# Taming the Toxin: Management of Acetaminophen Toxicity

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February 15th, 2025

# Objectives

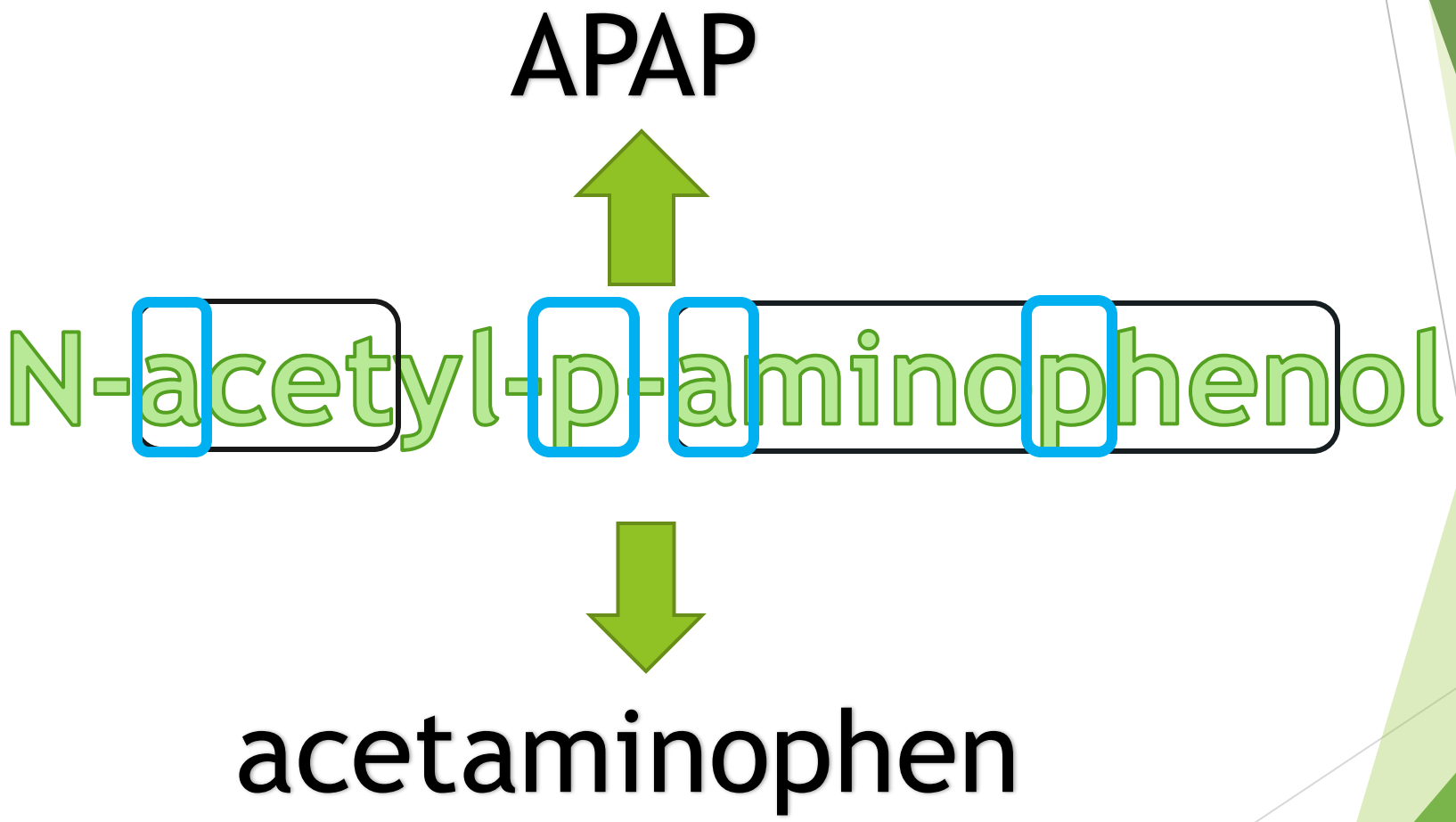
| | |
|---|---|
| Review | Review the pharmacokinetics and metabolism of acetaminophen |
| Describe | Describe the standard workup for an acetaminophen exposure |
| Review | Review the mechanism of action and dosing of n-acetylcysteine in the treatment of acetaminophen toxicity |
| Discuss | Discuss adjunct treatment options for the management of massive acetaminophen overdose |

# Acetaminophen (APAP) Overview

- Acetaminophen is one of the most widely used medications worldwide for its analgesic and antipyretic properties
- Widespread availability over-the-counter and inclusion in numerous combination products makes it a commonly observed agent in cases of overdose and toxicity
- Remains the most common cause of acute liver failure in the US in patients 15 years and older

Schult, RF, Acquisto NM. Acetaminophen and salicylates. Toxicology/Practice Issues. ACCP. 2018: 7-30.

