



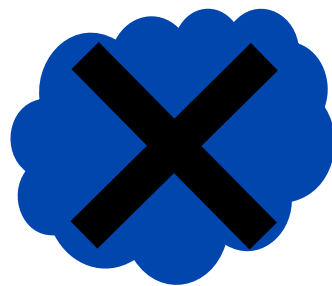
The Curious Case of Asparaginase

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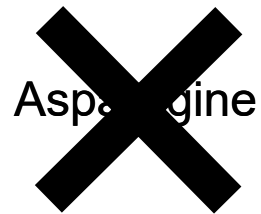
Objectives

- Describe clinical indications of asparaginase
- Review asparaginase formulations and their roles in therapy
- Discuss toxicities and management strategies related to asparaginase therapy

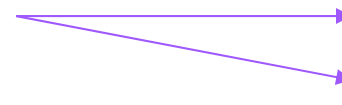
Mechanism



Leukemia cell



Asparaginase



Aspartic acid

Ammonia

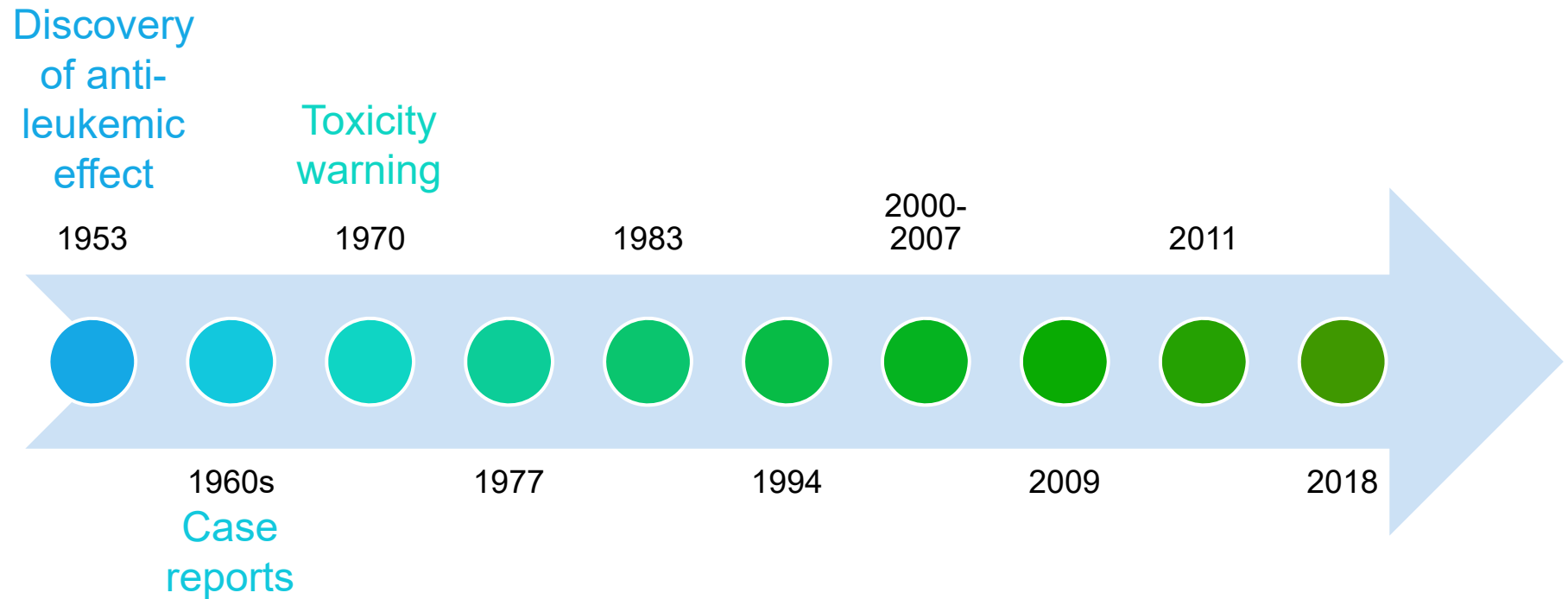


Healthy cell

Indications

- Acute lymphoblastic leukemia/lymphoma
 - Pediatric and adult patients
 - First-line and relapsed/refractory treatment
- Natural killer/T-cell lymphoma

