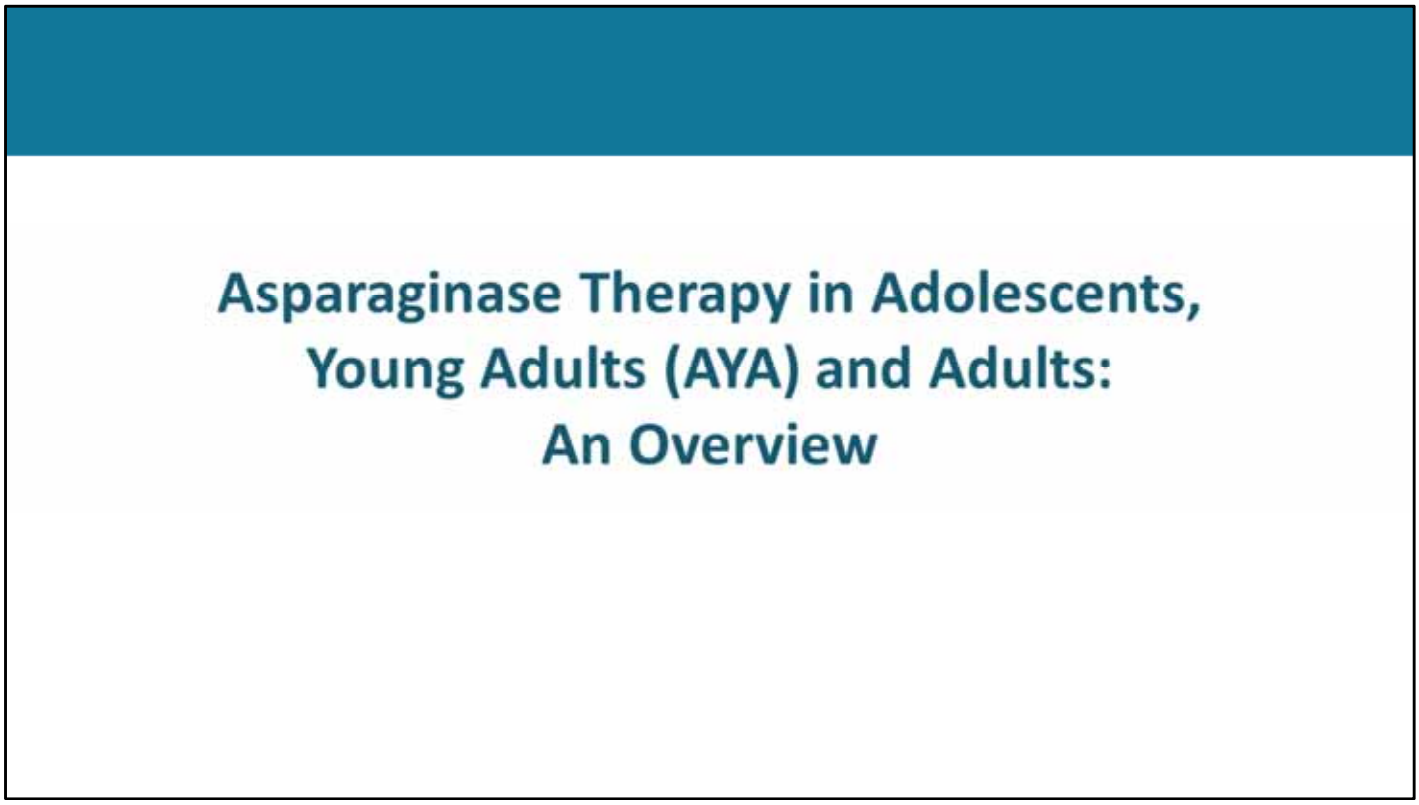


Those regimens are very intensive, probably the most complicated things that we do in patients in my experience. I've been doing this a really long time, 38 years. These are patients who, for females, get two years of therapy. The first six months are very intensive. For males, because they have sanctuary sites in the testes, are treated for three years. Those are patients who don't require transplant.

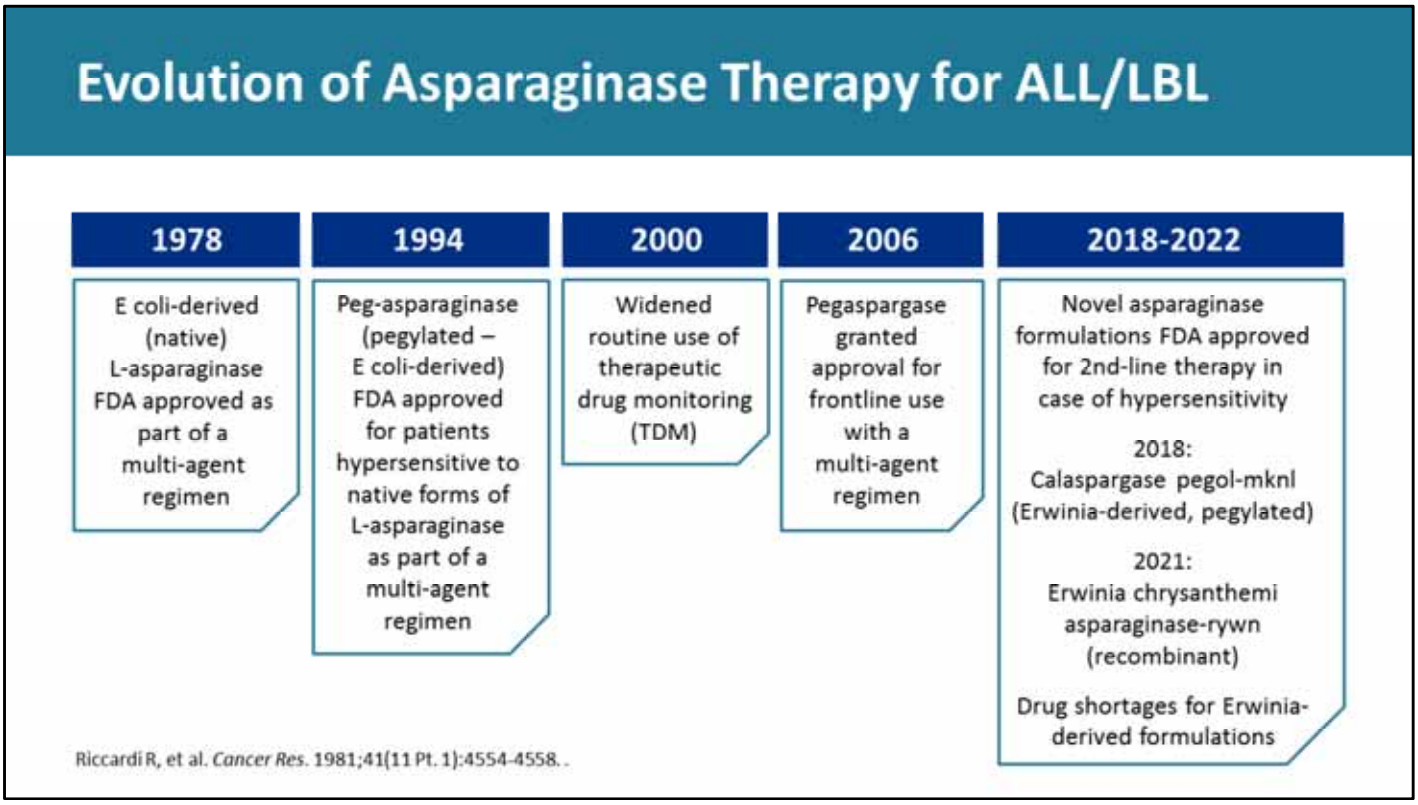
In patients who require a transplant, they may get some or all of that and then go to transplant. The therapy is basically in several phases. We have induction, you can see there are multiple drugs that are used here. Then you see that for those that are Philadelphia chromosome positive, we're going to add that TKI. If they're negative, there's no role for that.

All patients need a central nervous system prophylaxis, because that's another sanctuary site. Standard therapy does not penetrate the blood-brain barrier. You can see that asparaginase is very much a part of this initial therapy-induction, consolidation, and maintenance to some degree. It goes away toward the maintenance phase.

Then for those who have relapse or refractory disease, we'll move to some of the newer targeted therapies like blinatumomab and is inotuzumab. Then for those who are either multiple relapse or refractory or on a clinical trial, we'll start looking at things like CAR T therapy or an allotransplant, but it is very intensive. Asparaginase plays a very important role in the initial therapy for these patients.



Let's talk more about that. We're going to focus on asparaginase therapy in adolescents, young adults, and adults.



This is the trajectory over time. In the early or in the '70s, we had E. coli-derived or native L-asparaginase. This was approved as a part of this multi-agent regimen that I just described.

It wasn't until 1994 that we had a pegylated version of that also E. coli-derived. This was for primarily patients who had reactions to that native formulation E. coli-derived L-asparaginase. Again, part of that multi-agent regimen. In 2000, we began to have data on therapeutic drug monitoring. We're going to talk more about that, or TDM.

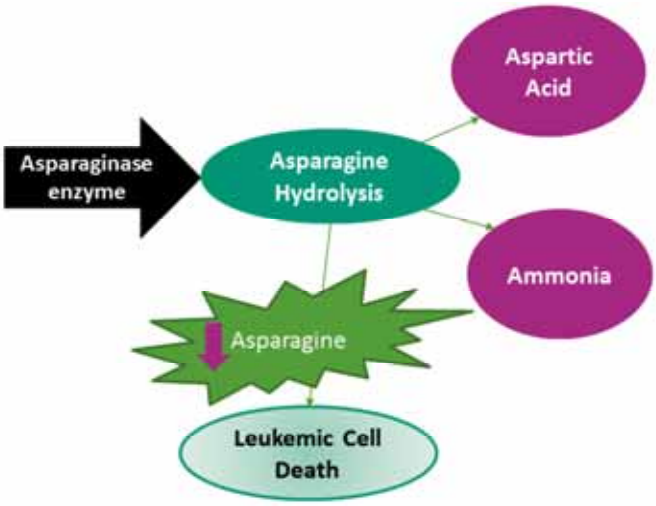
It wasn't until 2006, where we had PEG-asparaginase as a newly approved frontline agent to be used in these regimens moving ahead of the E. coli-derived native. In other words, you didn't have to wait to react to that, you could just start with PEG-asparaginase. It largely took over that frontline setting, given the number of patients that reacted to that native E. coli-derived formulation.

Then more recently, we have novel compounds. There are FDA-approved for second line. In case of hypersensitivity, we have calasparaginase, also a pegylated compound. This is Erwinia-derived, so it's different than E. coli. They're completely different bacterial entities. Then in 2021, or Erwinia chrysanthemi asparaginase, which is a recombinant formulation, also not E. coli-derived. These are very different compounds.

We have had drug shortages. For that reason, there has been some stratification in prioritization to make sure everybody has access to these very important drugs.

Asparaginase Mechanism of Action

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



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

I'll come back to that, but let's talk first about how asparaginase works. Asparaginase is an enzyme. It hydrolyzes asparagine into aspartic acid and ammonia. You can see that in the cartoon on the right.

As you have asparagine hydrolysis or breakdown, you decrease asparagine and that causes leukemic cell death. Leukemia cells require asparagine to grow and progress. Less asparagine is good, that's reducing the risk of leukemic transformation or leukemic progression. When that breaks down, you can have also the development of aspartic acid and ammonia. This is really important when we're looking at adverse events because as you break down asparagine, you can produce ammonia as a part of that process. We'll come back to that. Really important to understand less asparagine is good, that means less leukemic cell death.

The other important thing about asparaginase exposure over time is that the five-year event-free survival is inferior in patients who have incomplete therapy. Less than 25 weeks of therapy compared to at least 26 weeks, the five-year survival is 73% in those that do not complete therapy versus 90%. Really important to make sure people are receiving the amount of asparaginase that they should according to protocols to improve their response and survival
over time. Also, we need to measure ammonia levels. This is something that is not intuitive. You have to add it, it's not part of a metabolic panel, but it's something that's really important in differentiating whether patients are having hypersensitivity reactions or perhaps this process of silent inactivation in which we consider this ammonia level as a part of that process.

FDA-Approved Asparaginase Formulations

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

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

These are the different formulations, and again, their type or species. They're derived from either E. coli or Erwinia, and it's really important to understand those are very different compounds. They are not cross reactive in that sense. Then because of the shortage of drugs globally, there's been a prioritization to use the calasparaginase for pediatric only, 1 month up to age 21 and only the pegylated formulation is available in pediatrics. Then you can use a PEG-asparaginase in age greater than 22. Then also the Erwinia chrysanthemi as a second line if they've had hypersensitivity to one of the E. coli-derived like PEG-asparaginase for those patients.