# APAP Overview



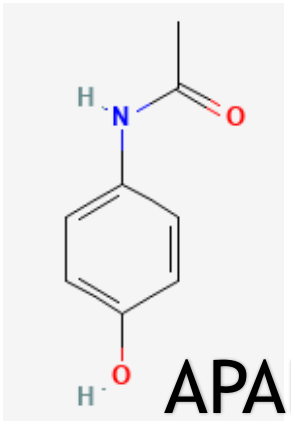
# APAP: Pharmacodynamics / Kinetics

- Therapeutic serum level: 5-20 mCg/mL
- Peak effect: 10-60 minutes (delayed in acute overdose)
- Half-life elimination: prolonged following toxic doses
  - Neonates: ~7 hours
  - Infants: ~4 hours
  - Adolescents: ~3 hours
  - Adults: ~2 hours
- Metabolism: primarily hepatic

Acetaminophen. Lexi-Drugs. Lexicomp.

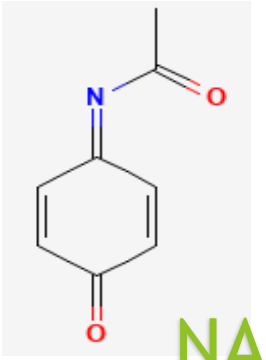
# APAP: Metabolism

APAP Sulfate ← Sulfation (20-40%) — APAP — Glucuronidation (40-60%) → APAP glucuronide



