

Management of Acetaminophen Toxicity: Current Evidence-based Recommendations and Alternative Antidotal Therapies

A Presentation for HealthTrust Members
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Learning Objectives for Pharmacists

Recall

current evidence-based recommendations for managing acetaminophen toxicity.



Recognize

the role of fomepizole in massive acetaminophen toxicity



Identify

alternative off-label regimens for use of N-acetylcysteine in the treatment of acetaminophen poisoning.



Learning Objectives for Pharmacy Technicians

Recall

current evidence-based recommendations for managing acetaminophen toxicity.



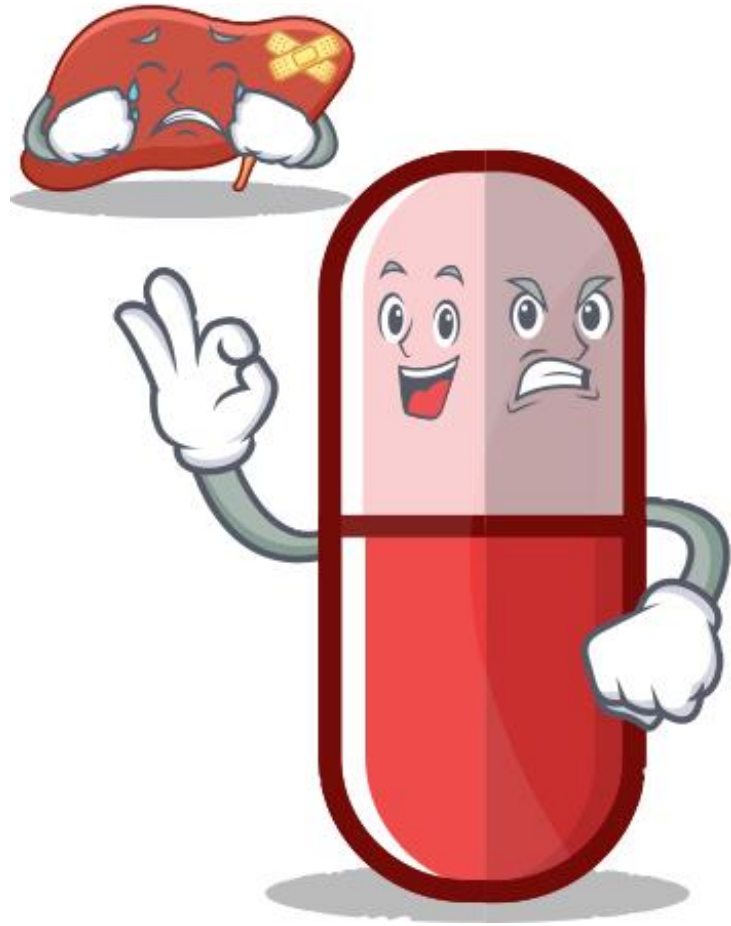
Identify

preparation and storage requirements for fomepizole in massive acetaminophen toxicity.



Recognize

preparation and storage requirements for N-acetylcysteine in the treatment of acetaminophen poisoning.

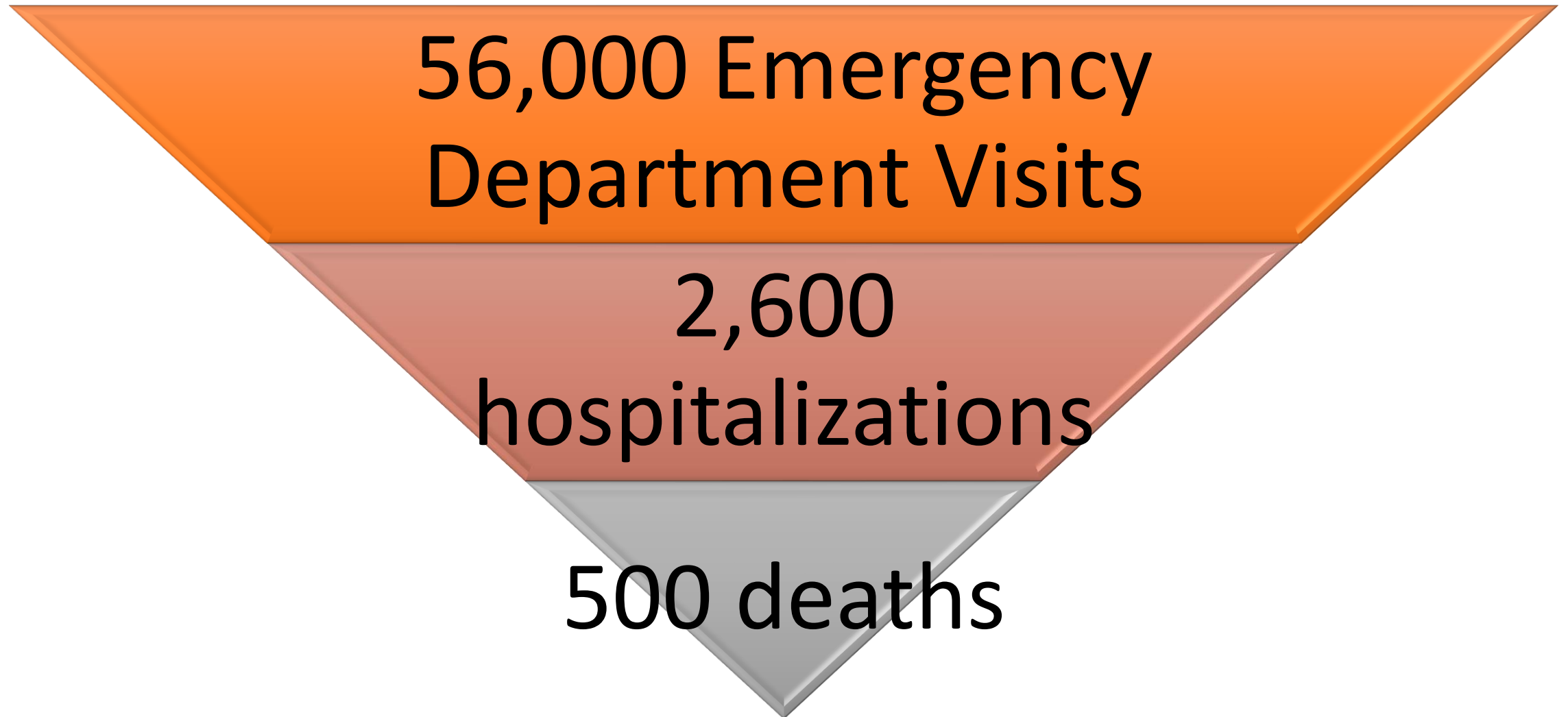


Acetaminophen Toxicity

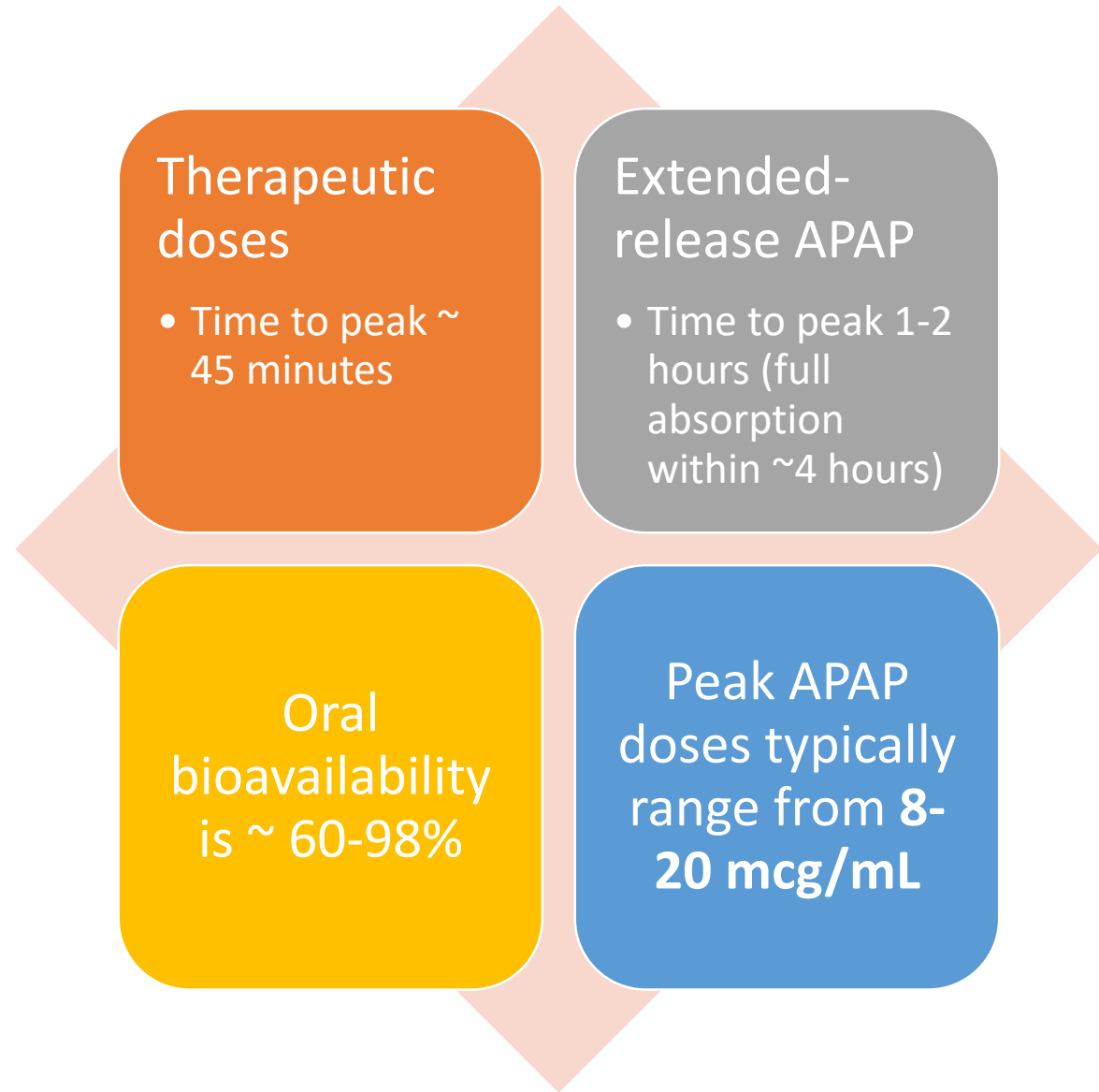
Case Study

- MH is a 39-year-old female
- Presents with **unknown** acetaminophen ingestion
- What do we do next?