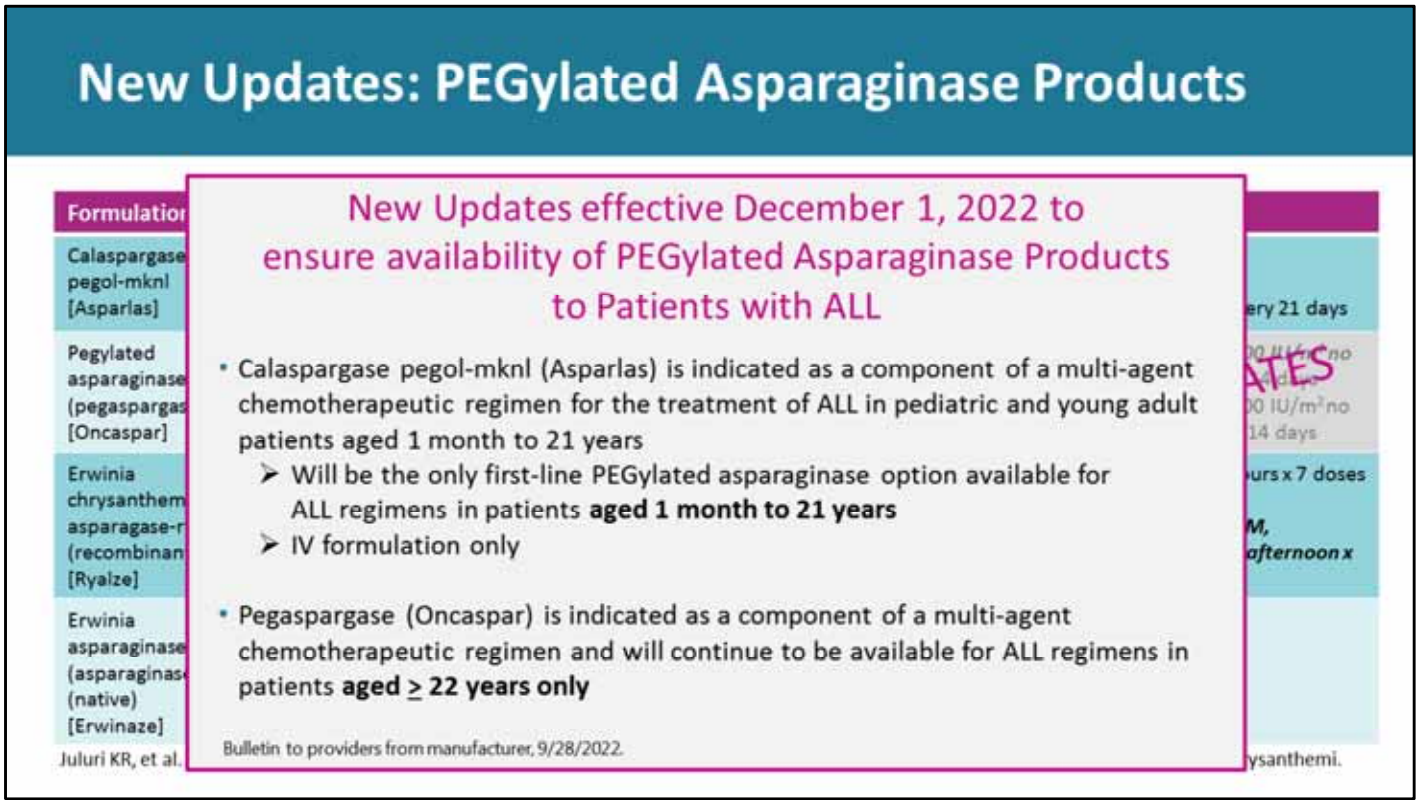
New Updates: PEGylated Asparaginase Products

Formulation	FDA Approved Indication	Half-life	Administration
Calaspargase pegol-mknl [Asparlas]	As a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in pediatric and young adult patients aged **1 month to 21 years**	IV: 12.7-17.3 days	2500 IU/m^2 Route: IV No more frequently than every 21 days
Pegylated asparaginase (pegaspargase) [Oncaspar]	As a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with: First-line acute lymphoblastic leukemia (ALL) ALL and hypersensitivity to native forms of L-asparaginase	IM: 5.7 days IV: 4.9-5.3 days	Patients aged ≤21 years: 2500 IU/m^2 no more frequently than every 14 days Patients aged >21 years: 2000 IU/m^2 no more frequently than every 14 days NEW UPDATES
Erwinia chrysanthemi asparagase-rywn (recombinant) [Ryalze]	As a component of a multi-agent chemotherapeutic regimen given by intramuscular injection for the treatment ALL and lymphoblastic lymphoma (LBL) in **adult and pediatric patients 1 month or older who have developed hypersensitivity to *E. coli*-derived asparaginase**	IM: 15.9 hours	Dose: 25 mg/m^2 Every 48 hours x 7 doses Or 25/25/50 mg/m^2 ***Monday AM, Wednesday AM and Friday afternoon x 6 doses***
Erwinia asparaginase (asparaginase) (native) [Erwinaze]	Treatment of patients with ALL as part of a multi-agent chemotherapeutic regimen **This product in not commercially available in the US**	IM: 16 hours IV: 7.5 hours	25,000 IU/m^2 Route: IM or IV Frequency: 3x/week

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

Then this is really important as well. In addition to that age stratification, it's really important to understand that these are not interchangeable. They have different half-lives and routes of administration and that has everything to do with how frequently you give them, based on that half-life. You can see, for instance, the calasparaginase, which is again, primarily pediatric is given IV, the half-life is extended. You would give it no more frequently than every 21 days.

Whereas PEG-asparaginase is given IM or IV and it can have a variety of half-lives, but anywhere from 4.9 to 5.7 days. Then you go down to Erwinia chrysanthemi and it's given IM, and it has a very short half-life, 15.9 hours, so less than 24 hours. You can see that it's dosed much more frequently. Really important to understand the formulation, the half-life, the route of administration, and how frequently you would be administering that drug.



This is just echoing the stratification of age and really making sure that every patient with ALL or LBL has access, excuse me, to asparaginase in their treatment because it is so critical to their overall outcomes.

3 Currently Available Asparaginase Formulations

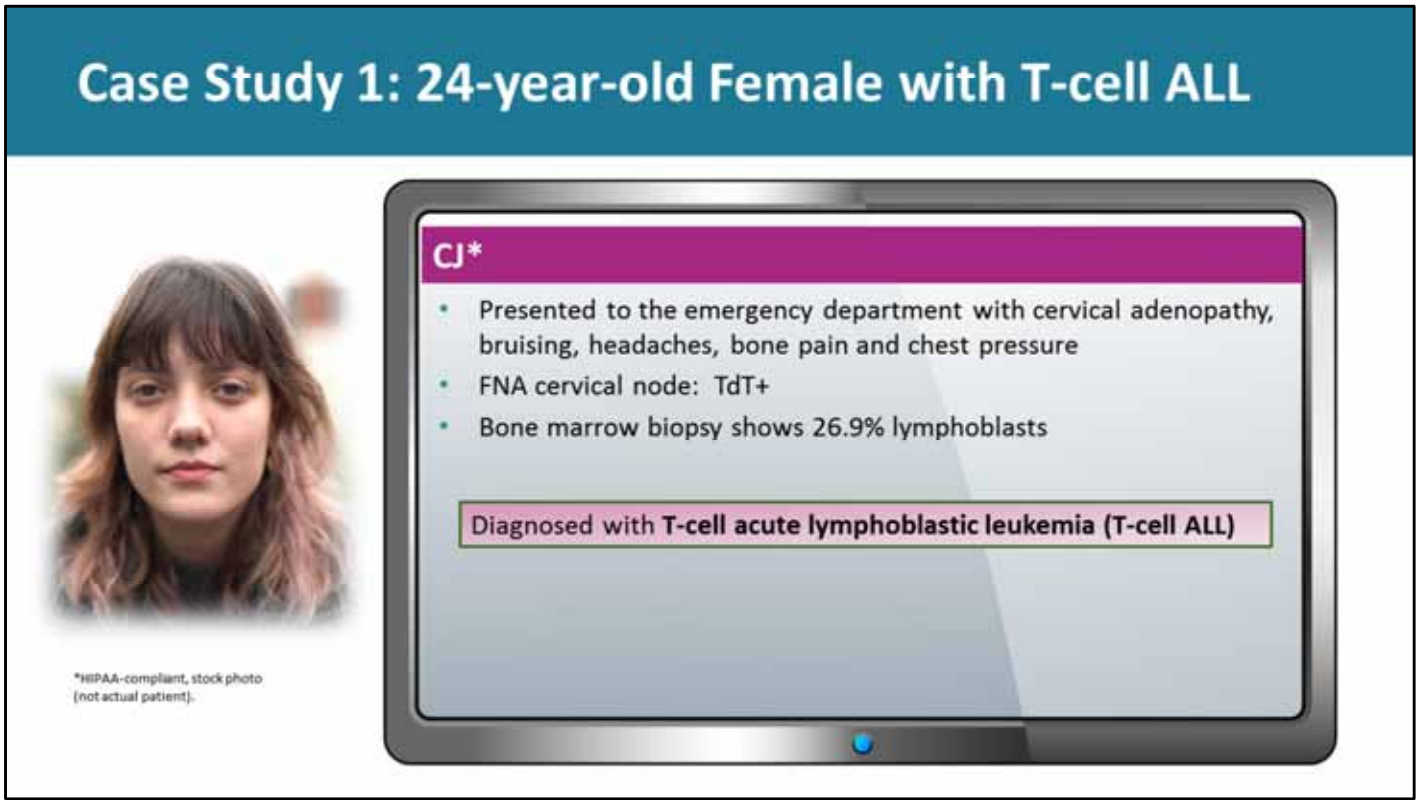
Formulation/ Species	Half-life based on route	Administration
Calaspargase pegol-mknl (E-coli) [Asparlas]	IV: 12.7-17.3 **days**	Age 1 month to 21 years Route: **IV only** Dose/Frequency: 2500 IU/m^2 no more frequently than every 21 days
Pegylated asparaginase (pegaspargase) (E-coli) [Oncaspar]	IM: 5.7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

Nursing Notes

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

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

These are really the ones that we're working with, because the others have been unavailable due to shortages. I won't go back through this again.



Here's our first case. This is our 24-year old female. She has T-cell ALL. She's presenting to the ER with cervical adenopathy, bruising, headaches, bone pain, and chest pressure. Has a biopsy and it's TDT positive, which is indicative of T-cell lymphocytes. The bone marrow biopsy shows 26.9% lymphoblasts, more than 25%. She's diagnosed with T-cell ALL, acute lymphocytic leukemia.

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

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

CJ*

Patient Notes	• Starting induction regimen (AALL0434 with nelarabine – a pediatric-based regimen)
Induction	• Daunorubicin 25 mg/m^2 IV once per day on Days 1, 8, 15, 22 • **Pegaspargase 2000 units/m^2 IV once on Day 4** • Vincristine 1.5 mg/m^2 (max dose of 2 mg/wk) IV once per day on Days 1, 8, 15, 22 • Prednisone 30 mg/m^2 PO twice per day on Days 1 to 28

She's starting her induction. This is a pediatric-inspired regimen. The AALL0434, very common. All those different drugs that I talked about previously. In T-cell, we add nelarabine, which is specifically a purine analog that specifically targets T-cell. It's T-cell targeted and adds a significant advantage to those patients with T-cell disease.
Then she gets the typical variation here of daunorubicin, PEG-asparaginase. Again, she's in that adult AYA category. The PEG-asparaginase, which again is the frontline, vincristine, prednisone. It looks a lot like things that you might see in lymphomas, like an R-CHOP type mixture. You can also see the complexity of the days in the week or the month so it is very intensive therapy.

The Rate and Risk Factors for Asparaginase Toxicities in Adults

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

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

What are the risk factors for patients receiving asparaginase? This is specific to asparaginase, not the whole regimen.

Hypersensitivity, this tends to be in the second dose and future doses. It's upfront. There are some polymorphisms that put people at greater risk, more common in younger patients with no pre-meds.

Then thrombosis, very common upfront. Some of that has to do with the presence of the disease. A lot of these people end up getting lines. You can also see all the factors that we typically think of in patients who are at risk for clotting as also risk factors.

Hypofibrinogenemia, low fibrinogen level is generally very much in the frontline also. These are the early onset side effects. Obesity is one of the risk factors for that.

Then high bilirubin, high LFT, hyperbilirubinemia is also during those initial cycles. This is true of each drug. Sometimes when you change to a different drug, you might see an early spike. Generally, that's closer to induction. Again, some of those risk factors are the dose of the PEG-asparaginase, if they have existing low albumin, low platelets, older age and obesity. Then certain genomic predispositions.

The Rate and Risk Factors for Asparaginase Toxicities in Adults

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

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

Then we start to see things that come on later or have variable onset, hyper-triglyceridemia. This can be pretty significant if they're already at risk for that. They have a high BMI or a younger age.

Hyperglycemia can be variable. Prednisone is a big part of this, but asparaginase can also cause a hyperglycemia just independently. Sometimes this is super high, greater than 500, particularly in people with preexisting diabetes.

Hyperammonemia, I talked a little bit about the mechanism of action. It's breaking this down into aspartic acid and ammonia. You can see high ammonia levels as those cells are breaking down, and that may be indicative of silent inactivation. Really important to measure those ammonia levels. We'll come back to that.

Pancreatitis, although rare can be severe. There are certain risk factors there as well.

Obesity and Asparaginase-Associated Toxicities

Select Grade 3/4 AEs, n (%)	BMI <30 kg/m² (n = 197)	BMI 30-40 kg/m² (n = 71)	BMI ≥40 kg/m² (n = 21)	P Value
Nonhematologic	152 (77.2)	57 (80.3)	18 (85.7)	.685
Hepatic toxicity	61 (31.0)	37 (52.1)	13 (61.9)	.001
Infection	43 (21.8)	19 (26.8)	9 (42.9)	.092
ALT increase	47 (23.9)	25 (35.2)	11 (52.4)	.009
AST increase	14 (7.1)	17 (23.9)	6 (28.6)	<.0001
Hyperbilirubinemia	23 (11.7)	22 (31.0)	10 (47.6)	<.0001
Pancreatitis	4 (2.0)	2 (2.8)	2 (9.5)	.123
Hyperglycemia	52 (26.4)	28 (39.4)	10 (47.6)	.030

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

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

When we look at one of the risk factors, I've talked about obesity and BMI across many of these, you can see that this makes a big difference in terms of the significance of a number of these toxicities. Certainly, liver or hepatic enzyme elevation, hyper-bilirubinemia, pancreatitis, hypertriglyceridemia. You can see that there is definitely, in some cases, a statistically significant increase in patients who are obese for these disorders, or at least a higher incidence overall.