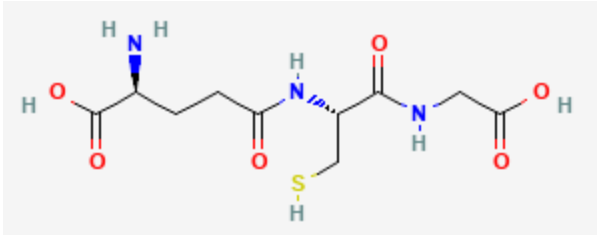
APAP

CYP2E1 (5%) →



NAPQI

Glutathione

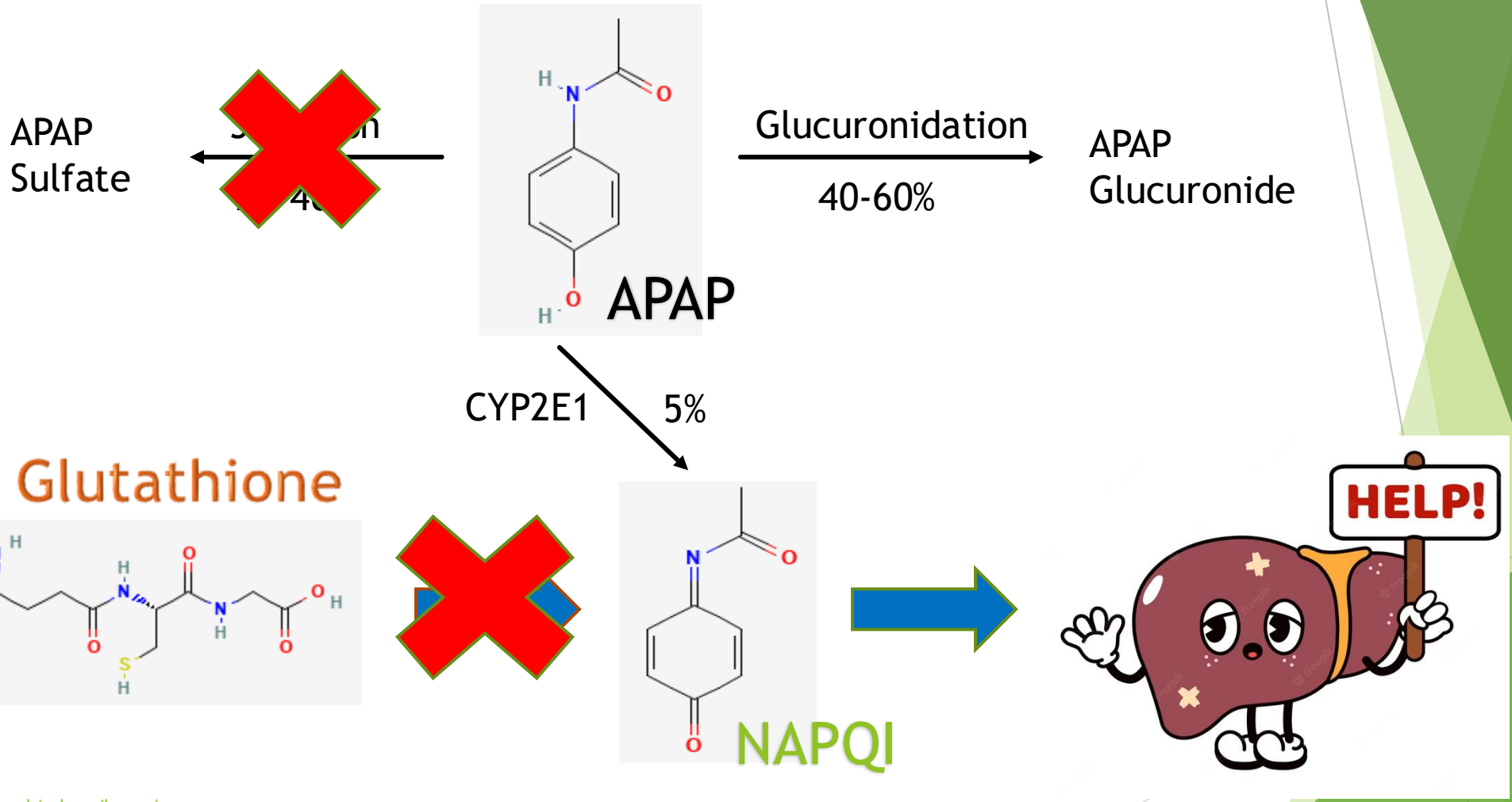


→ APAP glutathione
APAP-cysteine
APAP mercapturate

https://pubchem.ncbi.nlm.nih.gov/

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

# APAP: Toxicity




https://pubchem.ncbi.nlm.nih.gov/

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

# Phases of Toxicity

- Phase I (12-24 hours post exposure)
  - Generally asymptomatic presentation
  - If symptomatic: nausea, vomiting, malaise
- Phase II (24-36 hours post exposure)
  - Onset of hepatotoxicity (transaminase concentration > 1000 IU/L)
- Phase III (72-96 hours post exposure)
  - Fulminant hepatic failure
  - Hepatic encephalopathy, coma, possibly hemorrhage, acute renal failure
  - Lab abnormalities: hypoglycemia, lactic acidosis, prolonged PT
- Phase IV (7 days post exposure)
  - Resolution of most lab abnormalities within a week of exposure
  - ALT and serum creatinine may take several weeks to normalize

Schult, RF, Acquisto NM. Acetaminophen and salicylates. Toxicology/Practice Issues. ACCP. 2018: 7-30.

# APAP Poisoning Consensus Statement

JAMA Network Open

Consensus Statement | Emergency Medicine

## Management of Acetaminophen Poisoning in the US and Canada
### A Consensus Statement

Richard C. Dart, MD, PhD; Michael E. Mullins, MD; Theresa Matoushek, PharmD; Anne-Michelle Ruha, MD; Michele M. Burns, MD; Karen Simone, PharmD; Michael C. Beuhler, MD; Kennon J. Heard, MD, PhD; Maryann Mazer-Amirshahi, PharmD, MD, PhD; Christine M. Stork, PharmD; Shawn M. Varney, MD; Alexandra R. Funk, PharmD; Lee F. Cantrell, PharmD; Jon B. Cole, MD; William Banner, MD, PhD; Andrew I. Stolbach, MD; Robert G. Hendrickson, MD; Scott N. Lucyk, MD; Marco L. A. Sivilotti, MD; Mark K. Su, MD; Lewis S. Nelson, MD; Barry H. Rumack, MD