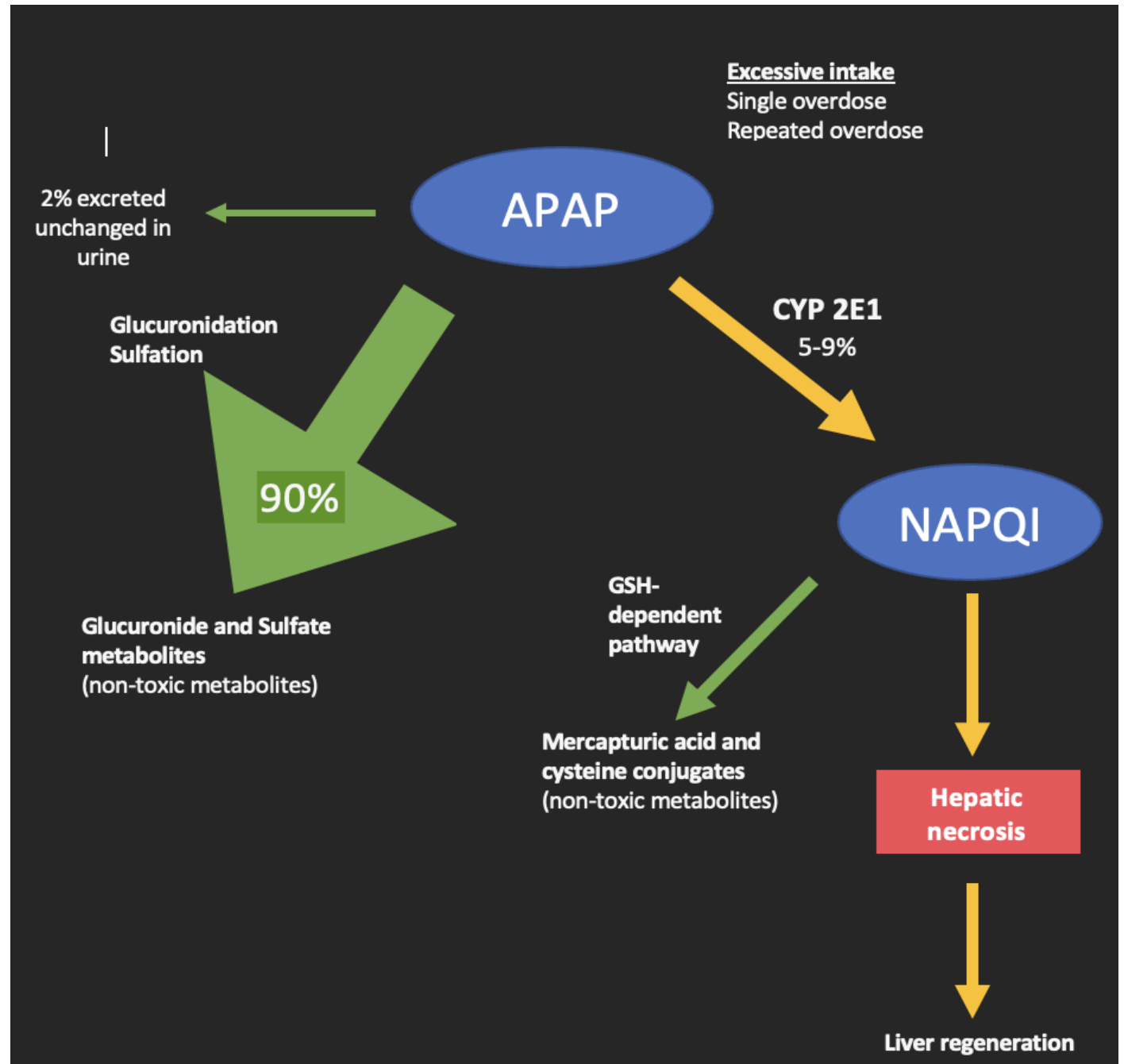
Epidemiology



Therapeutic Ingestion

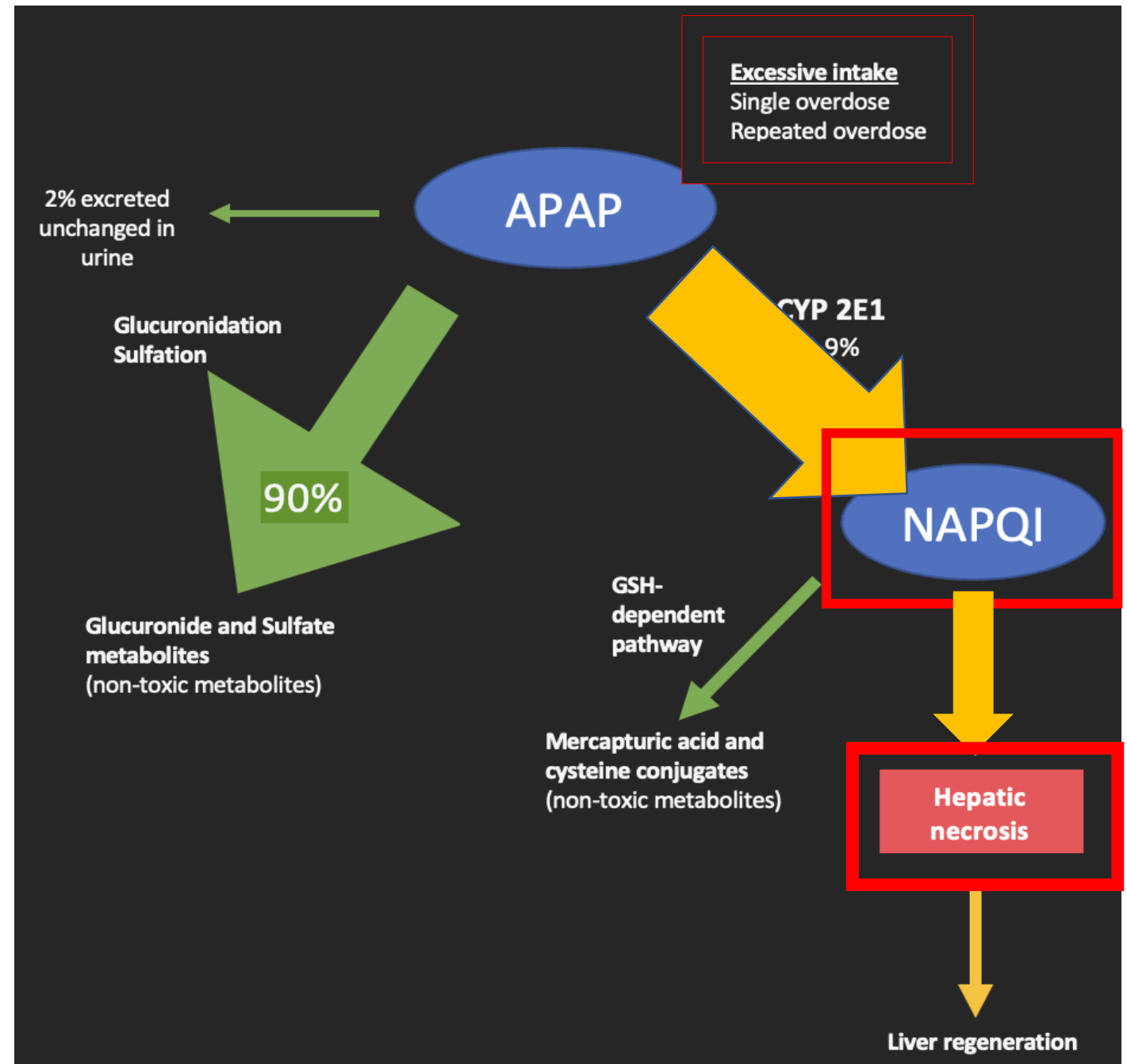


Metabolism



Toxicokinetics

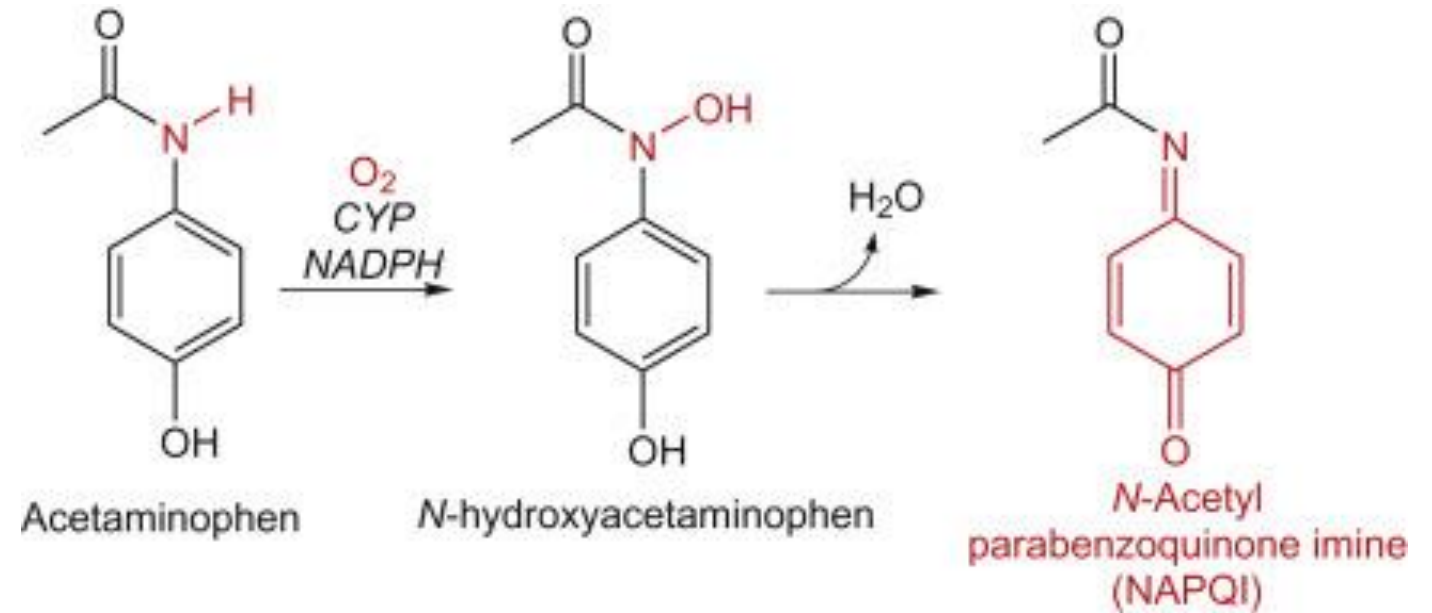
- Absorption
 - Majority occurs within 2 hours
 - Peak plasma concentrations generally occur within 4 hours
- Toxic metabolite
 - N-Acetyl parabenzoquinone imine (NAPQI)
 - Result of CYP2E1 enzyme and glutathione depletion