Obesity and Asparaginase-Associated Toxicities

Select Grade 3/4 AEs, n (%)	BMI <30 kg/m² (n = 197)	BMI 30-40 kg/m² (n = 71)	BMI ≥40 kg/m² (n = 21)	P Value
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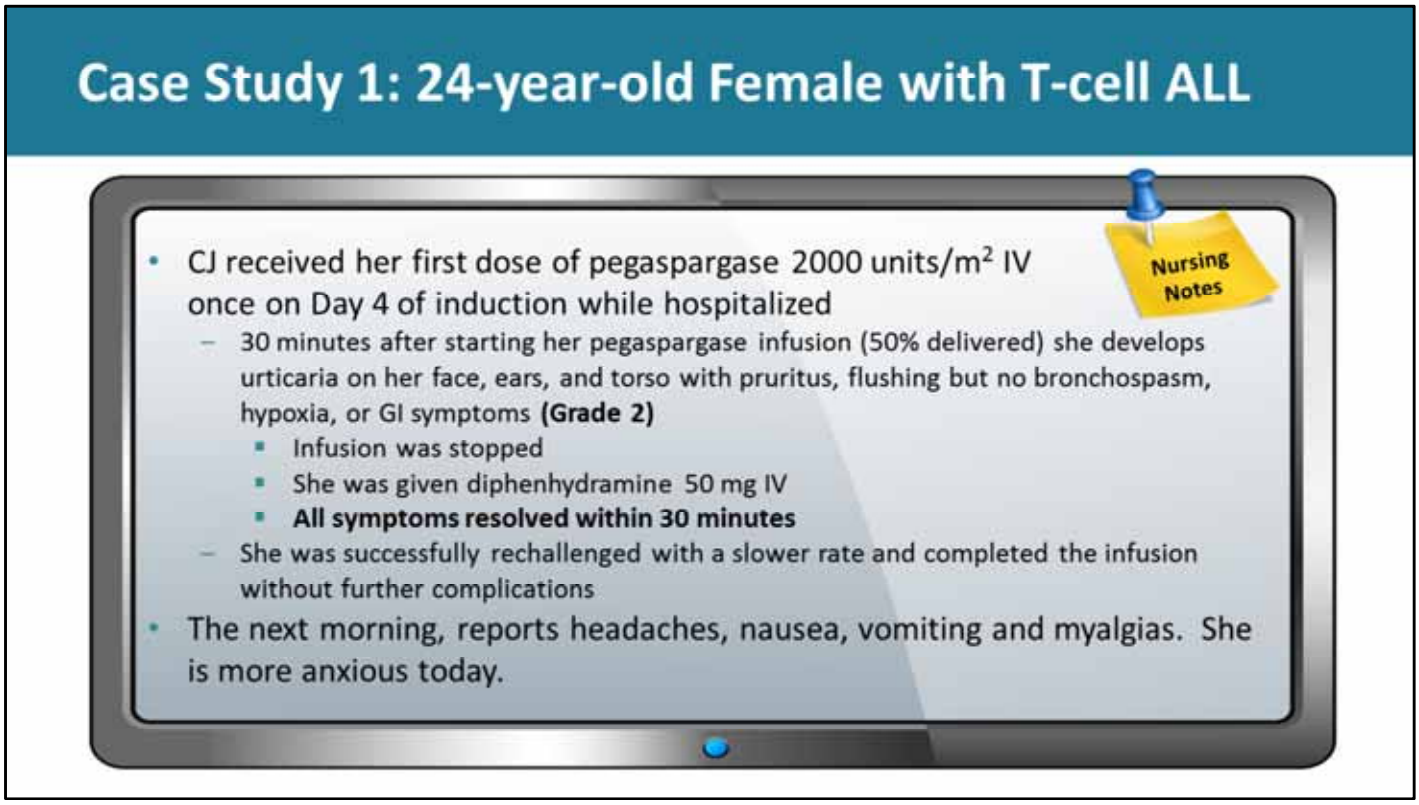
- Grade 3/4 toxicities in CALGB 10403 study of pediatric ALL regimens in AYA patients aged ≤40 yr (N = 289)

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

That's just highlighting those that are statistically significant.



Now, we're back to our case. She's received her first dose of PEG-asparaginase on day four, which is typical. She's in the hospital because she was admitted, this is newly diagnosed.

We get going right away. 30 minutes after starting her PEG-asparaginase, she's gotten 50% of the dose, she now has urticaria, pruritus. Flushing but no bronchospasm, hypoxia or GI symptoms so it's a grade two. Infusion is stopped. We give additional meds. All symptoms resolved in 30 minutes, and she's successfully re-challenged at a slower rate. However, the next morning, she reports a headache, nausea, vomiting, myalgias, and she is more anxious than usual.

Adverse Event Profile for Asparaginase: Hyperammonemia

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

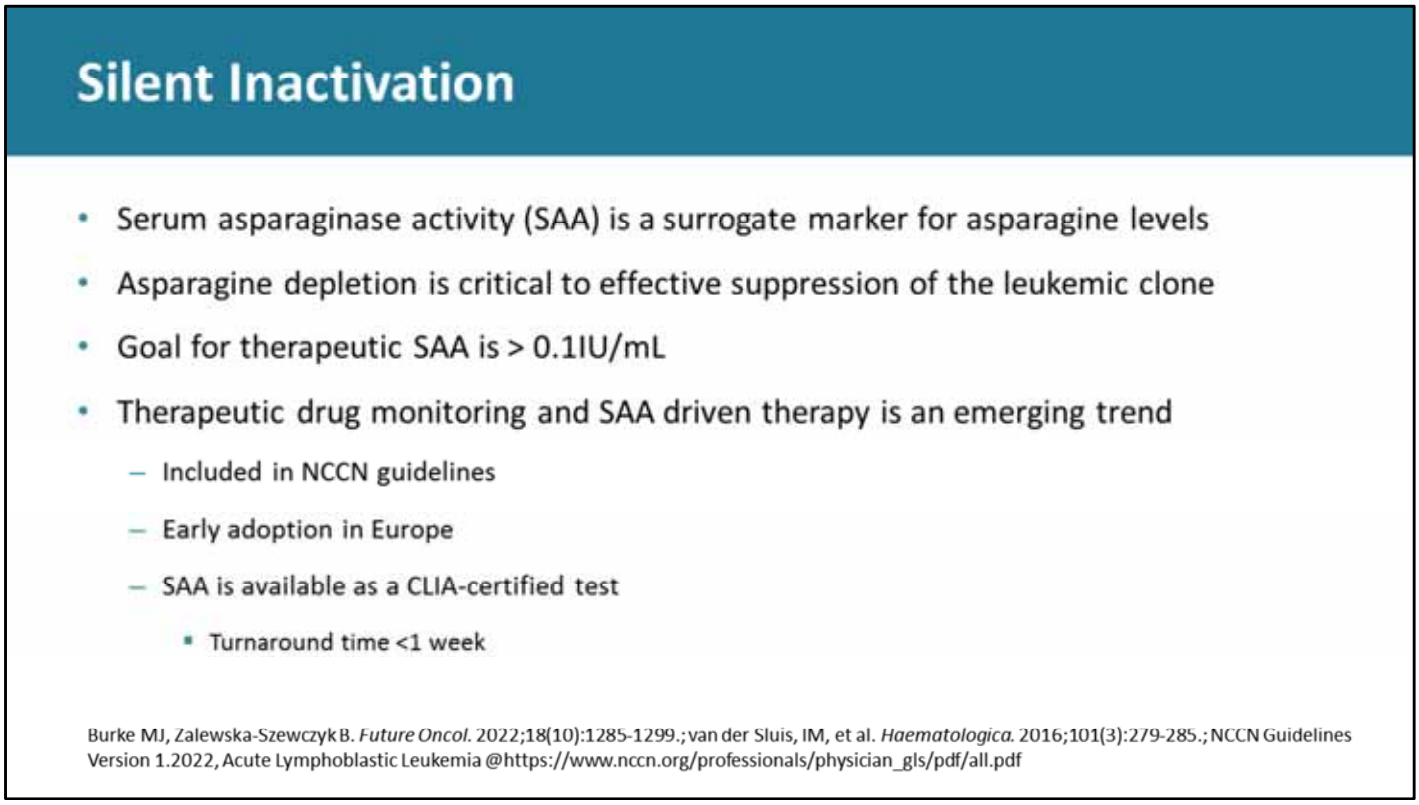
Age	Male (µ/dL)	Female (µ/dL)
1 to 6 m	42–137	42–137
7 m to 1 y	34–108	34–108
2 to 12 y	33–97	33–97
13 to 30 y	36–136	29–112
31 to 40 y	40–160	30–130
41 to 50 y	40–200	31–155
51 to 70 y	40–200	34–178
71 to 80 y	31–169	31–169
>80 y	28–135	28-135

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

When we look at ammonia, if you think about high ammonia levels, we often think about the chronic liver disease population or the alcohol-induced cirrhosis in those patients. When you think about how the drug works and breaking down asparaginase into aspartic acid and ammonia, those high levels can indicate silent inactivation as I mentioned.

The normal ranges vary by age and gender so it's really important to understand that that is a thing. Generally, in the lab, they'll report normal levels for a patient based on age, but it's important for you to check on that. Also, just to check the level in anyone who we think may have had a mild reaction or is having these symptoms that we're going to blame on the drug itself. In fact, it may be the breakdown of the asparaginase in this higher level of ammonia. We always think, oh, nausea, vomiting, headache, fatigue, anxiety, that's probably prednisone and the drug. In fact, it can be an ammonia level.

There are risk factors for this primarily pre-existing liver disease. Again, this anxiety, malaise, weakness, nausea, vomiting, and abdominal cramping may be ammonia. We don't really know how best to prevent it in people that have chronic liver disease or alcoholic cirrhosis. We try to get increased protein intake, limit protein breakdown, limit strenuous activity. We use lactulose, benzoic acid, and then you can also use arginine or sodium butyrate. It's important to just measure the level so you understand whether they may have silent inactivation.

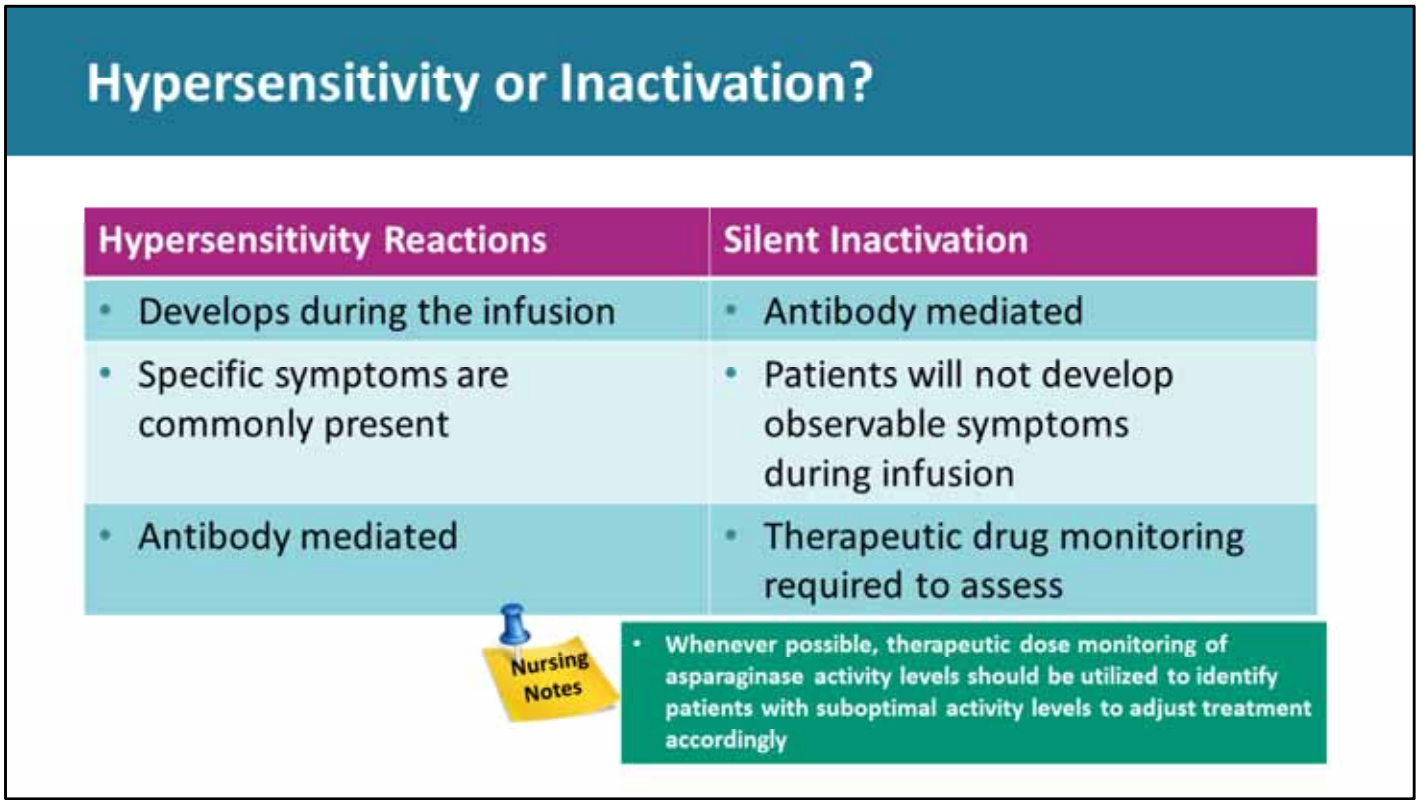


That basically is a surrogate marker. Serum asparaginase activity is a surrogate marker for asparagine levels. We can measure that. Remember, asparagine is--we want to reduce that because that's what feeds the leukemia. Asparagine depletion is critical to effective suppression of the leukemic clone. We want a higher asparaginase level, which gives us a lower asparagine level. More asparaginase, less asparagine, less leukemia.