Timeline



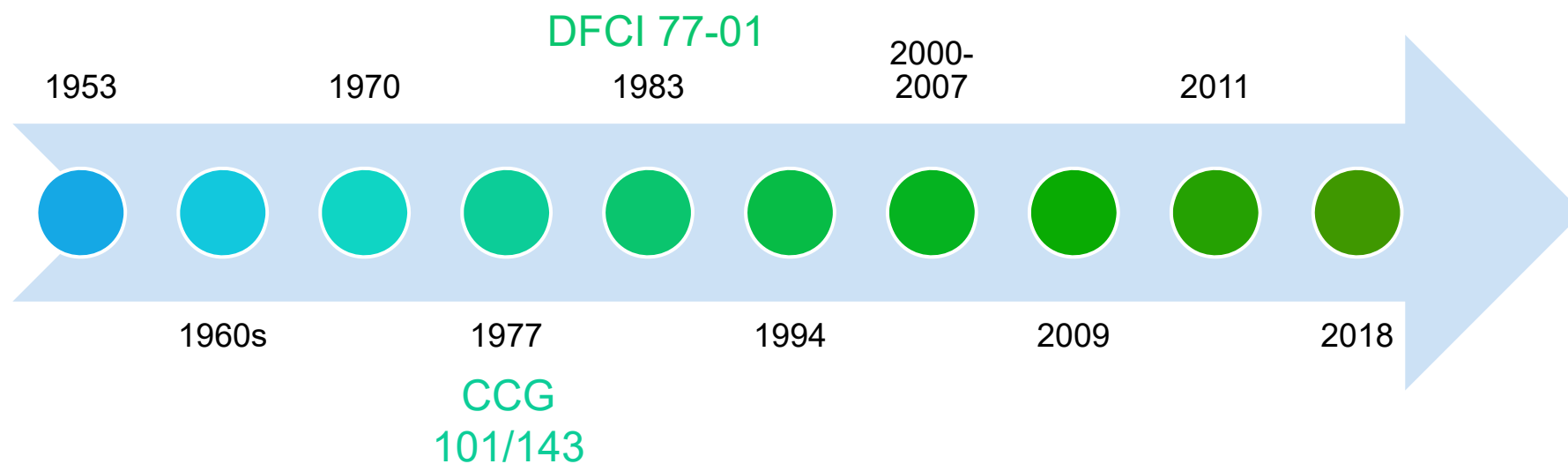
Asparaginase Toxicities in Adults

- 143 adults treated with L-asparaginase
 - Doses ranged from 10 – 5,000 units/kg/day

	No. of evaluated patients	% of patients with toxicity
Abnormal AST	123	63
Abnormal bilirubin	105	51
Hypersensitivity	127	26
Pancreatitis	49	10

- Toxicity occurred most frequently in older patients and patients receiving 5,000 units/kg/day

Timeline





Addition of L-asparaginase in Induction

CCG 101/143

Patients

- <16 years of age with ALL
- Previously untreated

Intervention

- Induction therapy
 - Vincristine and prednisone
 - Vincristine, prednisone, and L-asparaginase

Endpoints

- Overall remission rate
- Toxicities

Addition of L-asparaginase in Induction

	Asparaginase CCG 101/143 N=815	No asparaginase CCG 903 N=499
Remission, No. (%)	758 (93)	429 (86)

	CCG 101/143 No. (%)
L-asparaginase toxicity	35 (4.3)
Hyperglycemia	20 (2.5)
Allergic reactions	6 (0.7)
Acute pancreatitis	4 (0.5)
Hepatotoxicity	1 (0.1)
Discontinuation due to L-asparaginase toxicity	2 (0.2)
Death due to L-asparaginase toxicity	1 (0.1)