Toxicokinetics

- **Doses leading to toxicity**

- **Adult:** > 10 g or 150 mg/kg
- **Child:** > 200— 350 mg/kg
- **Massive:** >30 g or > 500 mg/kg



Types of Acetaminophen Poisoning

Intentional (~50%)

- Suicide attempt

Unintentional (~50%)

- Chronic users for pain (by itself or combination products)
- Acetaminophen ingested with alcohol daily
- Repeated supratherapeutic ingestion (RSTI)
- Chronic liver disease

Risk Factors for increased toxicity

Glucuronidation decreased capacity

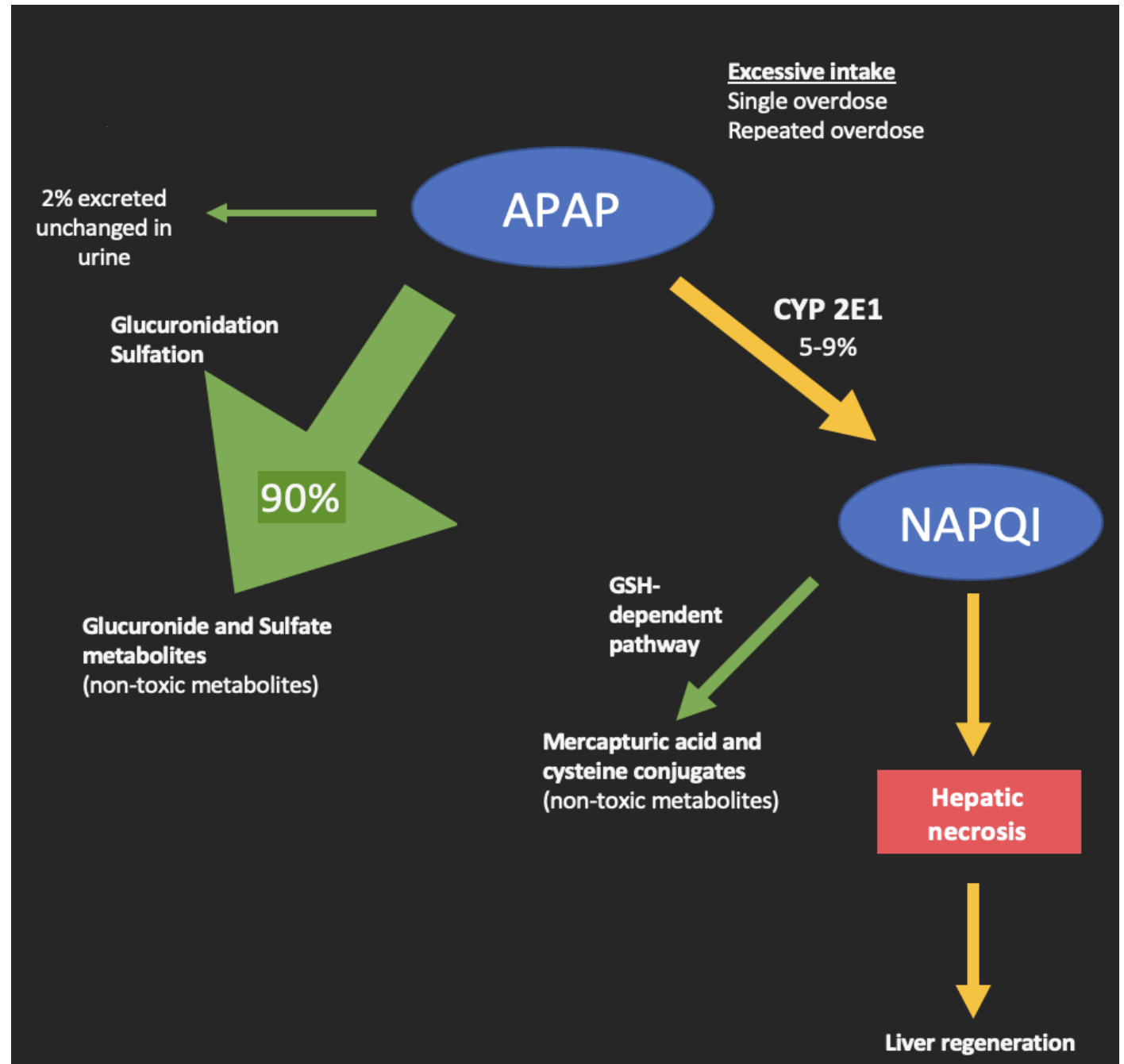
- Gilbert's Disease
- Zidovudine/trimethoprim/sulfamethoxazole

CYP2E1 Inducers

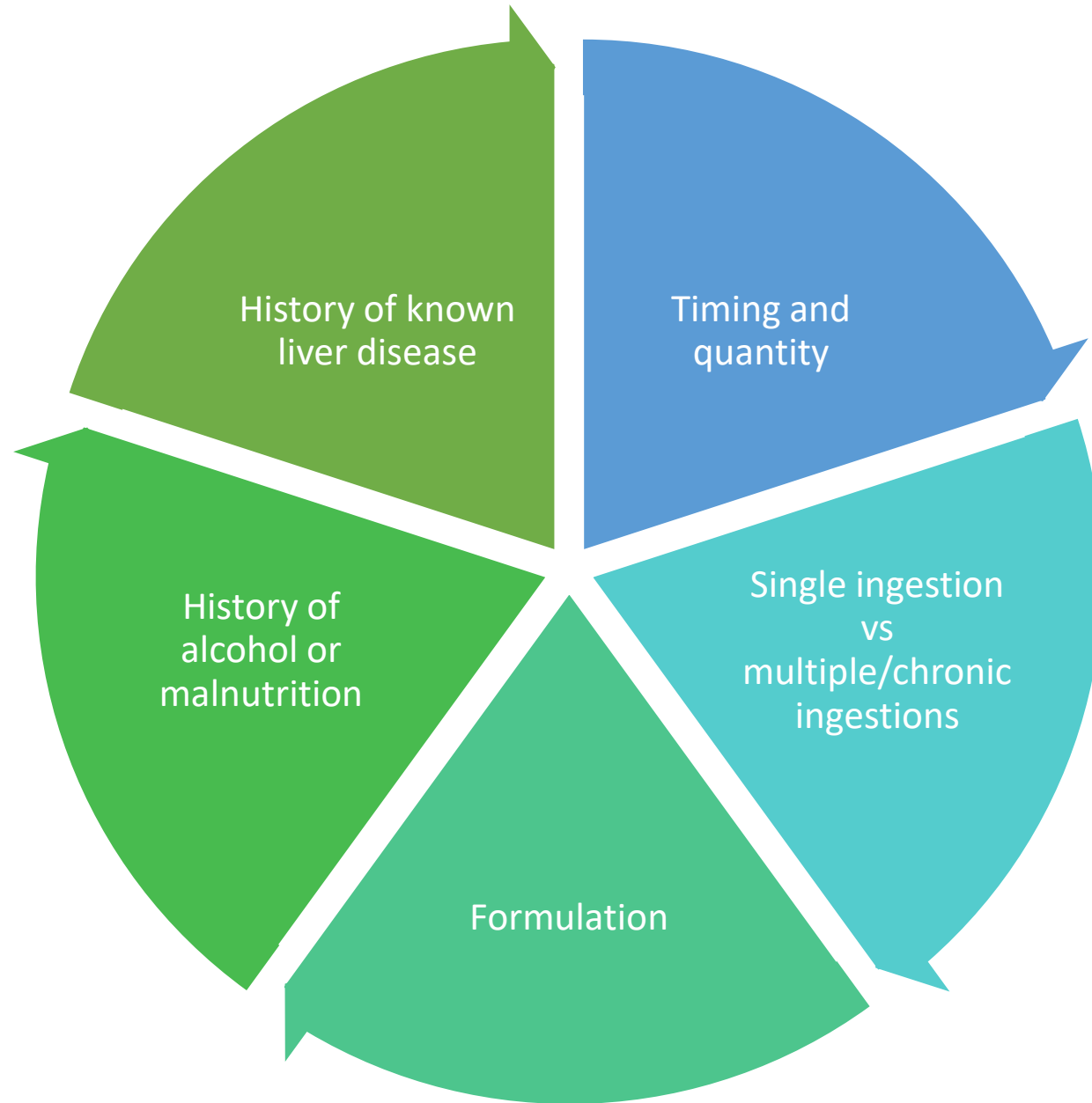
- Isoniazid
- Rifampicin, phenobarbital
- Phenytoin, phenobarbital