*JAMA Network Open*. 2023;6(8):e2327739.
Corrected on September 28, 2023. doi:10.1001/jamanetworkopen.2023.27739

# Definitions: Acute Ingestion vs RSI

Single acute ingestion

- Any amount ingested in X hours
- Previous definitions: 1 hour, 8 hours
- Consensus statement definition: amount ingested within a 24 hour period

Referral dose

- Ingestion of ≥ 200mg/kg or ≥ 10g of APAP (adult & pediatric patients)

*Note: practice variation still exists depending on poison center / toxicologist

Alhelail MA, et al. Clin Tox. 2011(49): 1-18.
Dart RC, et al. JAMA. 2023;6(8):e2327739.

# Definitions: Acute Ingestion vs RSI

Repeated supratherapeutic ingestion (RSI) – per consensus statement

- Ingestion occurs during a period of > than 24 hours
- 24-48 hours: 6g / day or 150 mg/kg/day (whichever is less)
- > 48 hours: 4g / day or 100 mg/kg /day (whichever is less)
- Unknown amount / ingestion history unknown

*Note: practice variation still exists depending on poison center / toxicologist

Dart RC, et al. JAMA. 2023;6(8):e2327739.

# Initial Workup & Treatment

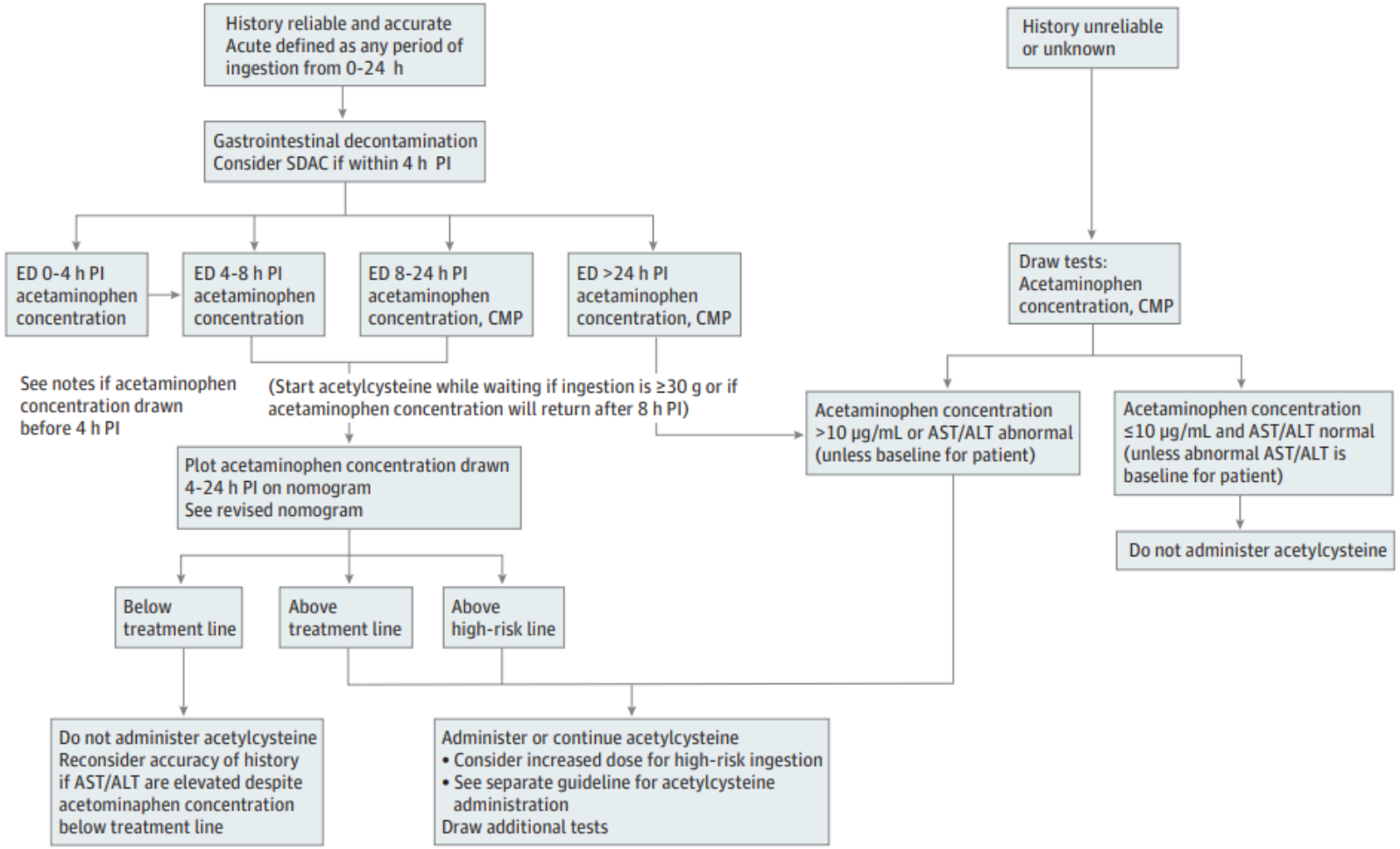
- Single acute ingestion
  - APAP level **at least** 4 hours post ingestion & plot on nomogram
    - Initiate NAC if above treatment line
    - Initiate NAC if >30g ingested or unable to attain level within 8h of ingestion
  - Consider single dose activated charcoal (SDAC) if < 4 hours post ingestion