L-asparaginase in Intensification

DFCI 77-01

Patients

- < 20 years of age
- Untreated non-T-cell ALL

Endpoints

- Disease-free survival

Induction

Vincristine
Prednisone
Doxorubicin
Asparaginase
CNS prophylaxis

Randomize

Intensification

Vincristine, prednisone,
doxorubicin plus weekly
asparaginase

Vincristine, prednisone,
doxorubicin

Continuation

Vincristine
Methotrexate
Mercaptopurine
Prednisone

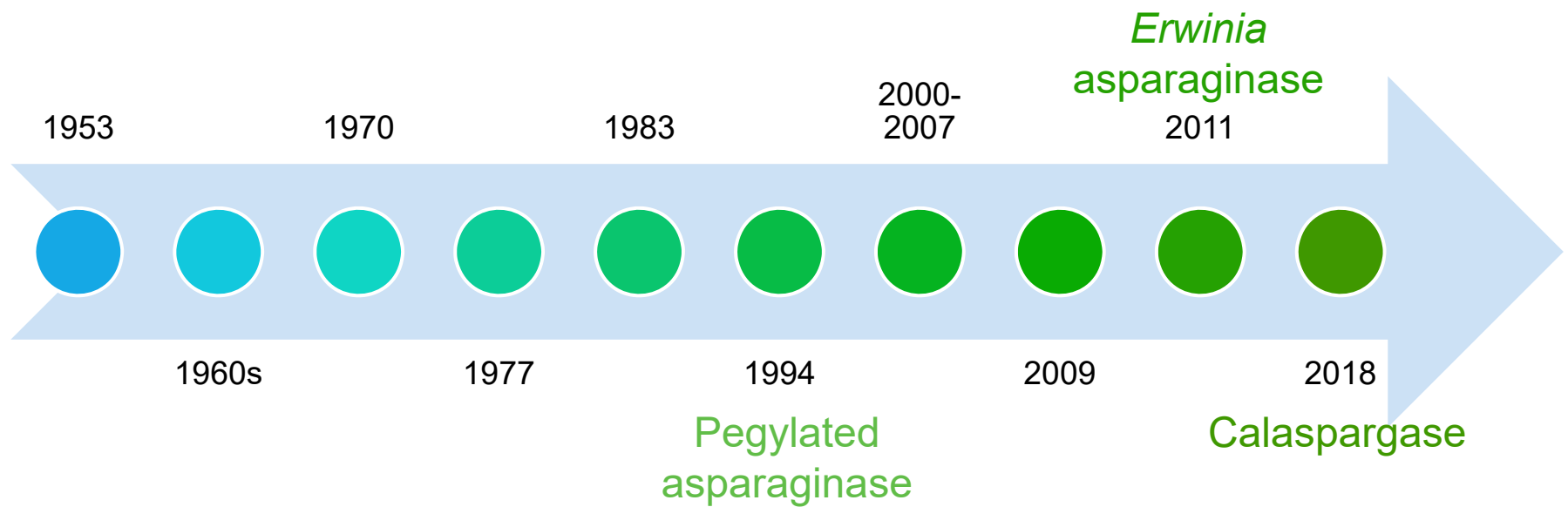
L-asparaginase in Intensification

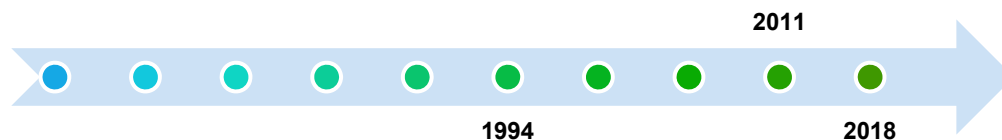
	Induction only N=36	Induction + intensification N=36	P-value
4.75 years median follow up			
Relapses, No. (%)	18 (50)	7 (19.4)	NR
DFS, %	42	72	0.04

Which of the following statements is true?

- A. Asparagine is an essential amino acid for both leukemia cells and healthy cells
- B. Asparaginase has been a main component of adult ALL treatment since the 1970s
- C. There is no association between cumulative asparaginase doses and treatment outcomes
- D. One of the most significant benefits of asparaginase is duration of response

Timeline





Asparaginase formulations

	L-asparaginase
Formulation	<i>Escherichia coli</i>
Half-life	IM: 34-49 hours IV: 8-30 hours
Dosing	6,000 units/m ² IM or IV 3 times weekly
Price of induction	NA
Role in treatment	NA