Glutathione Depletion

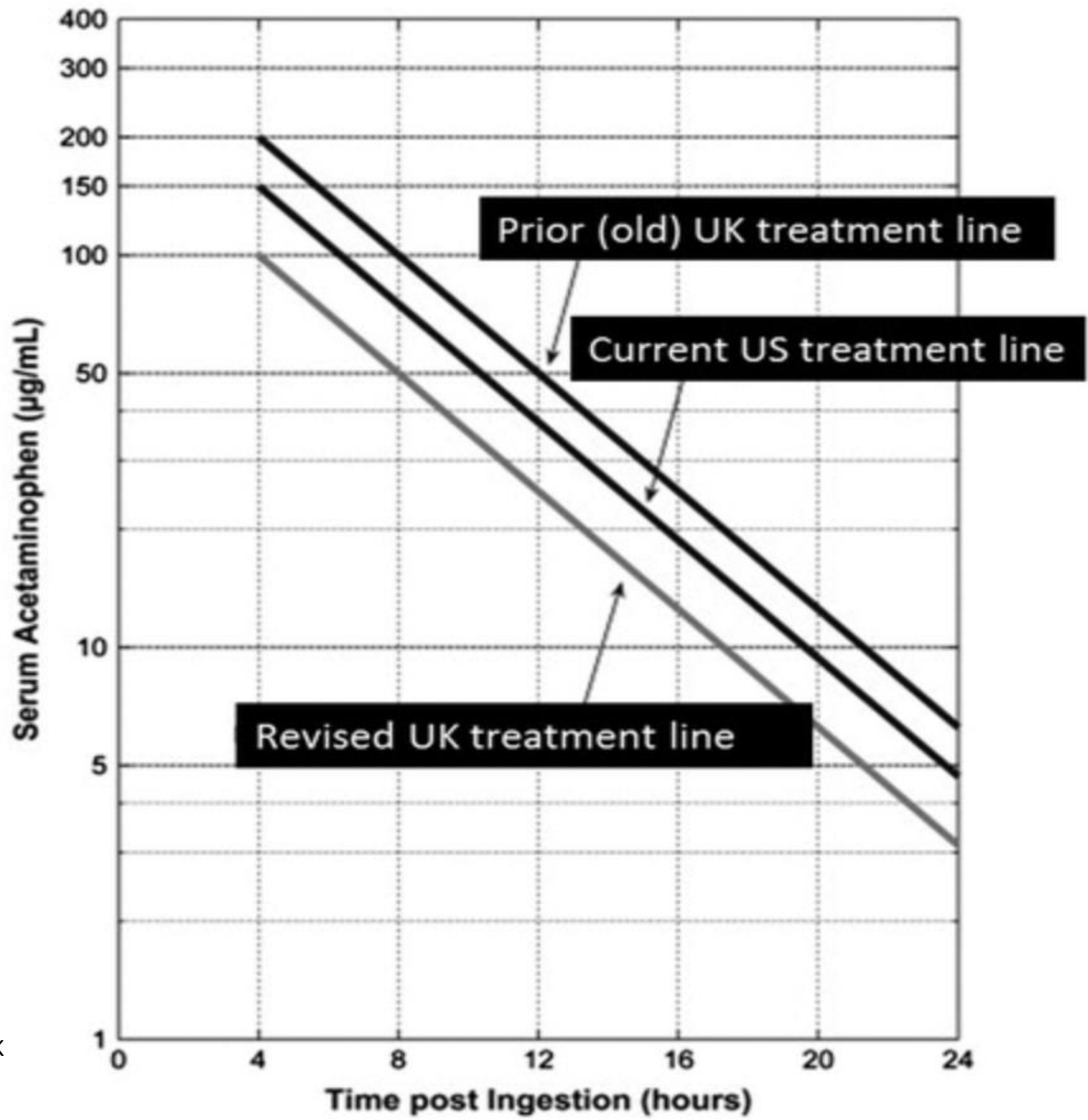
- Chronic alcohol ingestion
- Chronic acetaminophen use
- Chronic liver disease
- Malnutrition



Patient Evaluation



Rumack-Matthew Nomogram



Source: Levine M, et al. Estimating the impact of adopting the revised UK acetaminophen treatment nomogram in the US Population 2017
Nelson LS, Goldfrank LR et al. *Goldfrank's Toxicologic Emergencies*, 2019

Stages of Toxicity

Stage 1	Stage 2	Stage 3	Stage 4
Incubation (0-24 hours)	Latent (24-72 hours)	Peak liver toxicity (72-96 hours)	Resolution (4 days – 2 weeks)
N&V, diaphoresis, anorexia	Resolution of stage 1 symptoms	N&V, anorexia, malaise reappear	Patients who survive will make a complete recovery
Other symptoms usually suggest co-ingestion	Right upper quadrant pain	Hepatic failure	
Labs are generally normal during this period	AST/ALT elevation, nephrotoxicity	AST/ALT elevation, hepatorenal syndrome, INR elevation, Lactic acidosis	

Management

Gastrointestinal Decontamination

- Activated Charcoal

Dose: 25-100 g (1g/kg)

Contraindications

- Unable to protect airway

May be given via orogastric tube

Antidotal Therapy

N-Acetylcysteine (NAC) is the mainstay treatment

Prevents toxicity mainly as a **glutathione precursor** and **substitute**

Two options

- **21 hour IV** and a **72 hour oral** regimen

Potential side effects

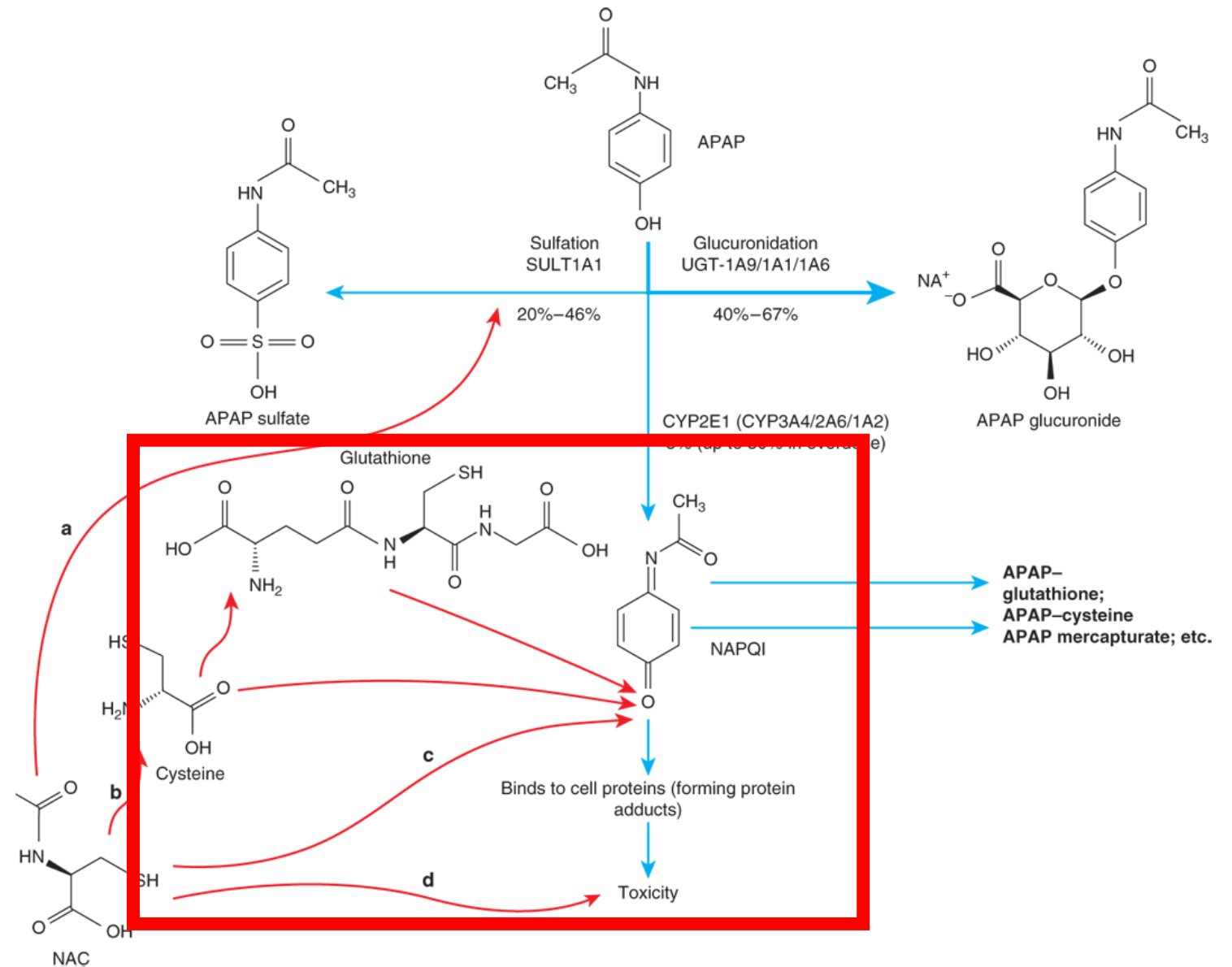
IV N-Acetyl Cysteine Dosing

- IV 21-hour regimen
 - 3 doses/bag regimen (300 mg/kg total dose)
- Loading dose
 - 150 mg/kg (max 15 g) over 1 hour
- Second dose
 - 50 mg/kg (max 5 g) over 4 hours
 - 12.5 mg/kg/hr
- Third dose
 - 100 mg/kg (max 10 g) over 16 hours
 - 6.25 mg/kg/hr

PO N-Acetyl Cysteine Dosing

- 72-hour regimen
- 18 doses (1,330 mg/kg)
- Loading dose
 - 140 mg/kg
- Maintenance dose
 - 70 mg/kg every 4 hours
 - Repeat dose if emesis occurs within 1 hour of administration

Mechanism of action of N-Acetyl Cysteine



Source: L.S. Nelson, M.A. Howland, N.A. Lewin, S.W. Smith, L.R. Goldfrank, R.S. Hoffman: Goldfrank's Toxicologic Emergencies, Eleventh Edition
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When to start N- Acetyl Cysteine

- Patients at risk for hepatotoxicity
 - If plot is over the treatment line
 - If > 30 g or co-ingested with antimuscarinics
- AST elevated
- AST is normal and acetaminophen level is > 10 mcg/mL
- Evidence of liver failure



Continuation/Cessation of NAC

- Continuation:
 - Detectable acetaminophen levels
 - Elevated AST
- Acetaminophen level at 20-24 hours remains elevated
 - High dose NAC
- Cessation:
 - Liver failure
 - No liver failure



Liver Transplant Evaluation

King's College Criteria

Arterial pH < 7.3 (after resuscitation and > 24 h since ingestion)

OR

Hepatic encephalopathy > grade 3

Serum Creatinine > 3.4 mg/dL

INR > 6.5

Modified King's College Criteria

Criteria as above

OR

Arterial lactate concentration > 3.5 mmol/L after early resuscitation (4 hours)

OR

pH < 7.3 **OR** lactate > 3.0 mmol/L after fluid resuscitation (12 hours after admission)

Pharmacists and Tech Assessment Question 1

Which of the following are current recommendations for the management of acetaminophen toxicity?

- a) Activated Charcoal within 1 hour after ingestion
- b) Fomepizole
- c) N-acetylcysteine
- d) A & C

Pharmacists and Tech Assessment Question 1 :

Correct Response

Which of the following are current recommendations for the management of acetaminophen toxicity?

- a) Activated Charcoal within 1 hour after ingestion
- b) Fomepizole
- c) N-acetylcysteine
- d) A & C



Massive Acetaminophen Overdose

What is massive acetaminophen overdose?

- Acetaminophen Extra Strength 500 mg
 - 1,000 tablets x 500 mg = **500 g** acetaminophen
- Currently no consensus on what constitutes a massive overdose
- Current literature has suggested 2 definitions
 - > **30 g** ingestion
 - > **300 mcg/mL** level at 4 hours





What's the problem?