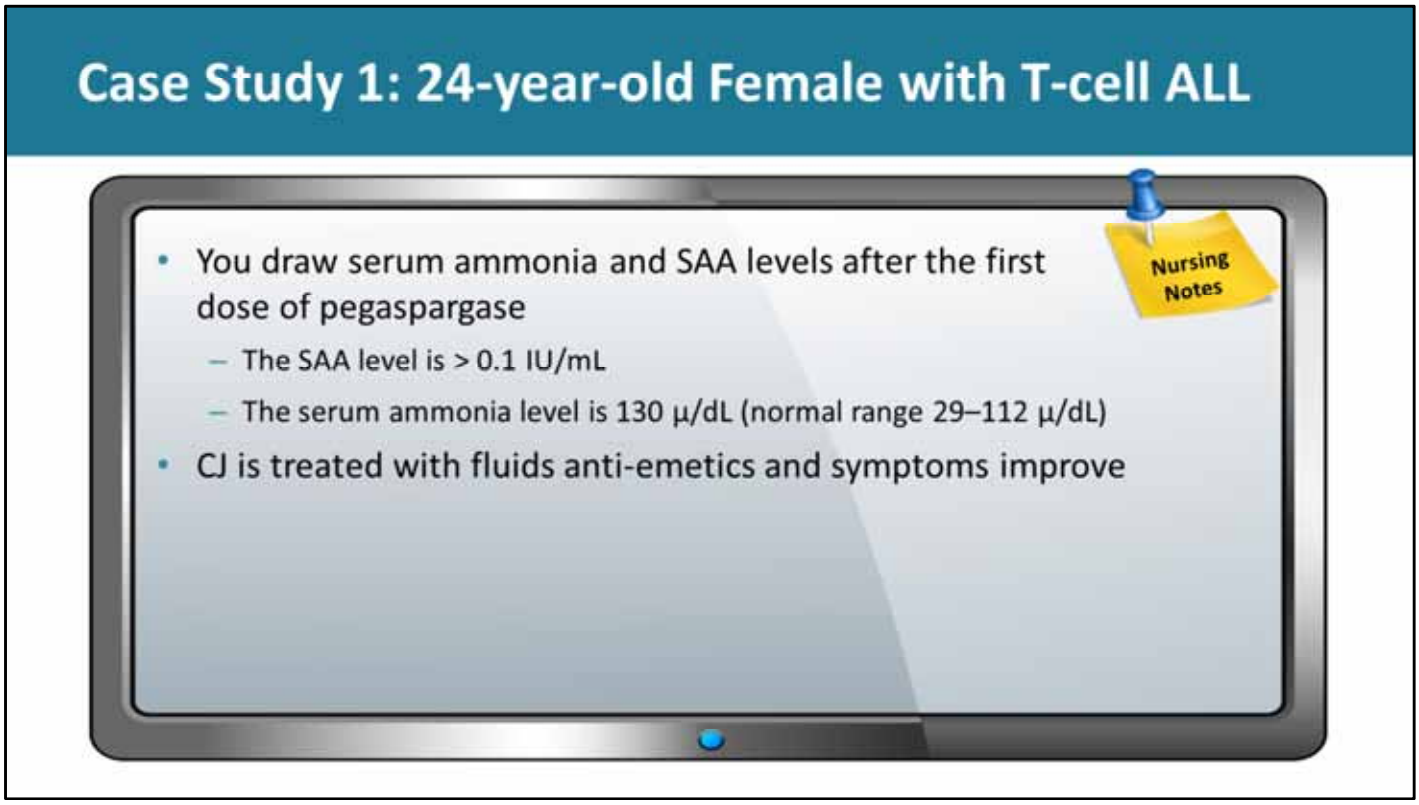
We monitor those, this therapeutic direct monitoring. It's included in the NCCN guidelines. Very early adoption in Europe, we're getting there in the United States. It is a CLIA certified test, and the turnaround time is about a week.

This is just an example of how that test would look, and again, this would be dictated by your institution in terms of how you send this out. But again, really important to our goal is to be greater than 0.1.

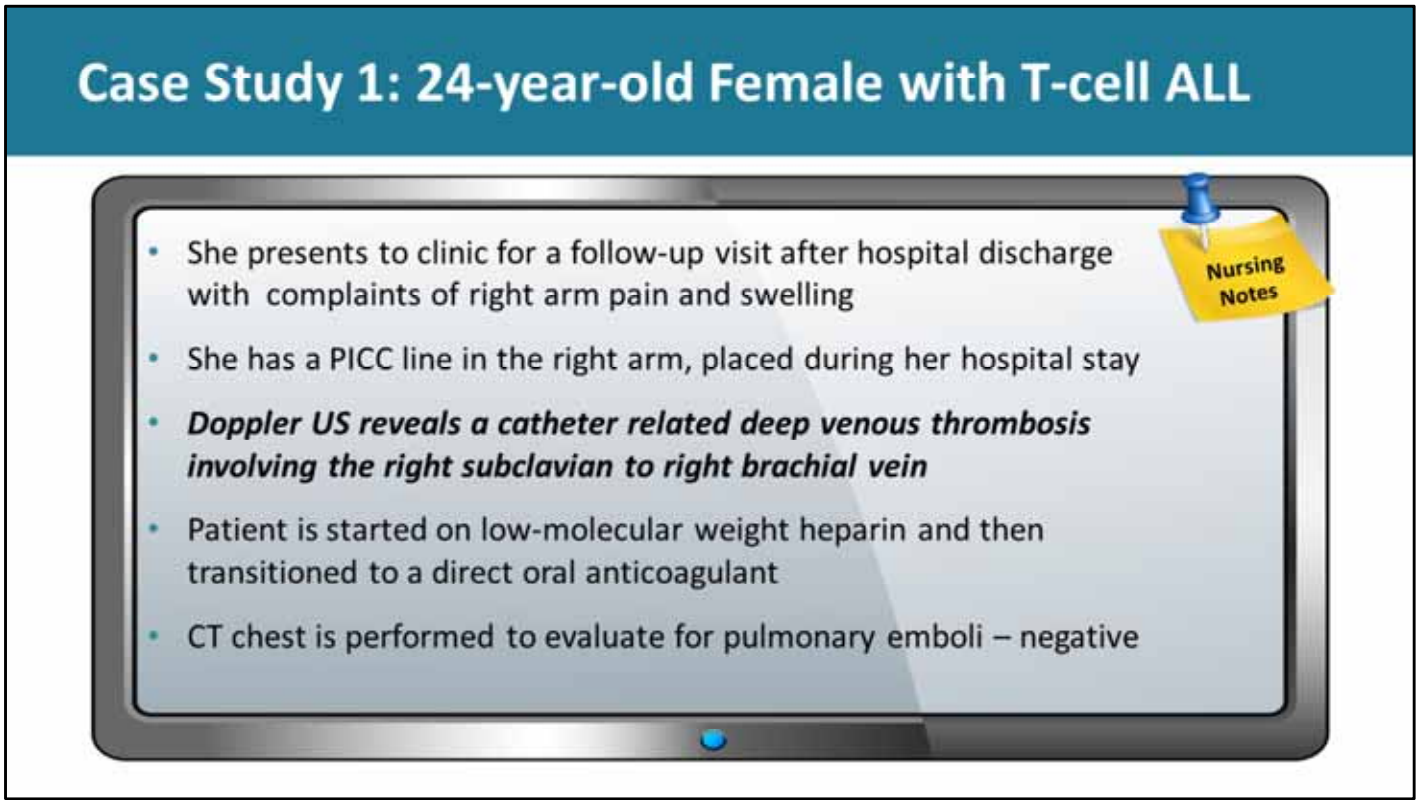
Again, higher asparaginase level, less asparagine, asparagine depletion, it means leukemic bone suppression.



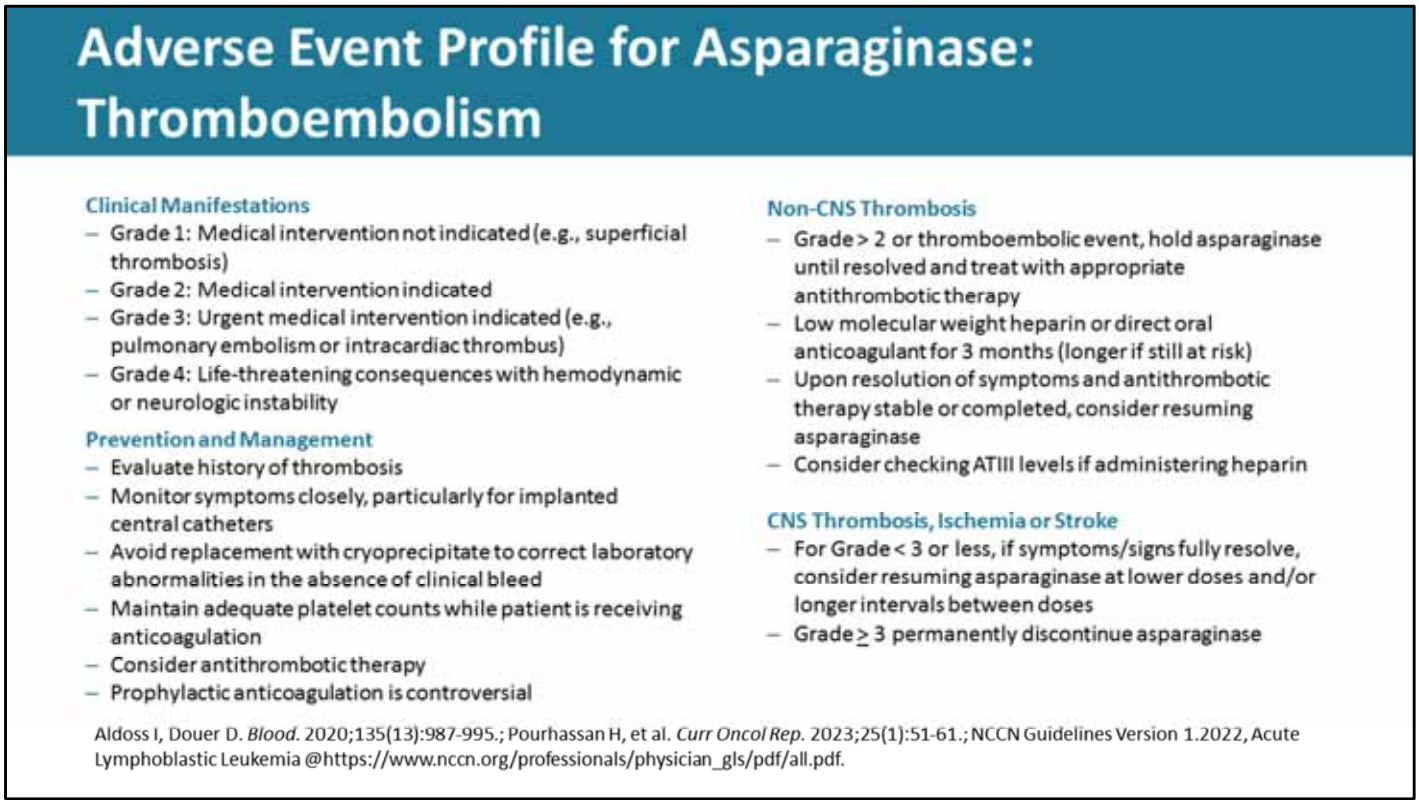
Then when we look at hypersensitivity versus inactivation. Hypersensitivity is generally surrounding the infusion itself and generally very much, sometimes immediate. It's sometimes delayed, but mostly immediate. It's antibody-mediated, whereas silent inactivation they may or may not develop symptoms during their infusion. It may come later or maybe very mild, and we think it's nothing but if there are questions, it's important to do that therapeutic direct monitoring so that we can detect the silent inactivation.



You've now drawn the serum ammonia level for this patient who's 24. Her serum asparaginase level is greater than 0.1. Yay. That's our threshold, that's our goal. The serum ammonia level, however, is 130 and the normal range is 29 to 112, so it's high. She's given antiemetics and fluids and her symptoms improve.