Asparaginase (ELSPAR) prescribing information. 07/2013

Asparaginase *Erwinia chrysanthemi* (ERWINAZE) prescribing information. 11/2011

Calaspargase pegol – mkn1 (ASPARLAS) prescribing information. 12/2018

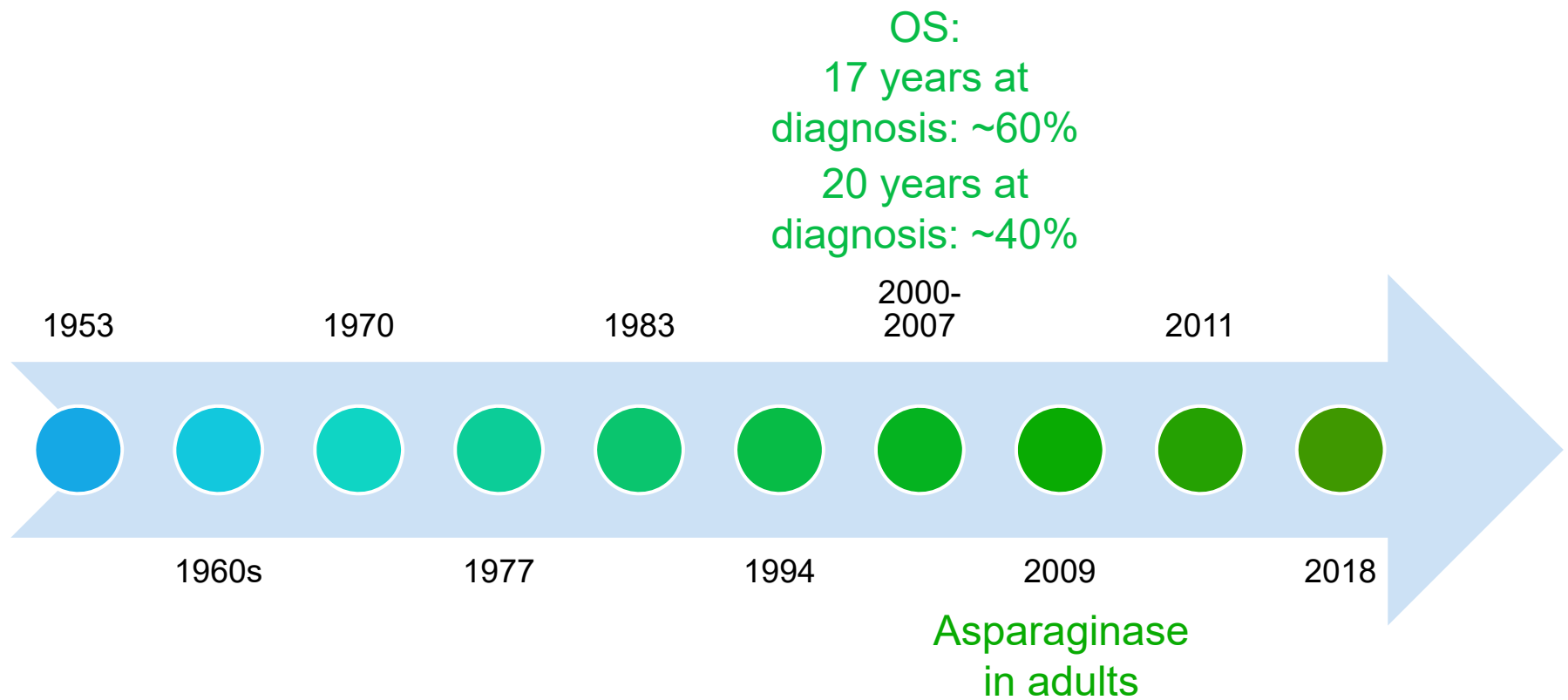
Pegaspargase (ONCASPARG) prescribing information. 03/2011

IM: intramuscular; IV: intravenous; NA: not applicable

Which asparaginase formulation would be the best option in a patient with a history of anaphylaxis with pegylated asparaginase?

- A. *E. coli* L-asparaginase
- B. *Erwinia* asparaginase
- C. Calaspargase
- D. Continue with pegylated asparaginase