- Increased risk of hepatotoxicity
- NAC failure
- What can we do?
 - Higher dose NAC
 - Additional agents?
 - Hemodialysis

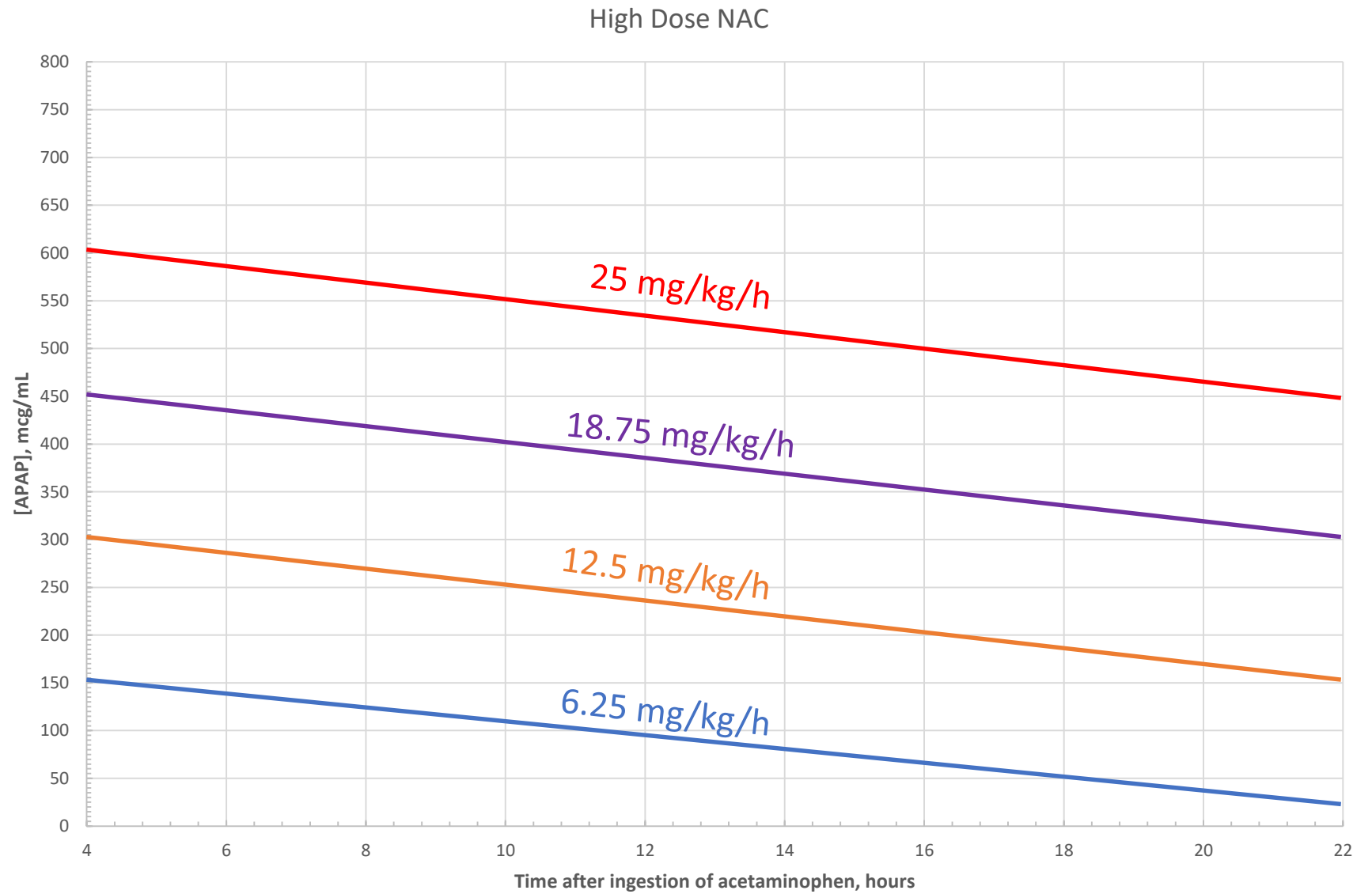


Risk of Hepatotoxicity with Massive Ingestions

Acetaminophen concentration range	Risk of hepatotoxicity (ALT > 1000 IU/L)
< 150 line	< 1%
150– 300 line	1 – 4%
301 – 500 line	7 – 13%
> 500 line	31 – 33%

Ingested dose	Predicted [APAP] _{4h}	Approximate APAP “line”	Predicted dose of NAC
16 g	157 mcg/mL	~150-line	6.25 mg/kg/h
32 g	314 mcg/mL	~300-line	12.5 mg/kg/h
48 g	472 mcg/mL	~450-line	18.75 mg/kg/h
64 g	629 mcg/mL	~600-line	25 mg/kg/h

High Dose NAC



N-Acetyl Cysteine in Obesity

Guidance in dosing is limited

Current recommendations cap dose at 100 kg

Small volume of distribution (0.5 L/kg) and high protein binding

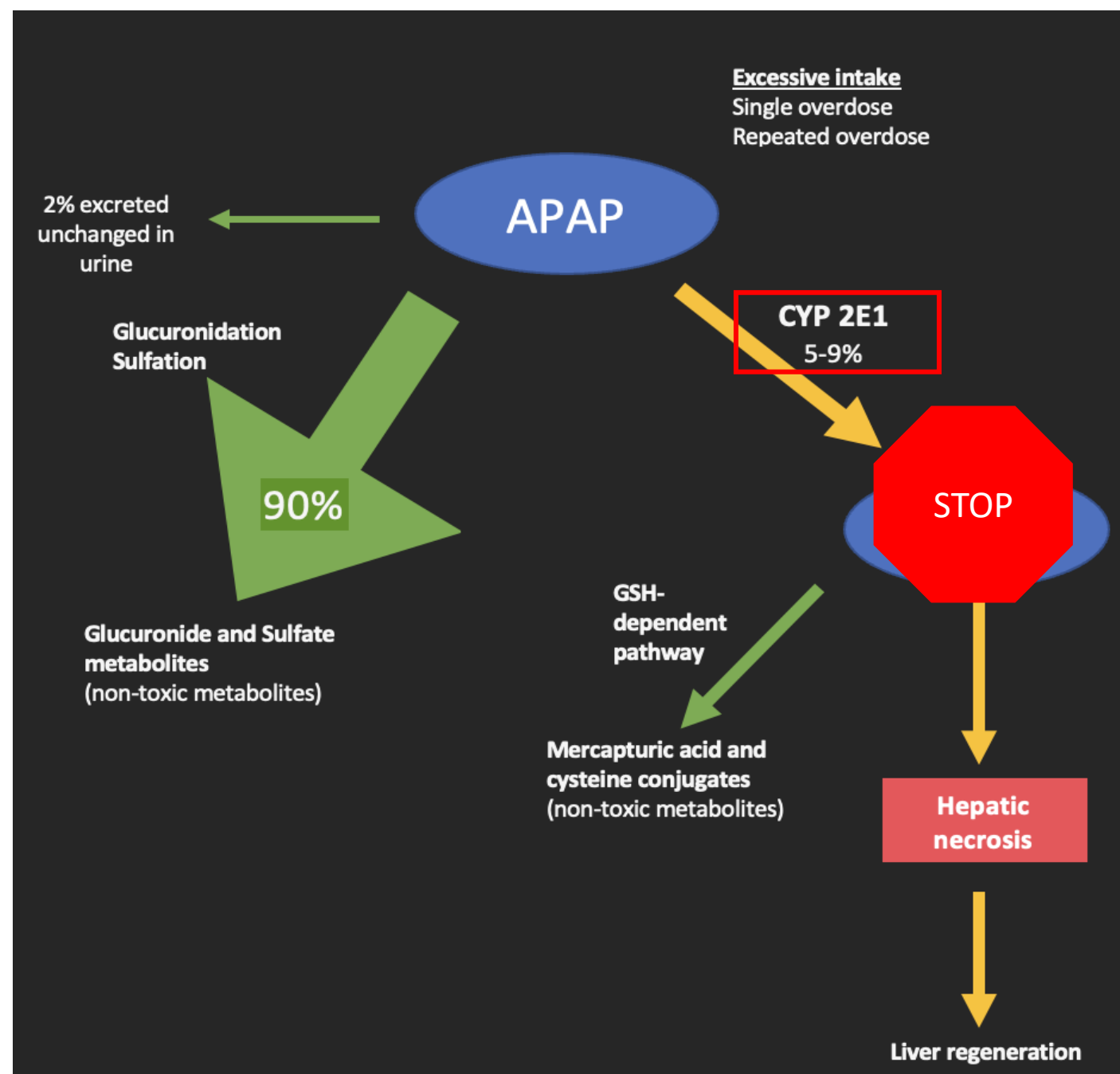
Reduces cumulative patient NAC dose

- Without additional risk of hepatotoxicity

Decrease in treatment cost

Another possible antidote?