- Repeated supratherapeutic ingestion
  - Does patient meet dosing criteria or any of the following:
    - Amount unknown
    - Signs / symptoms of hepatotoxicity
    - Suicidality / intent for self-harm
  - If yes → nomogram cannot be used
  - If elevated serum AST / ALT or APAP ≥ 10 mCg/mL → initiate NAC

Dart RC, et al. JAMA. 2023;6(8):e2327739.
Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.
Spiller HA, et al. J Emerg Med. 2006:30(1):1-5.

# Initial Workup & Treatment (Acute)

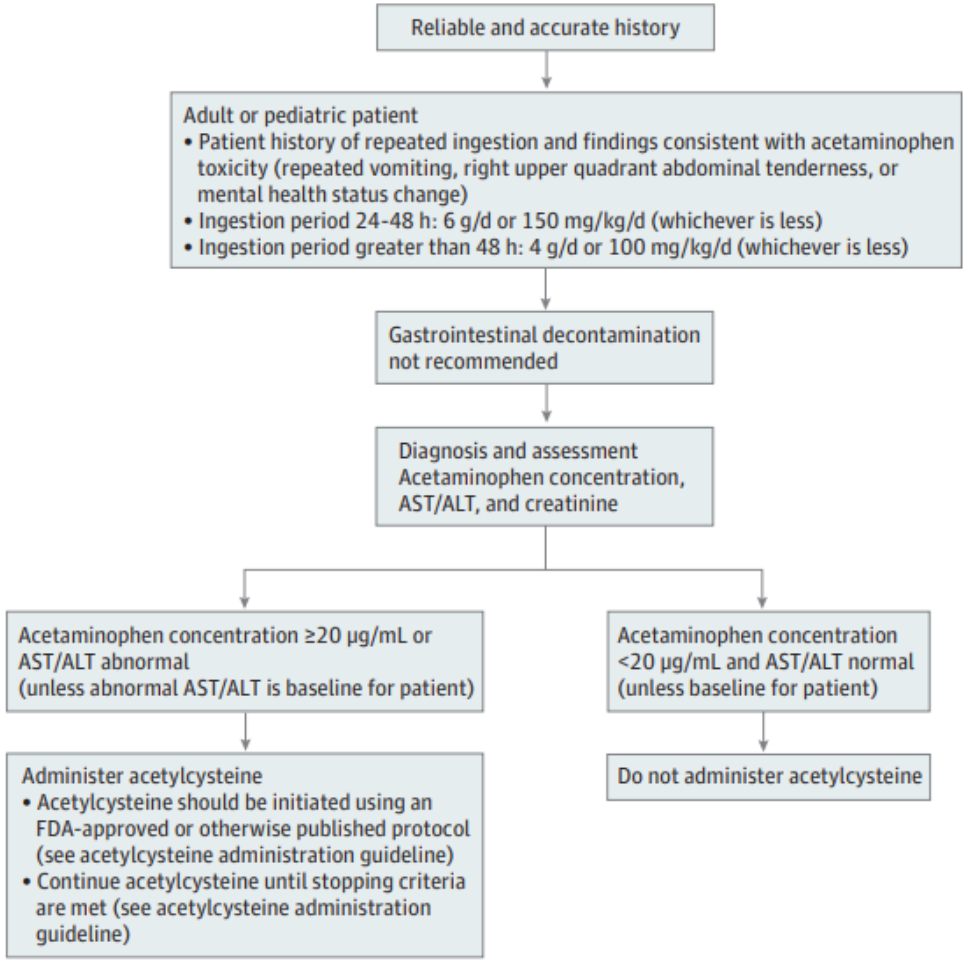
**Figure 1. Management of Acetaminophen Poisoning in a Medical Facility**