Timeline



Asparaginase in Adult Patients

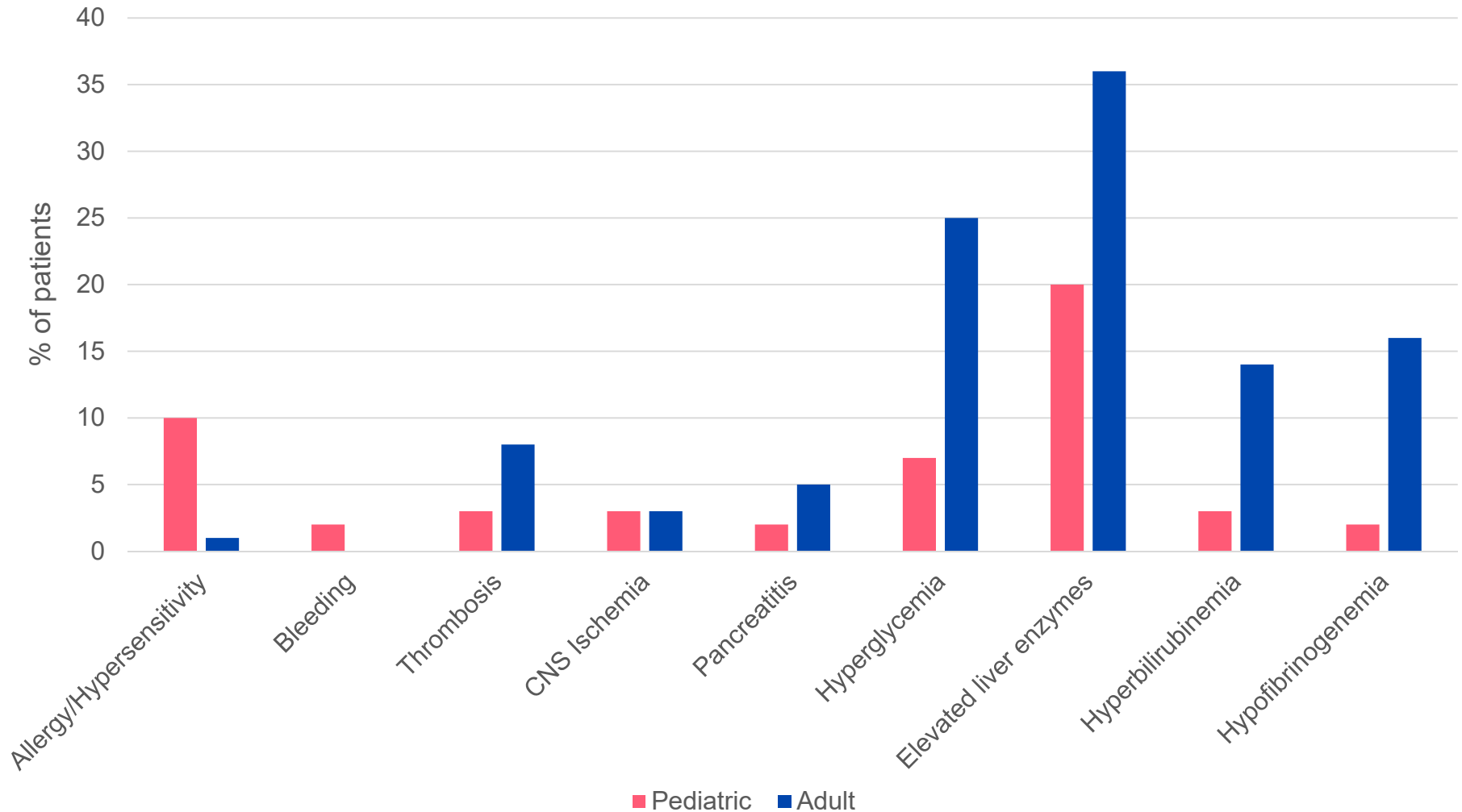
Study	No. of patients	Age range (years)	Formulation and Dose	Survival
GRAALL-2003	225	15-60	<i>E. Coli</i> L-asparaginase 6,000 IU/m ² for 8 doses	42 months: OS: 61% vs. 41%* (p <0.001)
*retrospectively compared to a study using only 1 dose of L-asparaginase				

- Patients >45 years
 - Lower cumulative L-asparaginase doses
 - Delayed time to consolidation therapy
 - Decreased OS

Asparaginase in Adult Patients

- Adult vs. pediatric based regimens
 - Better EFS and OS with pediatric regimens
- Lessons learned
 - Age limits
 - Decreased doses and dose capping

Grade 3-4 Toxicities of Pegylated Asparaginase



Pediatrics (0-18 years): 1,274 patients receiving 6,670 doses
Adults (14-68 years): 76 patients receiving 192 doses