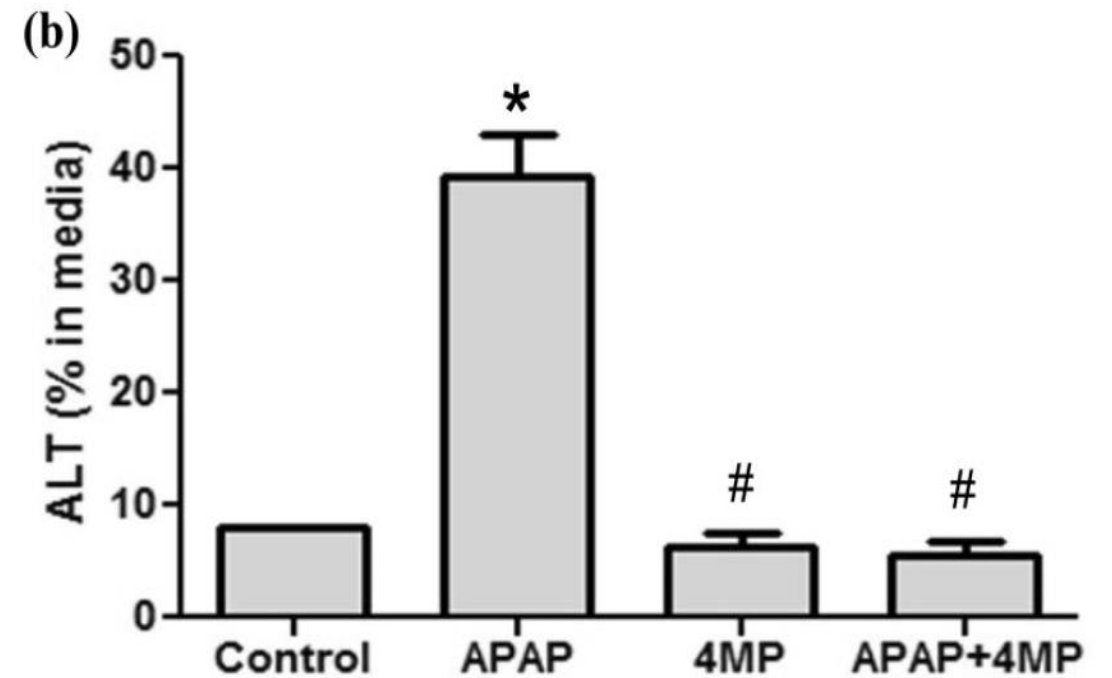
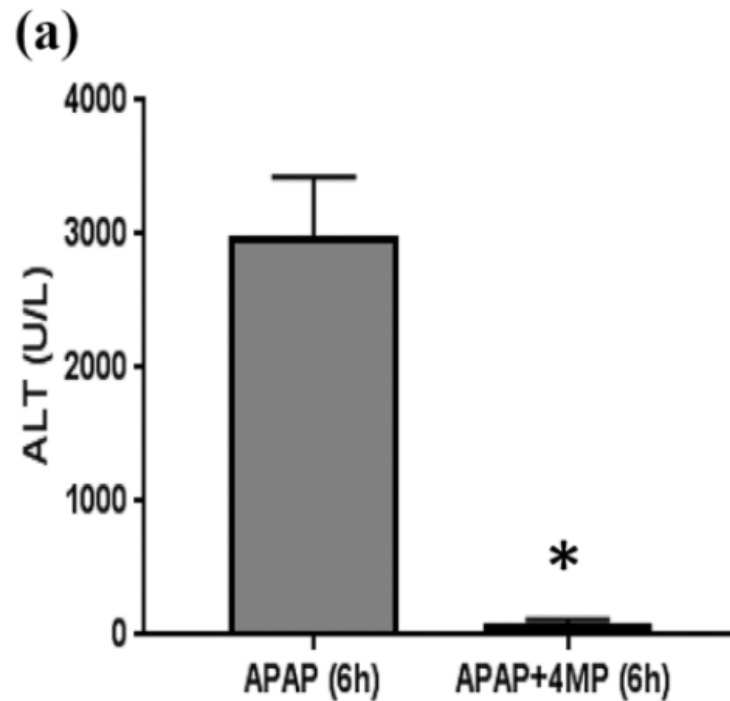
- Fomepizole (4-methylpyrazole)
 - Potent CYP2E1 inhibitor
- Mitochondrial death
- Fomepizole **inhibits c-Jun-N-terminal Kinase (JNK)**
 - Prevents further mitochondrial dysfunction



Source: Rampon G, et al. Use of fomepizole as an adjunct in the treatment of acetaminophen overdose: a case series. 2019

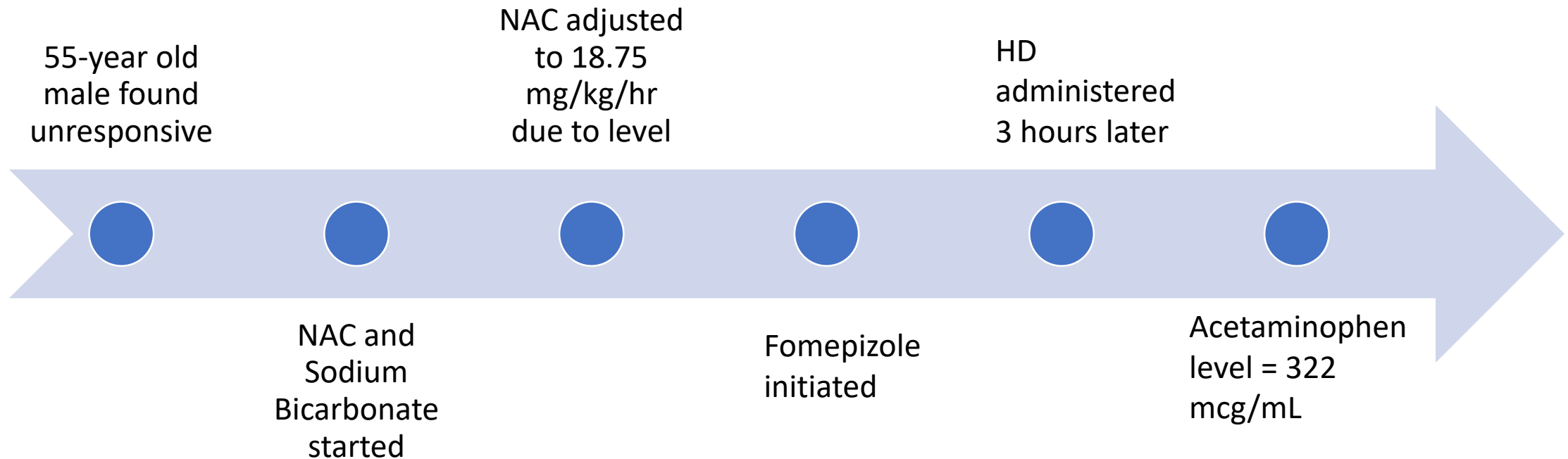
Bunchorntavakul C, et al. Acetaminophen and acute liver failure. 2018

Early literature



A Case Study

pH	Lactate	Anion Gap	Acetaminophen	QRS
7.08	17.5 mmol/L	32	883 mcg/mL	114 ms



Case Series Discussion

- Utilized standard dosing of fomepizole used for **toxic alcohols**
- Limitations
 - Study design
 - Subjective use of fomepizole
- Suggests safety of fomepizole in acute acetaminophen overdose
- Publication bias

Fomepizole Dosing

15 mg/kg IV once

- Over 30 minutes

10 mg/kg IV q12h PRN

- Over 30 minutes

HD

- Dose every 4 hours OR
- Continuous infusion of 1-1.5 mg/kg

CRRT

- Dose every 8 hours OR
- Continuous infusion of 0.5 mg/kg/hour

Pharmacist Assessment Question 2

What is the role of fomepizole in massive acetaminophen toxicity?

- a) Prevents toxicity by serving as a glutathione precursor
- b) Inhibits CYP450 2E1 decreasing production of NAPQI
- c) Inhibits the JNK pathway preventing mitochondrial dysfunction
- d) B & C

Pharmacist Assessment Question 2: Correct Response

What is the role of fomepizole in massive acetaminophen toxicity?

- a) Prevents toxicity by serving as a glutathione precursor
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- c) Inhibits the JNK pathway preventing mitochondrial dysfunction
- d) B & C

Pharmacist Tech Assessment Question 2

Preparation and storage requirements for fomepizole include which of the following?

- a) Store at temperatures < 20 C
- b) Dilute in at least 100 mL 0.9% sodium chloride or dextrose 5% water for injection
- c) Diluted solution can be used within 48 hours
- d) Only use polycarbonate syringes or polycarbonate-containing needles when preparing

Pharmacist Tech Assessment Question 2: Correct Response

Preparation and storage requirements for fomepizole include which of the following?

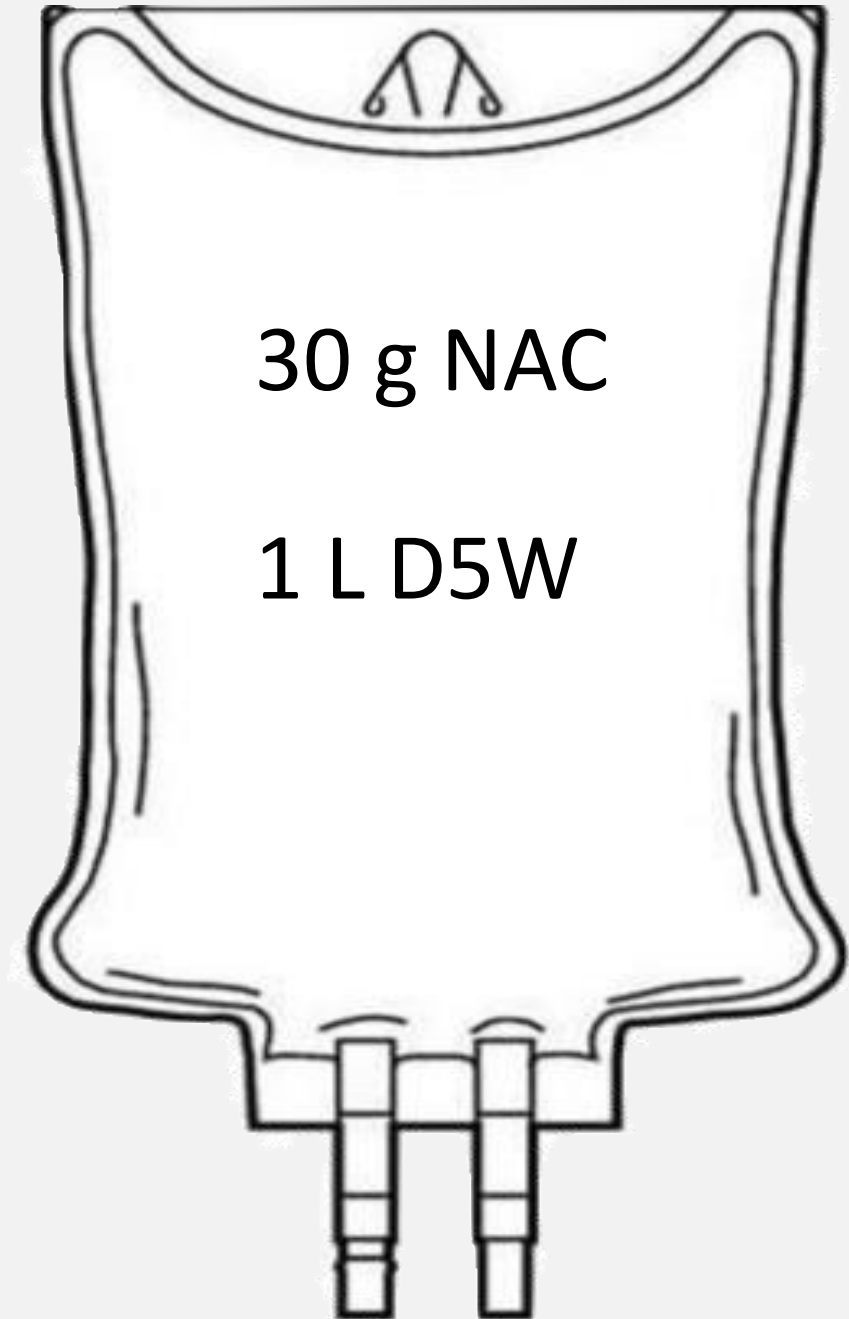
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Why Alternative IV NAC Regimens?