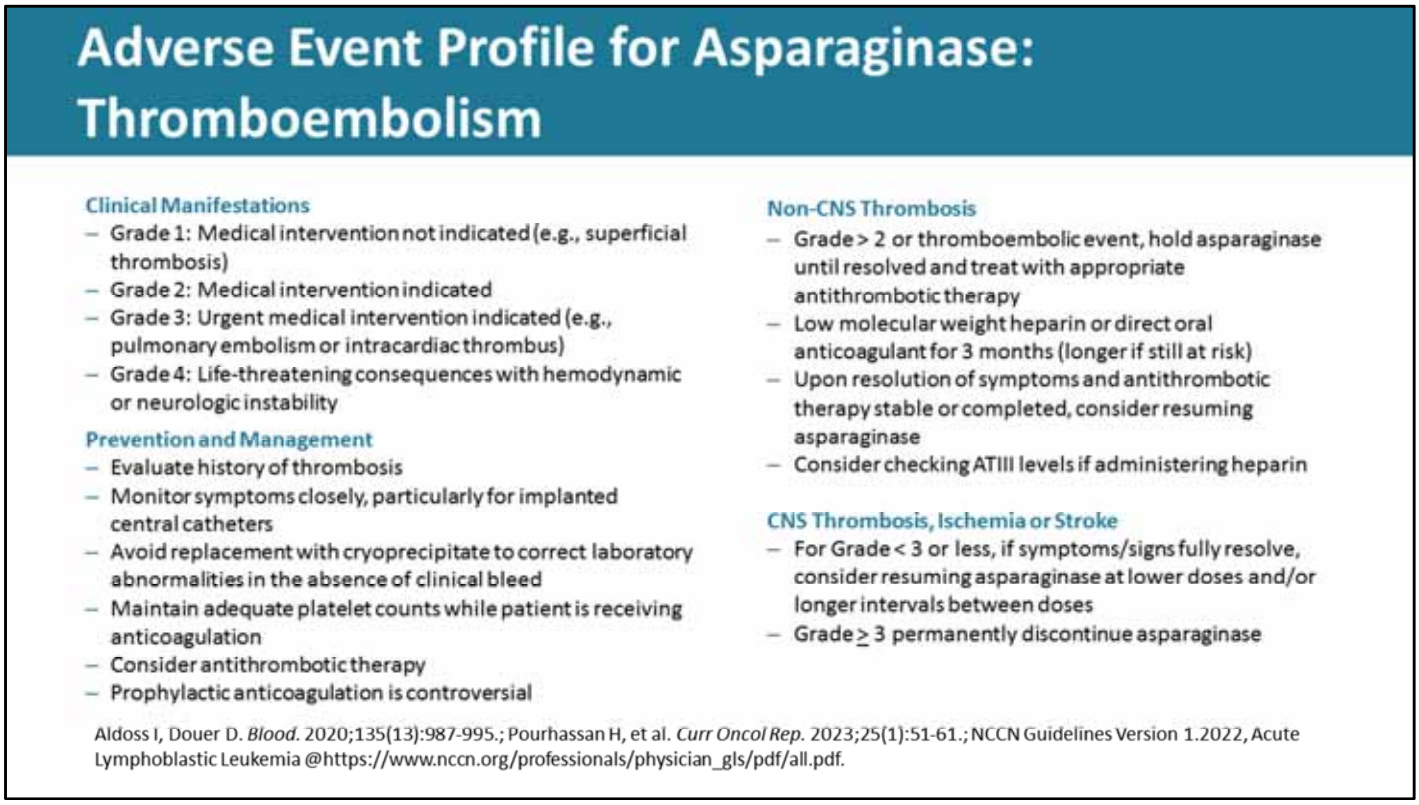


She comes to the clinic for follow-up after her discharge, she's still been in the hospital here. She now has a PICC liner in her right arm, placed her in her hospital stay, and she has swelling and pain. We get a doppler, sure enough, she's got a DVT and she started on low molecular weight heparin and then transition to a direct oral anticoagulant, do a CT to make sure that she doesn't have a PE and that's negative.



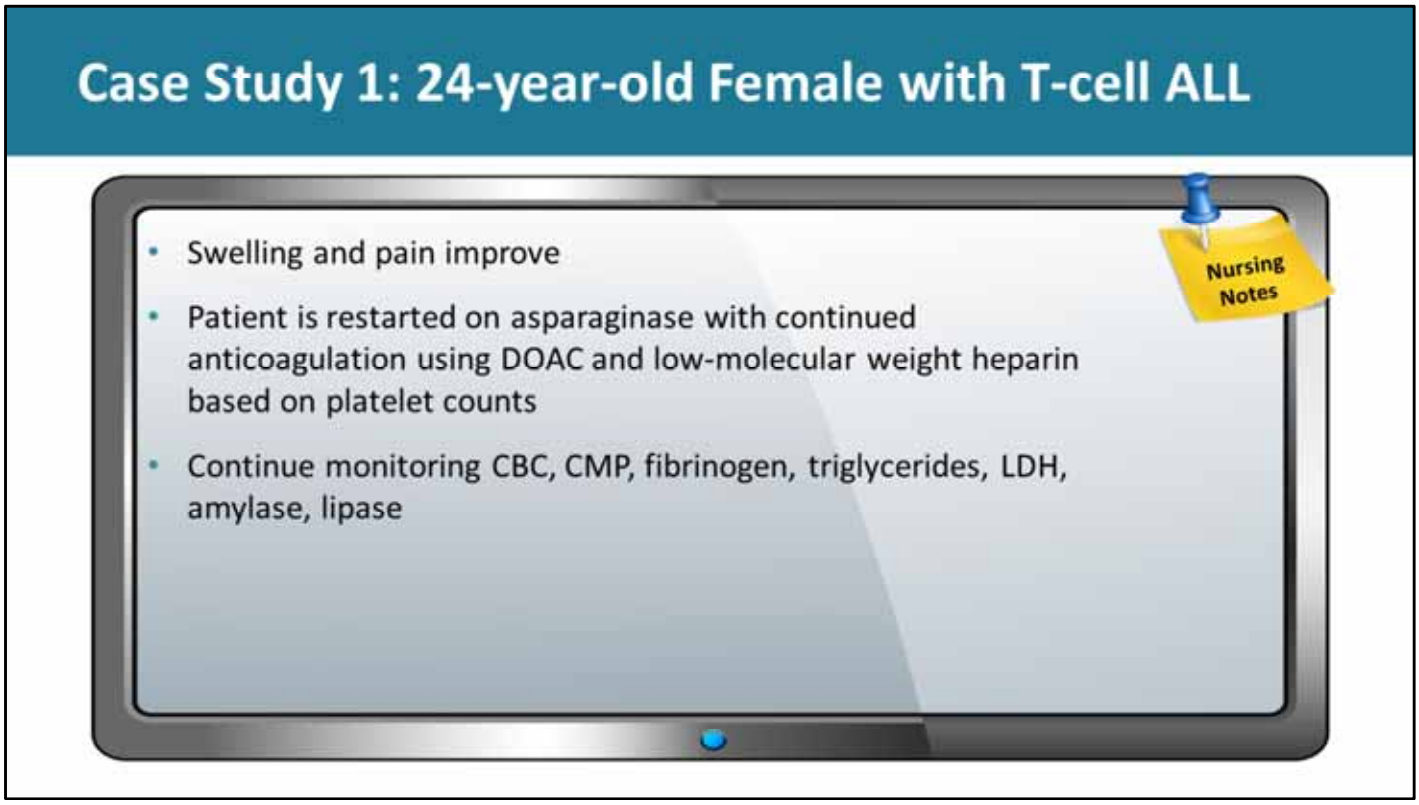
Thrombosis, as I mentioned earlier, is very common in the earlier phases of treatment. These are graded much like all adverse events using the CTCAE grading criteria. Generally, grade one, we just monitor. Grade two, there needs to be an intervention. Grade three and four is more severe. These are going to be more the PEs or intracardiac thrombosis. Grade four is life threatening and or these are neurological thrombi so strokes.

We want to evaluate the history of thrombosis in those patients. They may need prophylaxis. There's some work nationally, internationally about who's at risk and should we put them on prophylaxis in those early stages of therapy. That's not in the guidelines at this point. Monitoring them very closely, particularly if they have a line. In those patients who develop low fibrinogen levels, the treatment for that is cryoprecipitate because it contains clotting factors. If somebody has a clot, you do not want to be giving them clotting factors. Understanding their fibrinogen level during this process is really important. Remember this is combination therapy, so we just talked about Adriamycin. They can also get Cytoxan. Those drugs can cause myelosuppression and cytopenia so if they're on an anticoagulant, that you have to monitor their platelet count closely. It gets to be pretty complicated in these early phases of therapy.

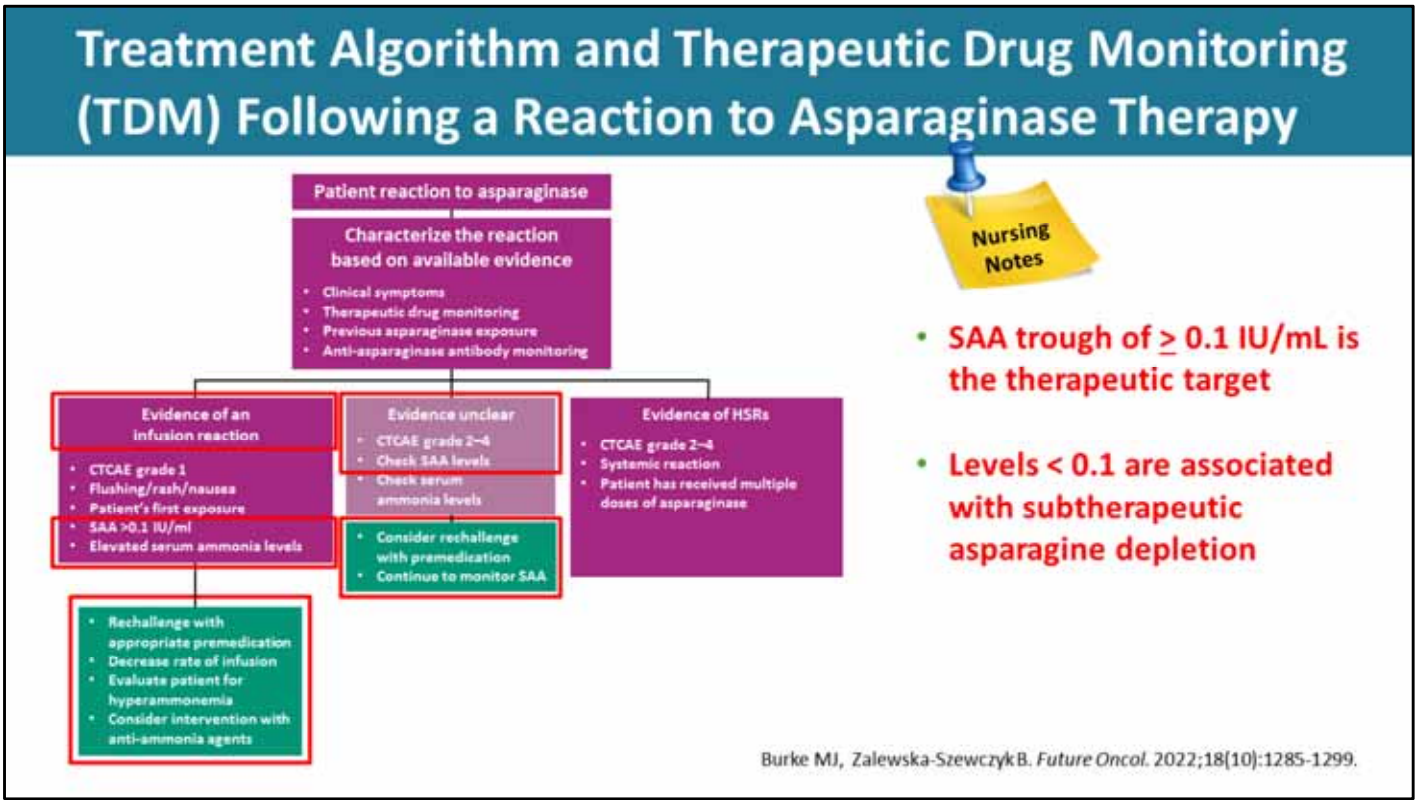


Then for non-CNS thrombosis, grade two or greater, DVT or even a PE, we start them on a low molecular weight heparin and then transition to a direct oral anticoagulant and then we can upon resolution of those symptoms, consider resuming asparaginase. We would continue the asparaginase. It's not a reason to stop indefinitely, but it is something where we're going to monitor them very closely.

If they have CNS thrombosis or ischemia or a stroke, if they're less than grade three, it's mild, we may consider resuming. If it's grade three or greater, we permanently discontinue asparaginase. Really important to monitor these patients closely for thrombosis.