Toxicities

Thrombosis and Bleeding

Hepatotoxicity

Pancreatitis

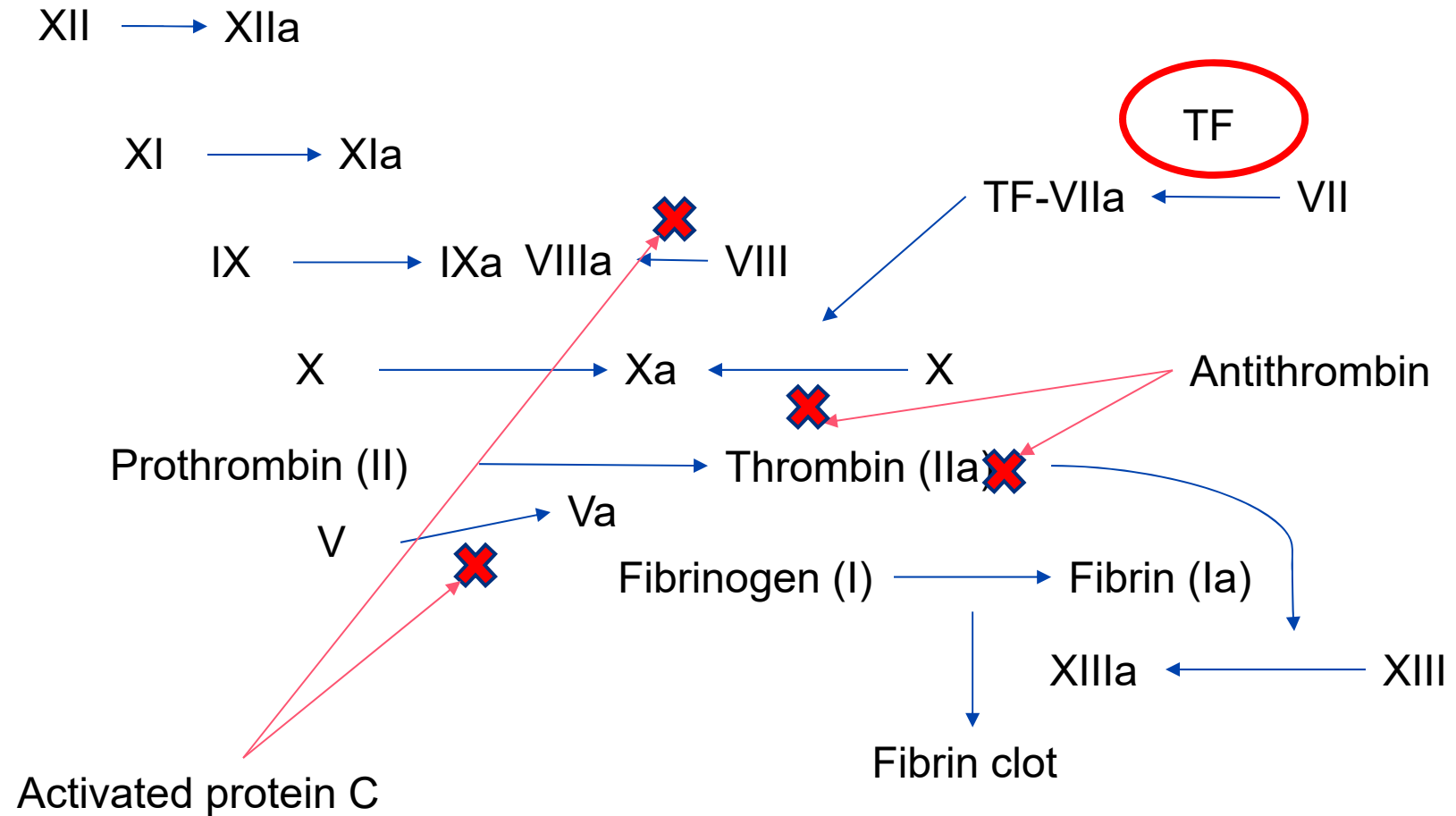
Hypersensitivity

Risks vs. benefits of asparaginase discontinuation

Thrombosis and Hemorrhage

	Grade 2	Grade 3	Grade 4
Non-CNS thromboembolism	Venous thrombosis (e.g. uncomplicated deep vein thrombosis)	Thrombosis (e.g. uncomplicated pulmonary embolism)	Life-threatening
Asparaginase implications	Hold asparaginase. Consider resuming asparaginase after completion of antithrombotic therapy. Consider checking ATIII levels if administering heparin		

Coagulation Cascade



Hemorrhage

- Monitor fibrinogen levels and replete with cryoprecipitate as indicated
- Hold anticoagulants/antiplatelet agents for severe thrombocytopenia

Platelets	Prophylaxis	Treatment
>50,000 x 10 ⁹ /L	Prophylactic dosing	Treatment dosing
30,000-50,000 x 10 ⁹ /L	Hold	Decrease to prophylactic dosing
<30,000 x 10 ⁹ /L	Hold	Hold

Thrombosis Management

- Thromboprophylaxis
 - LMWH
- ATIII monitoring and replacement

$$ATIII \text{ dose} = \frac{(80\% - \text{current ATIII}\%) \times \text{body weight}(kg)}{1.4}$$

ATIII

- Conflicting evidence if ATIII replacement effects thrombosis risk
 - Primarily data from single-center retrospective studies
 - Majority found decreased risk with ATIII repletion
- No difference in thrombosis rates when using replacement threshold of 60% instead of 80%
- \$4.38-\$4.66/unit

Hepatotoxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Transaminitis	AST/ALT > ULN – 3 x ULN	AST/ALT > 3 – 5 x ULN	AST/ALT > 5 – 20 x ULN	AST/ALT ≥ 20 x ULN
Asparaginase implications	Continue asparaginase		Hold until grade 1, then resume	Permanently discontinue

Hepatotoxicity Management

- Due to oxidative stress
- Avoidance of alcohol and other hepatotoxic medications
- Vitamin B complex and L-carnitine for grade 2 transaminitis or grade 3 hyperbilirubinemia

L-Carnitine and Vitamin B Complex

- Data from case reports only
- IV L-carnitine 50 mg/kg/day divided + various formulations of vitamin B complex

Age/Sex	Peak total bilirubin	L-carnitine dosing	Outcome
36/F	11.5 mg/dL	50 mg/kg/day divided in 6 doses	LFTs and bilirubin downtrending on day 2 of treatment
23/M	13.5 mg/dL	75 mg/kg q4h	Bilirubin trending down on day 3 of treatment
56/M	26.6 mg/dL	50 mg/kg/day (no vitamin B complex)	LFTs and bilirubin normalized

Pancreatitis

	Grade 2	Grade 3	Grade 4
Definition	Enzyme elevation or radiologic findings only	Amylase or lipase > 3 x ULN and symptomatic (severe pain, vomiting, interventions needed)	Life-threatening consequences
Asparaginase implications	Continue asparaginase with close monitoring	Permanently discontinue all asparaginase	

Pancreatitis Management

- Unknown mechanism
- Most common reason for asparaginase discontinuation
- Supportive cares
 - Pain control, fluids, nausea/vomiting management
- Immunocompromised and cytopenic

Hypersensitivity

	Grade 1	Grade 2	Grade 3	Grade 4
Definition	Transient flushing or rash, drug fever $<38^{\circ}\text{C}$	Urticaria, drug fever $\geq 38^{\circ}\text{C}$, responds to oral treatment	Symptomatic bronchospasm with or without urticaria, allergy-related edema/angioedema, hypotension	Life-threatening consequences
Asparaginase implications	Continue with same formulation	Consider anti-allergy premedication and TDM	Discontinue asparaginase formulation	

Infusion reactions $\neq$ hypersensitivity

Hypersensitivity Management

- Development of anti-asparaginase antibodies
- Timing of asparaginase with steroids
- Prepare for hypersensitivity/anaphylaxis
 - Steroids, antihistamines, oxygen, and epinephrine
- Change asparaginase product for future doses
 - Pegylated asparaginase to *Erwinia* asparaginase
- Controversial - pretreatment prior to each dose

Anti-Asparaginase Antibodies

- Antibodies result in decreased asparaginase activity and half-life
- Hypersensitivity is associated with undetectable asparaginase activity levels
- Silent inactivation has been estimated at 8-29%

Therapeutic Drug Monitoring

- Measuring asparaginase activity levels
 - Undetectable asparagine = activity level ~ 0.1 IU/mL
 - Reports vary from 0.03 IU/mL – 0.4 IU/mL
- Most studies target 14-day trough ≥ 0.1 IU/mL
- Silent inactivation = activity level < 0.1 IU/mL within 7 days post pegylated asparaginase dose

Therapeutic Drug Monitoring

Trough asparaginase activity levels >0.03 IU/mL vs. <0.03 IU/mL

- OS 31 months vs. 13 months ($p=0.01$)

Median asparaginase activity levels in patients achieving vs. not achieving CR

- 0.75 IU/mL vs. 0.45 IU/mL ($p=0.012$)

Individualized vs. fixed dose asparaginase

- 5-year EFS: 90% vs. 82% ($p=0.04$)