- Errors with severe consequences
- Infusion rates and concentrations
- Full staff attentiveness
- Treatment Delays
- Standardization
- Simplification

Single Bag Regimens

- Loading Dose
 - 150 mg/kg over 1 hour
- 8-hour presentation
 - 15 mg/kg/hr over 44 hours
 - 810 mg/kg over 45 hours
- Other presentations
 - 15 mg/kg/hr over 4 hours
 - 7.5 mg/kg over 16 hours
 - 330 mg/kg over 21 hours



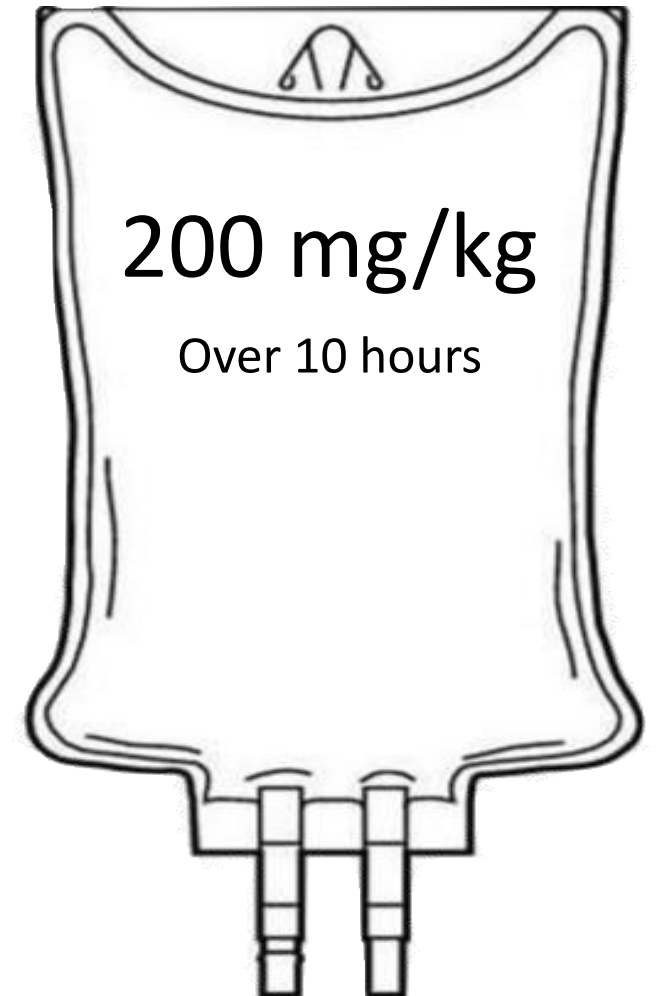
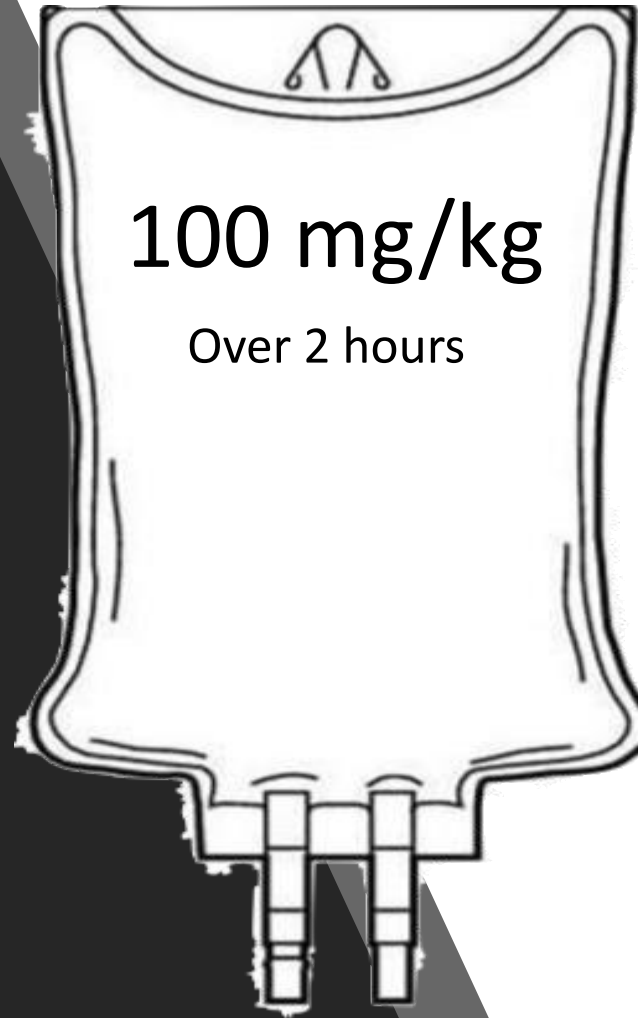
Single Bag Regimens

- 14 mg/kg/hr over 20 hours
- 430 mg/kg total dose
- Fewer errors
- Fewer treatment delays
- 12.5 mg/kg/hr
 - Second bag only needed if > 75 kg



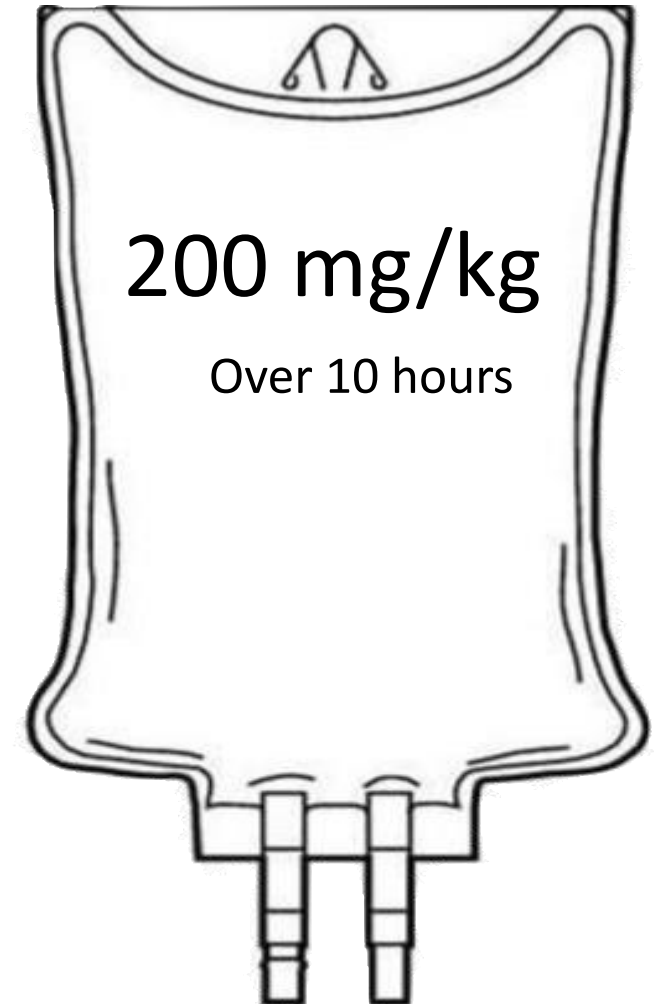
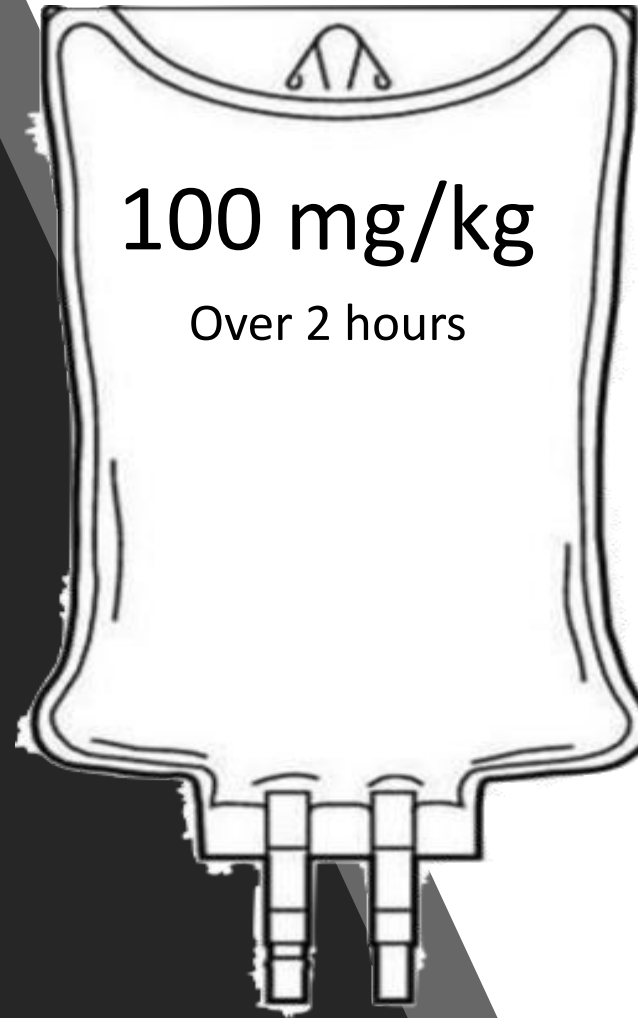
Condensed 12-hour Two Bag Regimens

- **SNAP** regimen
- 100 mg/kg
 - Over 2 hours
- 200 mg/kg
 - Over 10 hours
- Severe Reactions