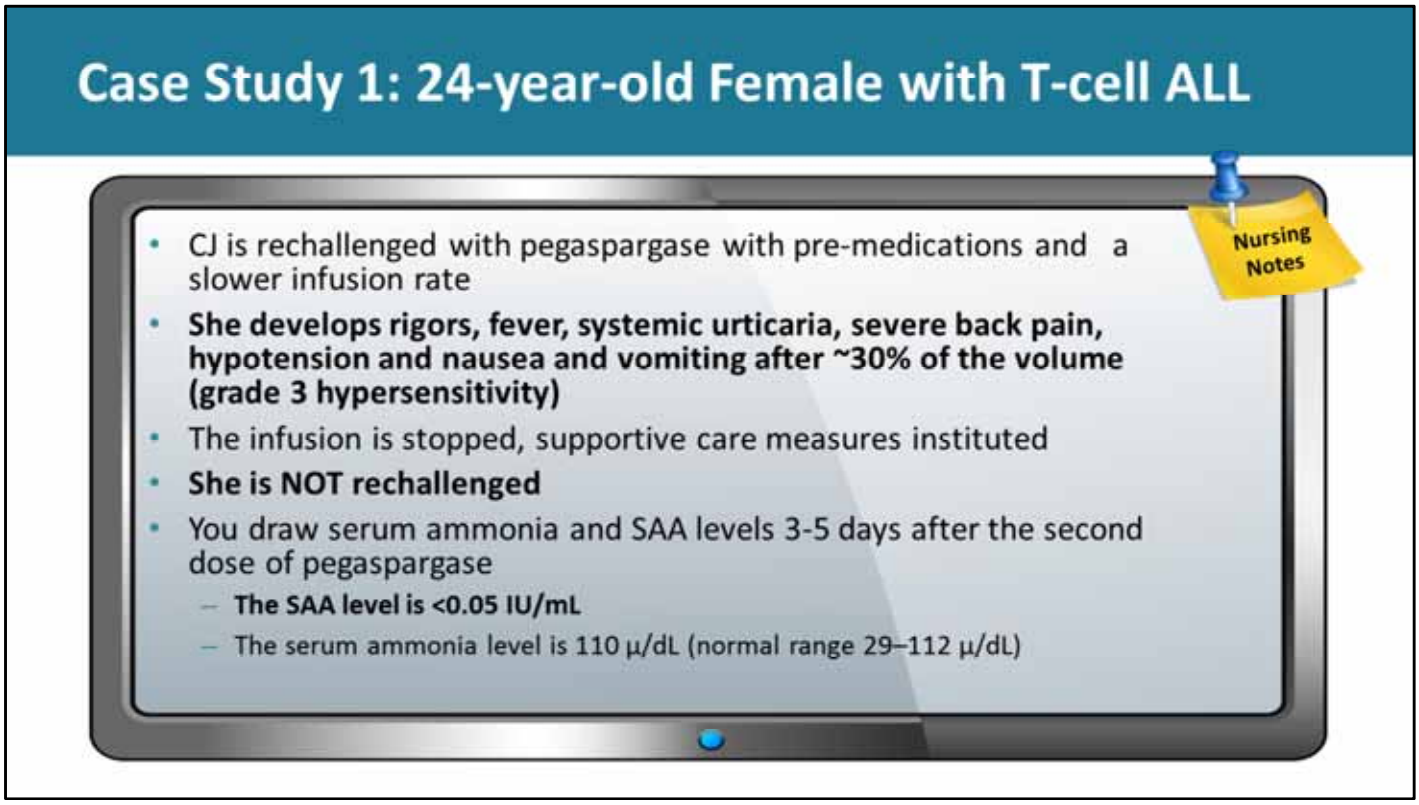
Our patient has started on anticoagulation. Her pain and swelling have improved. She resumes her asparaginase, but continues her anticoagulation and we're going to continue to monitor all of the labs that I've mentioned.



This is an algorithm. This is a really great paper that speaks to silent inactivation and therapeutic direct monitoring.

This algorithm is a little bit complicated. I won't spend a lot of time on it, but I think the idea here is if you have a question of hypersensitivity, the idea is that you're creating antibodies against asparaginase and then that asparaginase level may be subtherapeutic because now you've produced antibodies in your system, which is what happens when you're having drug reactions hypersensitivity or I should say, infusion reactions.
We we're going to measure that. If it's greater than 0.1, that's good. That means there's a therapeutic level. We're going to continue to monitor. We're going to also evaluate that ammonia level.

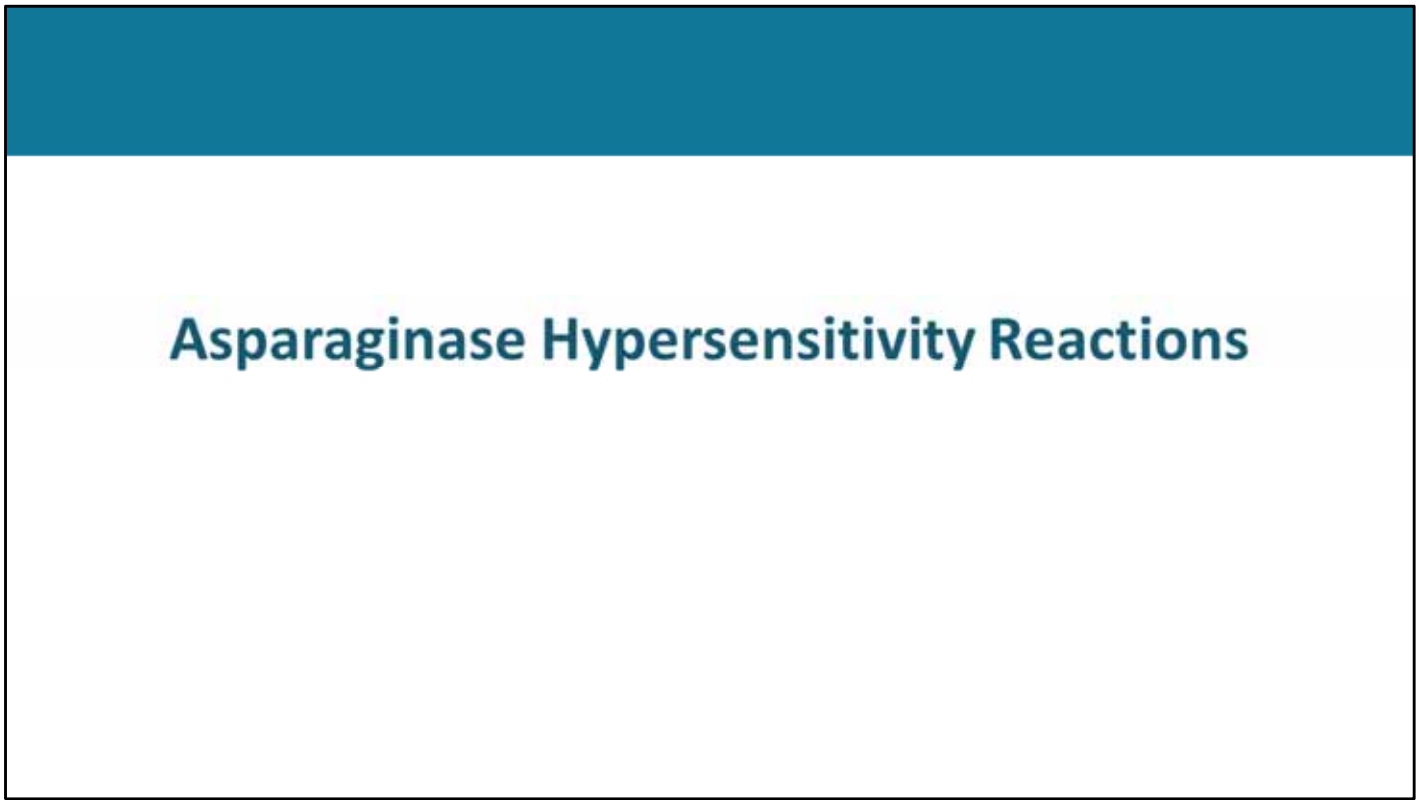
If the reaction is more severe, more antibodies, we're going to again check that level and then really decide how severe it was and whether they should be re-challenged based on that level of severity and obviously up those pre-meds.



She's re-challenged with PEG-asparaginase, but she develops now rigor's fever, systemic urticaria, severe back pain, hypotension, nausea, vomiting after just 30% of the volume. She's now a grade three because we now have more than one organ system involved. It is stopped and she's not going to be re-challenged. She's grade three or greater.

You're going to draw again, a serum ammonia level because anytime there's a reaction, you have to really understand, is there a high ammonia level? Is she subtherapeutic? We're going to draw a serum ammonia level and also draw an asparaginase level.

That level is less than 0.05. Below our threshold, which was 0.1, and her ammonia level is 110. It's normal. We can't really blame it on the ammonia. What we are seeing here really is subtherapeutic asparaginase levels or silent inactivation.



Let's talk more about hypersensitivity.

Differentiating Infusion Reactions and Hypersensitivity

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

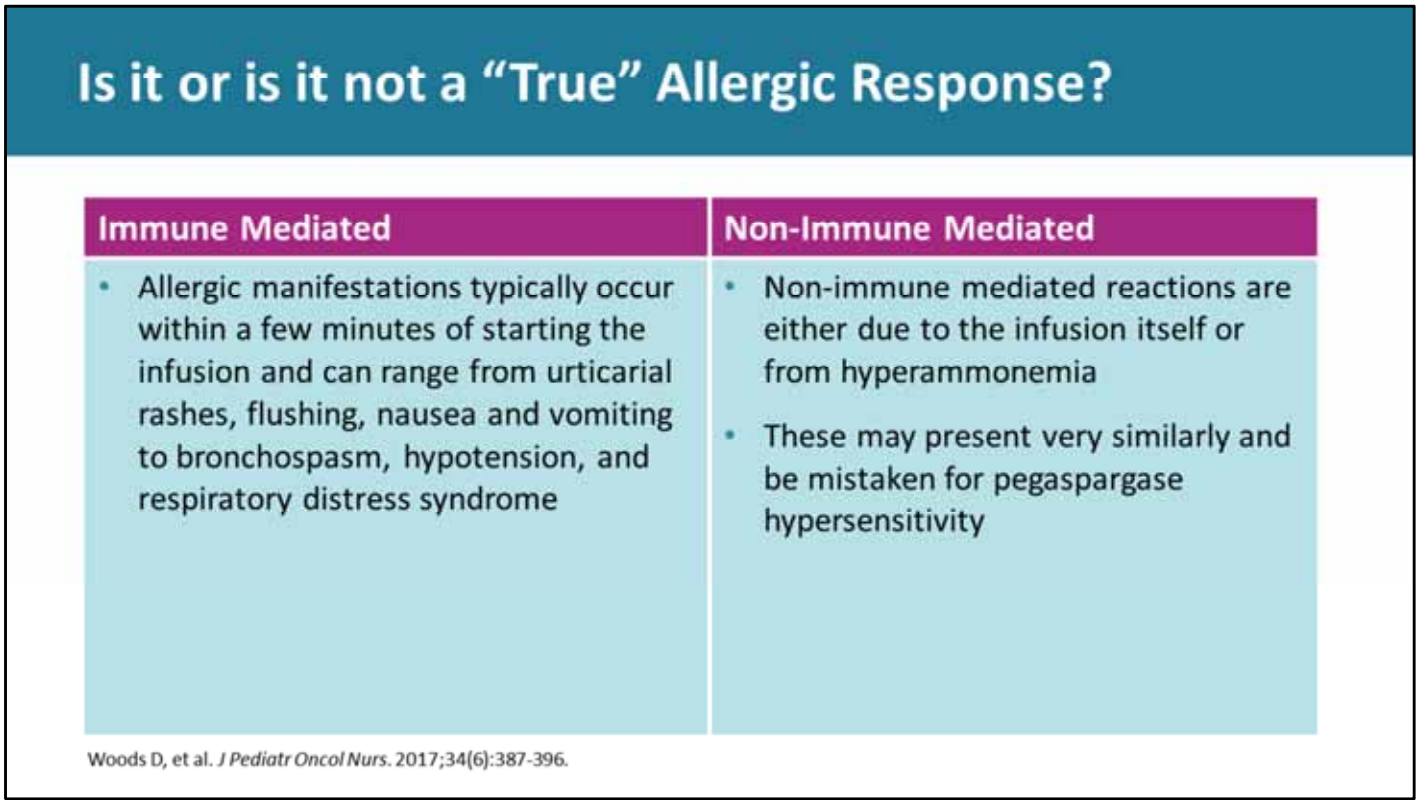
TDM = Therapeutic Drug Monitoring

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

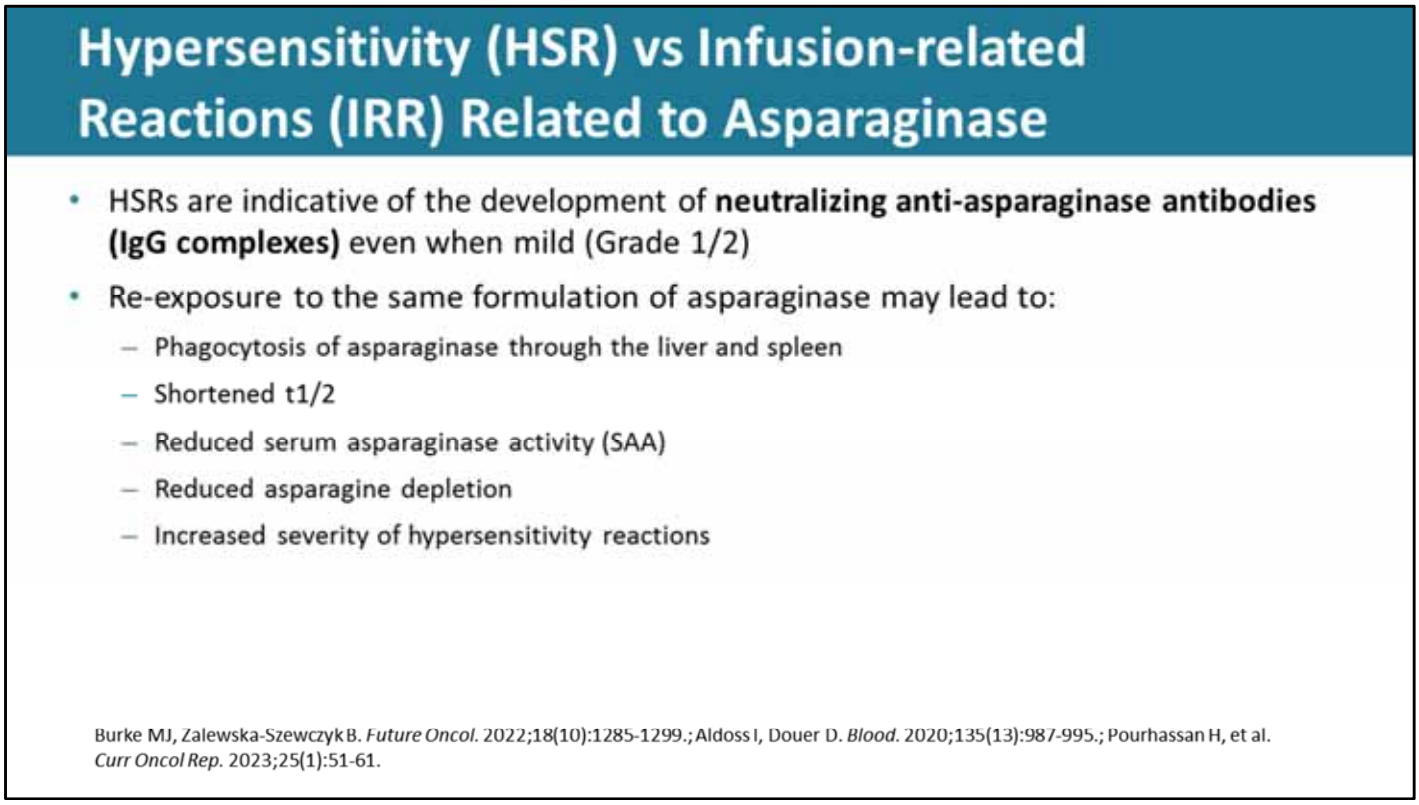
Just differentiating infusion reaction, allergic reaction, silent inactivation, and hyper ammonia. Again, some of these are antibody-mediated. If you think about antibody-mediated, that's the potential to produce antibodies to asparaginase.