Premedications

Benefits

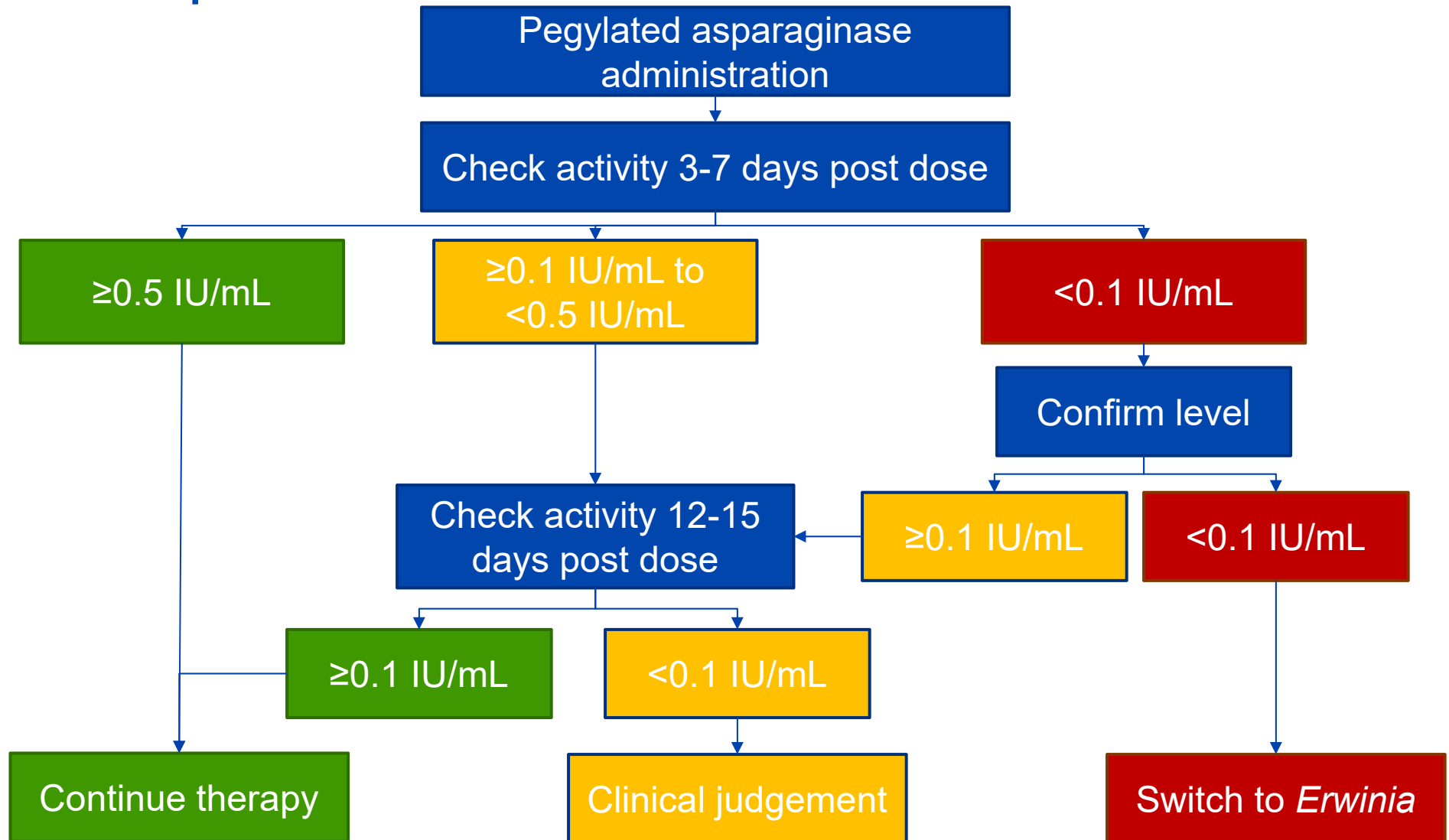
- Decreased hypersensitivity and infusion reactions
 - 15% vs. 4%
- Decreased rates of unnecessary change to *Erwinia* asparaginase
 - 24% vs. 6%

Drawbacks

- Increased risk of silent inactivation
 - Worse outcomes

TDM is recommended for any patient receiving premedication

Proposed use of TDM



Patient Case

- SC is a 21 year old female with ALL. She received her 4th dose of pegylated asparaginase (2,500 units/m² IV capped at 3,750 units).
- An asparaginase activity level is drawn 5 days after the dose and is 0.6 IU/mL.

Which of the following is the most appropriate response to her asparaginase activity level?

- A. SC has silent inactivation and should not receive any further doses of any asparaginase formulation
- B. SC has silent inactivation and should be changed to *Erwinia* asparaginase
- C. The level is inconclusive and should be rechecked again 12-15 days post-dose
- D. The level is appropriate and SC should be continued on pegylated asparaginase

Summary

- Asparaginase is one of the most effective medications for treatment of ALL
- Use of asparaginase requires vigilant monitoring
- Identifying asparaginase-related toxicities is imperative for management
- The use of TDM is expanding and there is growing literature to support its use