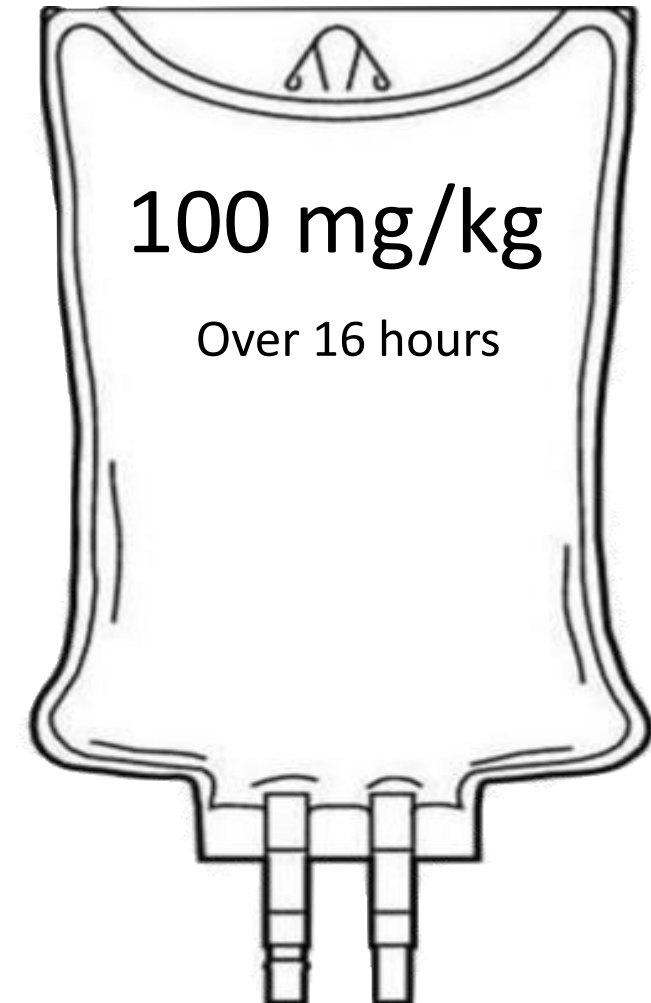
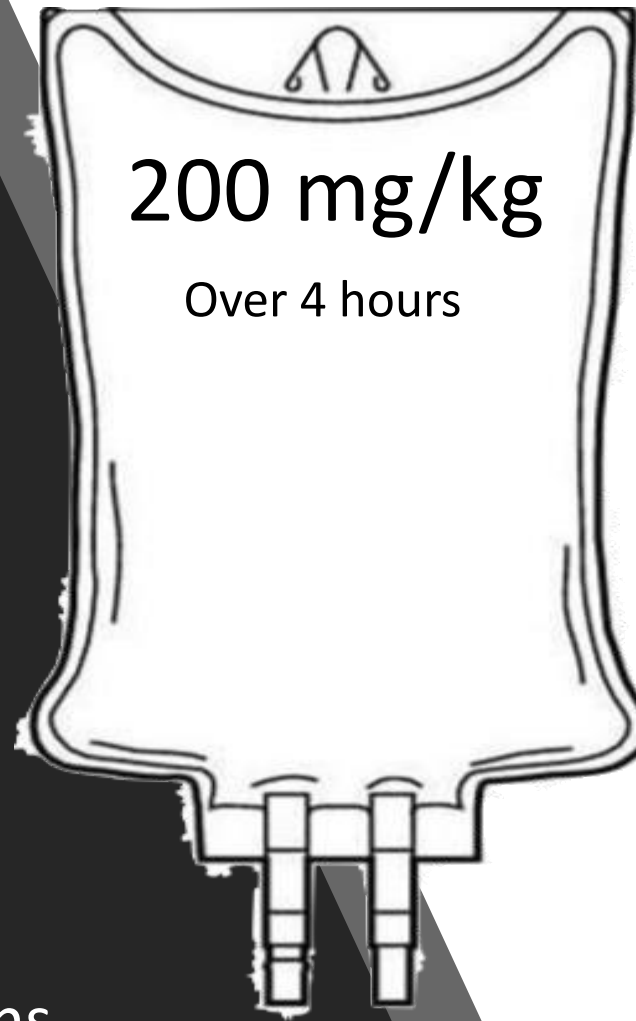
Condensed 12-hour Two Bag Regimens

- Antihistamines
 - More required in 3 bag regimen
- Hepatotoxicity
 - Rate was not statistically significant
- UK guidelines
 - 100-line vs 150-line



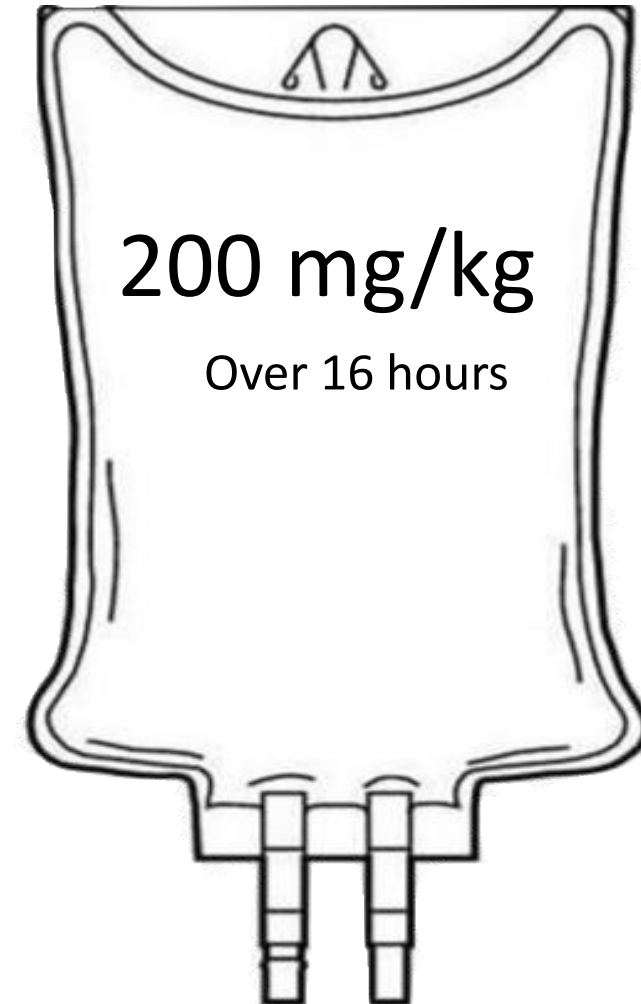
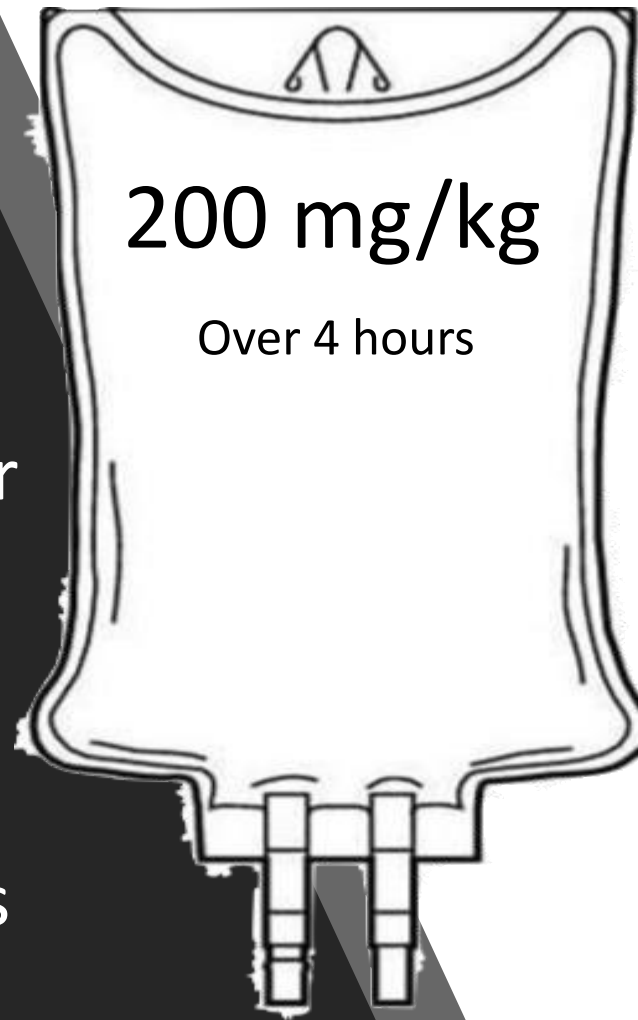
Non-Condensed Two Bag Regimens

- 200 mg/kg
 - Over 4 hours
- 100 mg/kg
 - Over 16 hours
- Adverse Reactions
 - Less likely with higher acetaminophen concentrations



Non-Condensed Two Bag Regimens

- Non inferiority for acute liver injury
- Adverse Reactions
- Decreased hepatotoxicity
- 200 mg/kg load over 4 hours
- 200 mg/kg over 16 hours (Doubling the dose)



Hemodialysis (HD)

Intermittent HD and Continuous Venovenous HD increase elimination of acetaminophen

Systematic review suggests use in:

Altered Mental
Status

Elevated Lactate

Metabolic
Acidosis with
acetaminophen
level > 700
mcg/mL

Acetaminophen
level > 900
mcg/mL treated
with NAC

Acetaminophen
level > 1,000
mcg/mL
regardless of
therapy

NAC infusion rates should be **doubled** during HD

Case Study

- MH is a 39-year-old female
- Presents with **unknown** acetaminophen ingestion
- What do we do next?

Case Study

What do we do?

Time of ingestion?	4:30 pm (presents within 1 hour)
Quantity of	Unknown

Clinical course:

Patient given 50 g activated charcoal per G-tube

Started on NAC 3 bag regimen

Repeat Acetaminophen level the following day: 41 mcg/mL

Fomepizole?	Worth trying?
Hemodialysis?	Warranted?

Summary

Acetaminophen toxicity has become more widespread due to an increased availability throughout multiple products

N-acetylcysteine is the mainstay treatment and nurses, physicians, and pharmacists play a role in safe administration

In massive acetaminophen toxicity, fomepizole may play a role to help prevent worsening hepatotoxicity

Alternative N-acetylcysteine regimens may reduce complex preparation and administration and reduce treatment related adverse drug reactions

Pharmacist Assessment Question 3

Which of the following would be an appropriate dosing regimen for N-acetylcysteine in the treatment of acetaminophen poisoning?

- a) 150 mg/kg over 1 hour followed by 14 mg/kg/hr for 20 hours (Single bag)
- b) 150 mg/kg over 1 hour followed by 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours (3 bag regimen)
- c) 100 mg/kg over 2 hours followed by 200 mg/kg over 10 hours (SNAP regimen)
- d) All of the above

Pharmacist Assessment Question 3: Correct Response

Which of the following would be an appropriate dosing regimen for N-acetylcysteine in the treatment of acetaminophen poisoning?

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- c) 100 mg/kg over 2 hours followed by 200 mg/kg over 10 hours (SNAP regimen)
- d) All of the above

Pharmacy Tech Assessment Question 3

Preparation and storage requirements for N-acetylcysteine include which of the following?

- a) Storing intact vials at 68 – 77 °F
- b) Discarding reconstituted solution after 24 hours
- c) Throwing out the vial if a pink/purple color change occurs after the stopper is punctured
- d) A & B

Pharmacy Tech Assessment Question 3: Correct Response

Preparation and storage requirements for N-acetylcysteine include which of the following?

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Thank you!

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