Again, you're going to need to check for that silent inactivation. Silent inactivation patients do develop these antibodies and they may not have signs or symptoms. Even in mild reactions, you're going to need to question this and monitor that for those patients who may not be reaching therapeutic levels. We talked about how important that is over time in the very beginning of this.

This therapeutic drug monitoring is really critical in these patients who may have either mild or more severe symptoms, where you're going to look for high ammonia level. If that's negative, definitely serum asparaginase levels to look for silent inactivation.



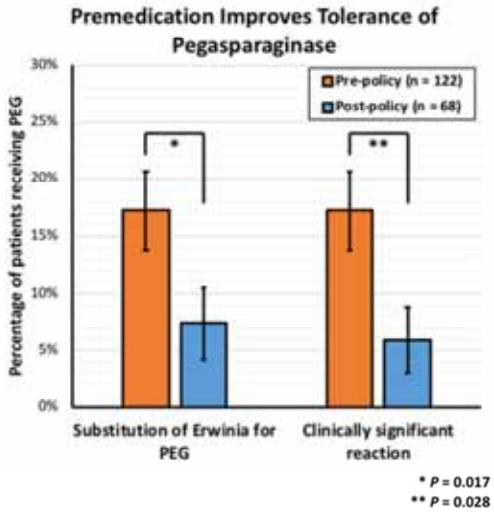
Then there's immune-mediated versus non-immune mediated. Again, those immune-mediated is where you're forming those antibodies, and the non-immune mediated are things like the hyperammonemia where it may mimic some of those symptoms that you think about, but it's really that breakdown of asparaginase.



Hypersensitivity reactions are indicative of the development of these neutralizing antibodies to asparaginase, as I mentioned, and re-exposure to the same formulation can lead to phagocytosis of asparaginase. You're just breaking it down so you're not getting therapeutic levels. You have a shorter half-life. You have lower asparaginase activity, so that less than 0.1. It reduces the asparagine depletion. More asparagine means more leukemia. Again, increases the severity of hypersensitivity reactions.

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

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



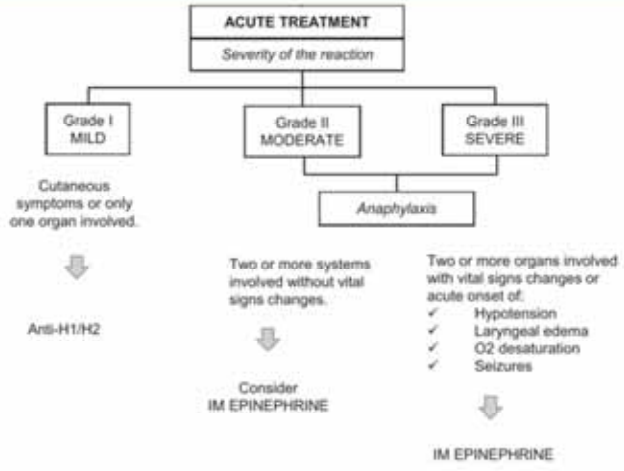
Burke MJ, Zalewska-Szewczyk B. *Future Oncol.* 2022;18(10):1285-1299.; Aldoss I, Douer D. *Blood.* 2020;135(13):987-995.; Pourhassan H, et al. *Curr Oncol Rep.* 2023;25(1):51-61; Cooper et al. Pediatr Blood Cancer. 2019 Aug; 66(8): e27797.

This is just looking at that premedication. It can reduce the risk of hypersensitivity, but it may mask those mild or even moderate reactions. For those patients who are heavily premedicated, we also need to consider just measuring those SAA levels to know that we are achieving therapeutic dosing.

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

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

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



Then we move on to, how do we prevent this? I think we're all pretty good at this. We're so used to giving monoclonal antibodies and all of the things that are associated- taxanes, platinums that are associated with hypersensitivity.

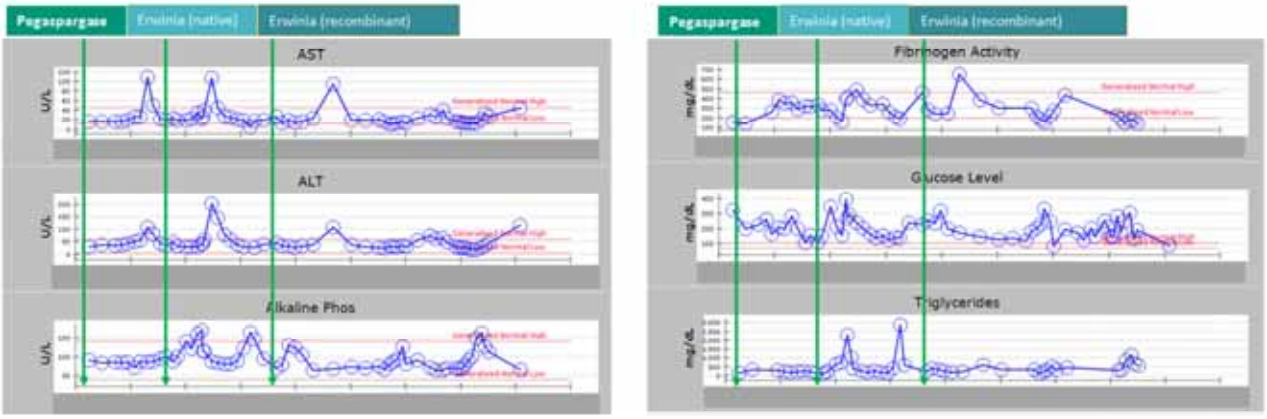
I think what's really important is just know the patient, know the plan, what's the risk of hypersensitivity, pre-medicate. In this case, know that you may also want to check for the SAA levels because that might mask those antibody or hypersensitivity reactions and the antibody formulation or formation.

Then have a plan. Have your intervention plan, rapid response team, whatever, standing orders in your center to be able to intervene quickly. Stop the infusion, give the meds, call for help. All the things that we know how to do.

In severe hypersensitivity, the thing that kills people are airway symptoms and this is where you need to move on to epinephrine in the more severe cases to protect that airway.

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

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



This is our 24-year-old female with T-cell ALL. She's moved to asparaginase Erwinia chrysanthemi because of the reaction to the PEG-asparaginase. Actually, it first started Erwinia native because it was that time and the Erwinia recombinant was not ready yet. This is just showing you that transition.

You see here, the liver enzymes, these big spikes as those drugs are introduced, but they resolve. They have these big peaks after the dose and then boom, a few days after the dose, but then resolve. Similarly, the fibrinogen activity is depleted. You can see it resolves on its own generally. Glucose levels can be very much elevated because of the asparaginase. Also, there's concurrent prednisone here, but they also generally resolve spontaneously. Then similarly, triglycerides can have a big peak and then resolve spontaneously.

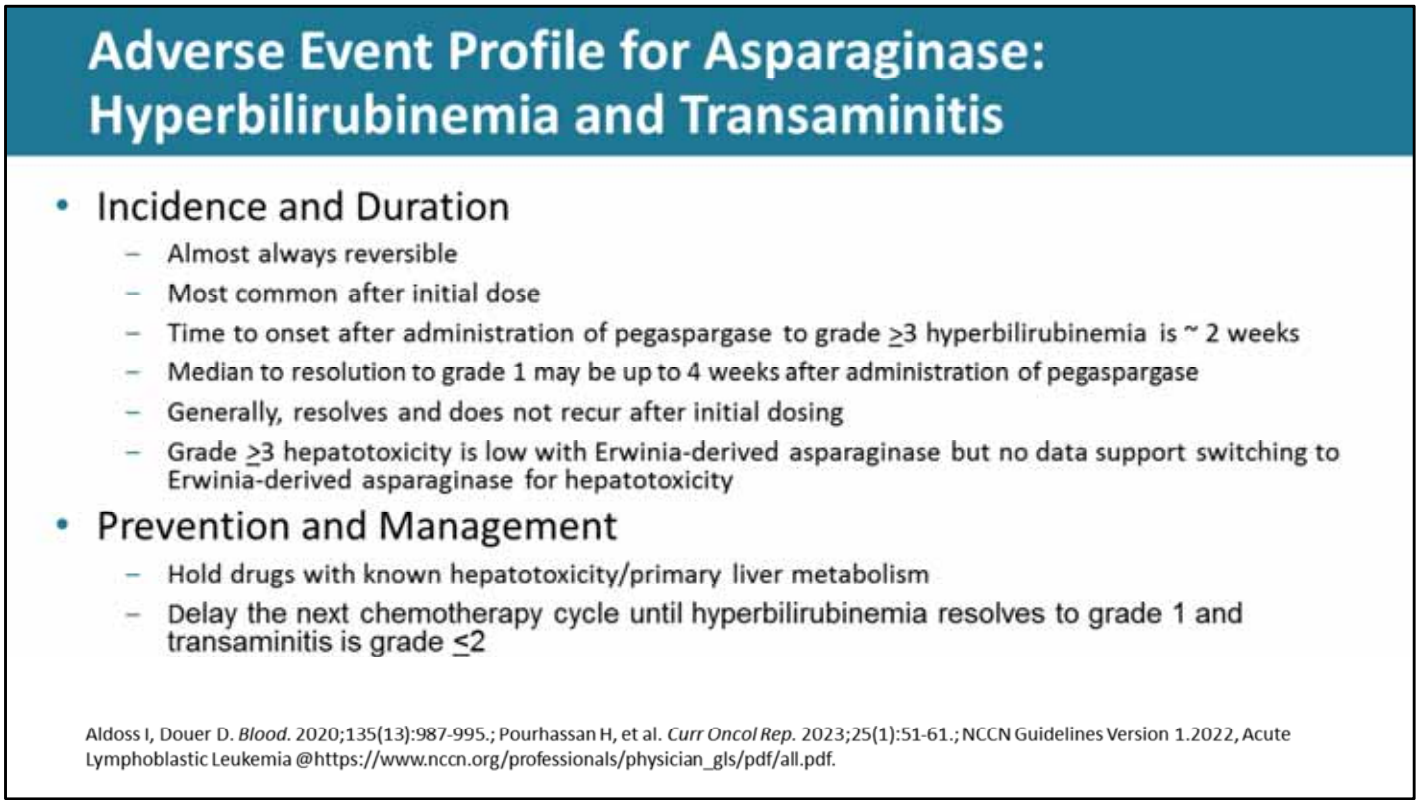
We do need to monitor these, but in most cases, these are not a reason to discontinue therapy.

Adverse Event Profile for Asparaginase: Hyperbilirubinemia and Transaminitis

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

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

Hyperbilirubinemia, grade three or greater is three times the upper limit, or 3 to 10 times the upper limit of normal. This is up to almost 40% of the adults treated. Transaminitis is common. You can see that risk factors, the induction cycle, so that initial exposure to the drug, even when we change drugs, that can happen. I just showed you that example. Higher doses of asparaginase, then other risk factors for the liver, obesity, low albumin, low platelet count, and then those polymorphisms that I mentioned previously.



It's almost always reversible as I mentioned. It's most common after the initial dose of these individual drugs. Time to onset is about two weeks. You saw it was a little bit of a lag after exposure where that would bump up and it can take up to four weeks to resolve. We do monitor those over time. Really important. What's very important though, is to look at what are the drugs are they taking? Are they hepatotoxic?
Do we make adjustments to their concomitant meds? Then you're going to just delay their therapy until that resolve to grade one or less and then resume. It's not by itself a reason to discontinue therapy.

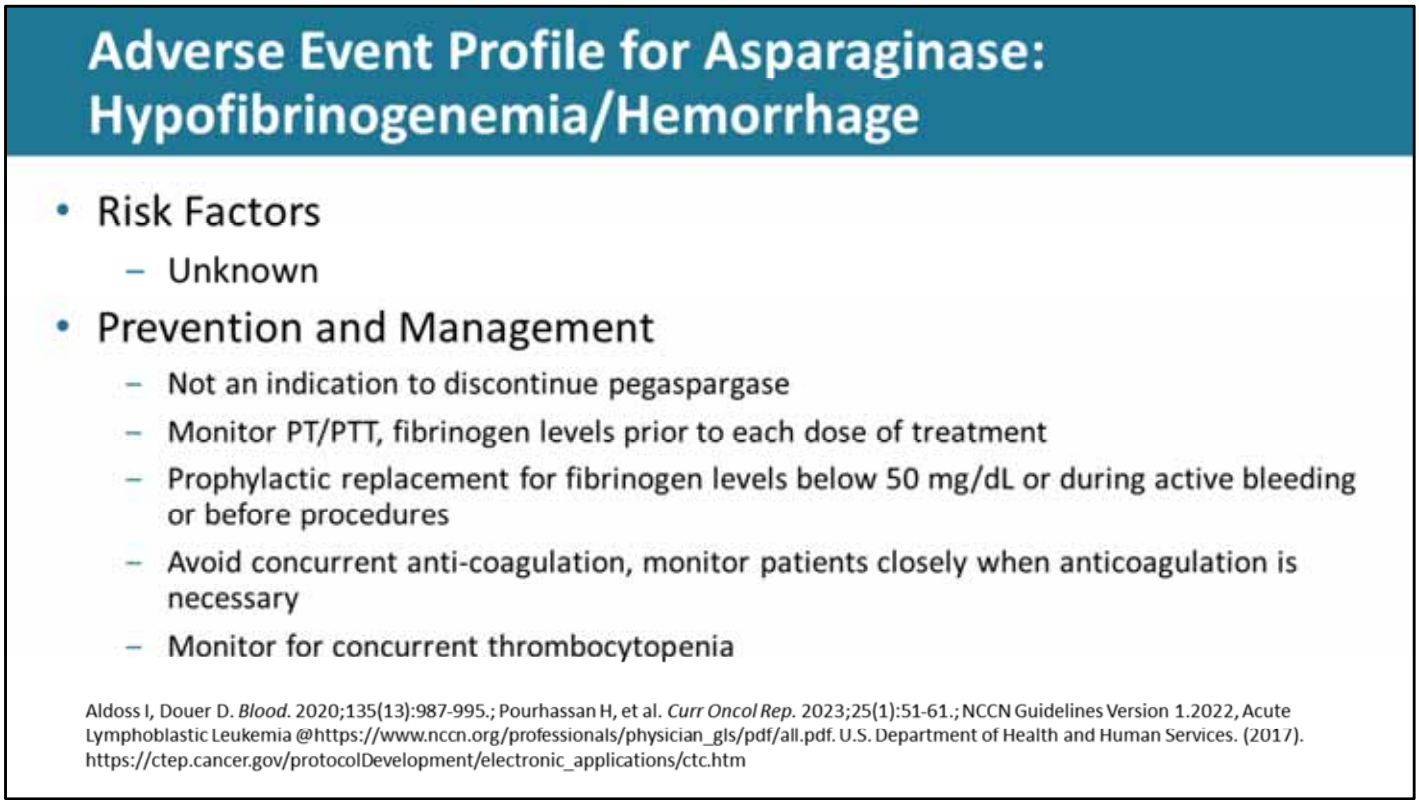
Adverse Event Profile for Asparaginase: Pancreatitis

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

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

Then when we look at pancreatitis, this again, there are risk factors, older age, Native American ancestry, higher cumulative doses, so continued exposure and those specific asparaginase formulation.

In this case, we're going to treat the pancreatitis, which is generally supportive care and really limiting other drug exposure. If it's only a grade two and radiological findings only, we may reintroduce the drug, but anything more than that, and we discontinue it permanently. Because this can be serious and life-threatening. Pancreatitis is one of those where even if it resolves over time, we're not going to re-expose them to asparaginase.



Then hypofibrinogenemia or hemorrhage, less fibrinogen, higher risk of bleeding. Also, not an indication to discontinue therapy. We are going to monitor those patients. That would include measuring that fibrinogen level, PT/PTT prior to each dose. If it's too low, we might pause and let that resolve, but also we're going to measure it after the dose. If it's less than 50, we're going to consider giving cryoprecipitate. Again, that contains clotting factors. Then monitor for that concurrent thrombocytopenia.

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

Hypertriglyceridemia, all the things we normally think about, diet, obesity, comorbidities like diabetes are going to increase that risk.

Adverse Event Profile for Asparaginase: Hypertriglyceridemia

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

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

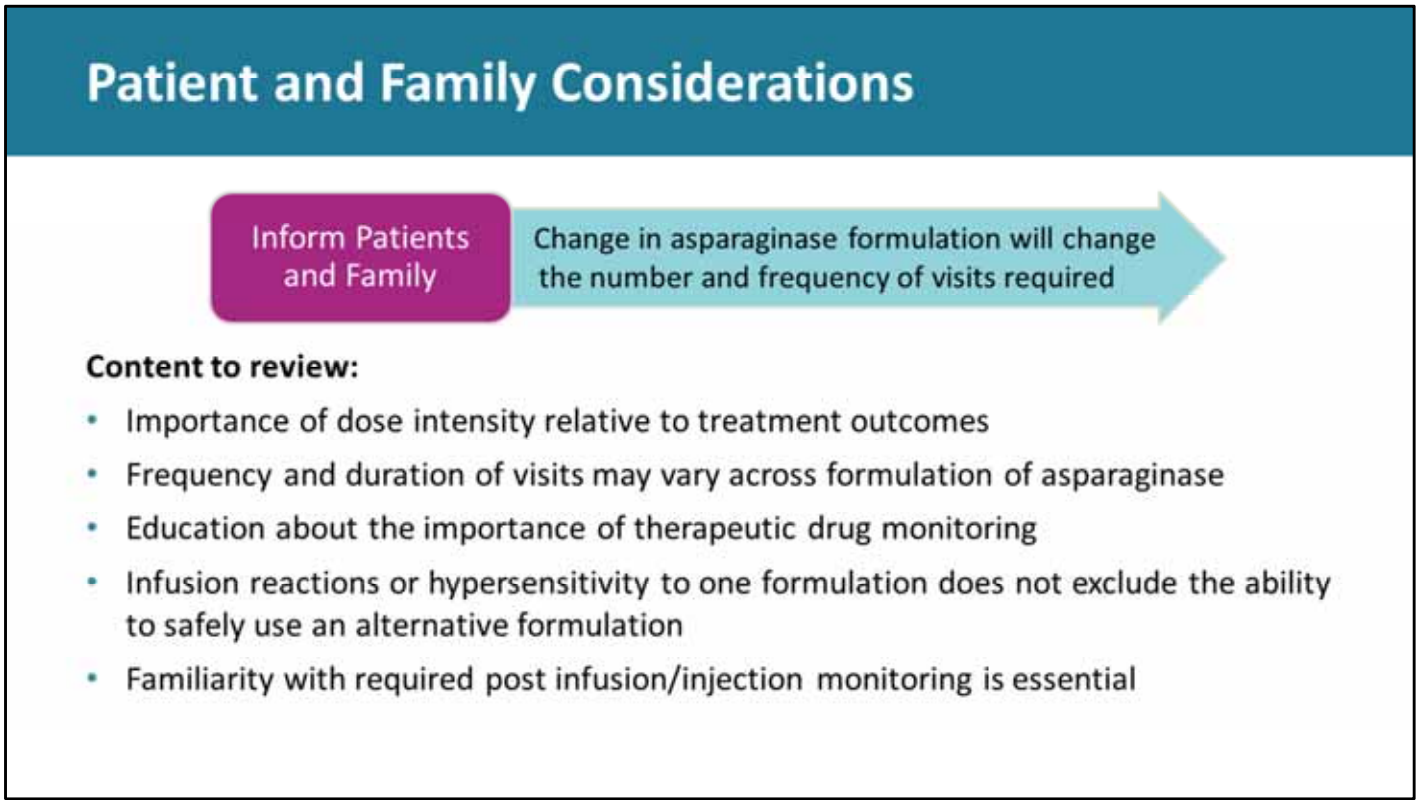
We're just going to basically use diet and exercise. We're also going to monitor those patients for pancreatitis, because those two things are related. Then we give drugs specifically triglyceride drugs, not cholesterol, but triglycerides. The fibrates, fenofibrate or gemfibrozil are really our most commonly used drugs.
Again, if it's significantly elevated, we may hold the drug temporarily or delay the next dose until that's normalized, but not discontinue permanently.

Adverse Event Profile for Asparaginase: Hyperglycemia

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

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

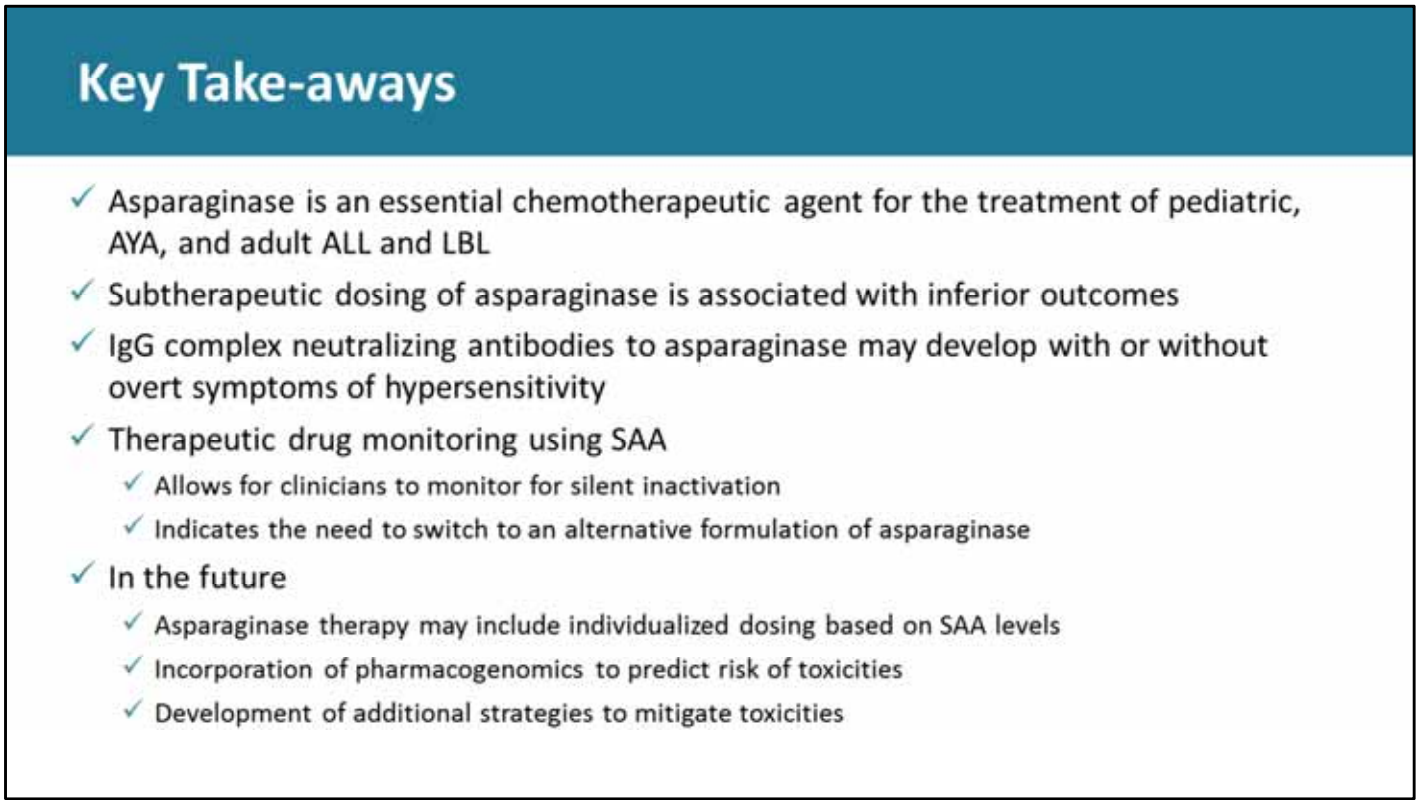
Hyperglycemia. Again, preexisting makes sense if they already have diabetes, concurrent steroids, which are very much a part of these regimens. Avoid simple sugars. If they're on diabetic medication, they may need to adjust that. If they're on an oral antidiabetic, they might need to start insulin during this time. Then we're going to really monitor them after each dose of asparaginase. We can continue therapy, it's not a reason to discontinue.



What are we going to talk to patients and family members about? This is complicated. It's a huge commitment.

It's really difficult for people to work during those initial months of therapy. It's roughly four to six months of therapy. Once they get into the maintenance phase, they get monthly doses of vincristine. Then otherwise, oral drugs. For those people who are T-cell, they get the nelarabine depending on the protocol every third or fourth cycle or month. There's a lot of intrathecal therapy over time. Once they get to maintenance, it's usually every three months. Some people do it every other month, but they can work. Theoretically, they can work, but during that initial phase, it's very, very difficult. They're in, they're out. They can be admitted and discharged. We try to do as much as we can in the outpatient setting, but it's really, really demanding to the patient and to their caregivers.

A lot of education around how important it is to receive all of the therapy on time in the maintenance space. Some of our younger patients are like, "I am over this." It's hard to get them to show up. Instilling a little bit of healthy fear and that this is cancer and we want you to have the best outcome. In order to do that, I need you to be here. Really being honest about the effect of missing doses is really, really critical.



Asparaginase, essential component of treatment for pediatric, adolescent, young adult, and adult patients with ALL and LBL. Subtherapeutic dosing of asparaginase is associated with inferior outcomes. We know that IGG complex neutralizing antibodies to asparaginase can develop even in mild or asymptomatic reactions and therefore have subtherapeutic levels. To make sure we're getting the dose that we need, we want to do therapeutic drug monitoring for those serum asparaginase levels or serum asparaginase assays and monitor for that silent inactivation. Again, our target greater than 0.1.

In the future, there's really a move and some of the clinical trials are looking at dosing asparaginase according to the serum level. Stay tuned for that. Also looking at pharmacogenomics in terms of risk for toxicities and other strategies to minimize or mitigate those toxicities.

Moderator: Thank you Dr. Kurtin for sharing your valuable teaching and expertise. And with that, we will conclude our program. Thank you again for your participation.