Dart RC, et al. JAMA. 2023;6(8):e2327739.

# Initial Workup & Treatment (RSI)

**Figure 4. Management of Repeated Supratherapeutic Ingestion of Acetaminophen**




Dart RC, et al. JAMA. 2023;6(8):e2327739.

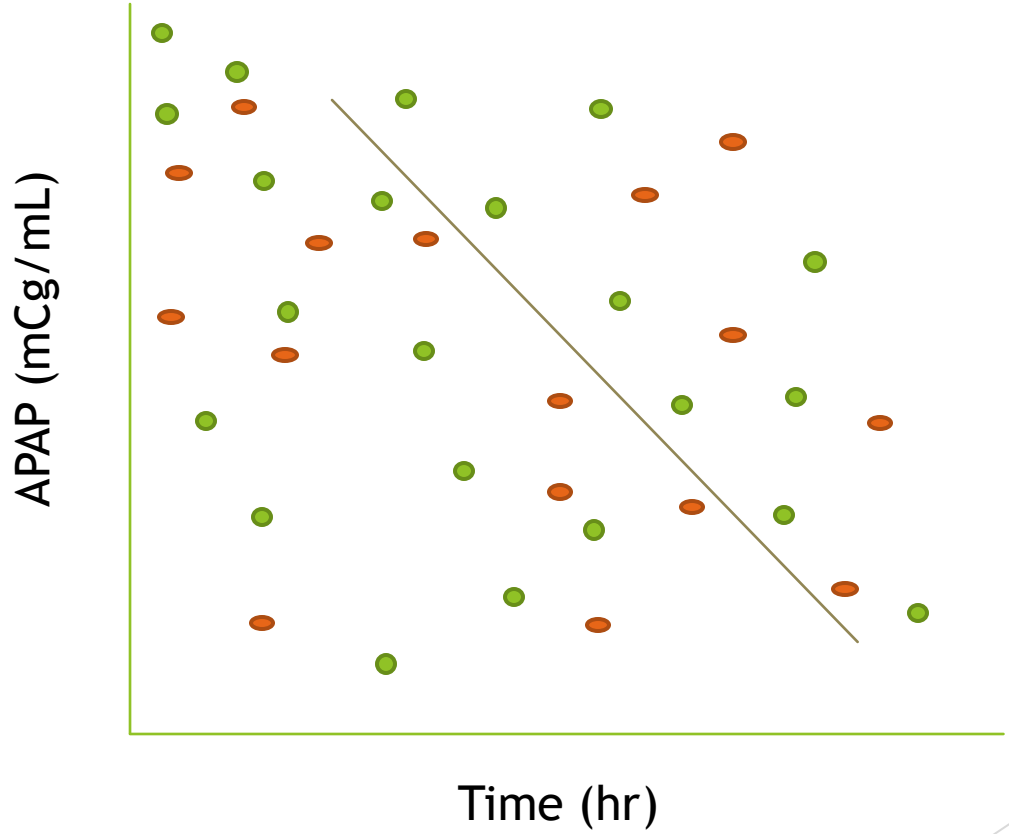
# King's College Criteria

- If patient critically ill / rapidly deteriorating – consider the following to assess need for transplant center referral:
  - Arterial pH < 7.3
  - INR > 6.5 (PT > 100 sec)
  - Creatinine > 3.4 mg/ dL
  - Grade III or IV hepatic encephalopathy
- Other predictors of poor prognosis w/o transplant:
  - Lactate > 3.5 mmol/L after fluid resuscitation (< 4 hours) OR lactate > 3 mmol/L after full fluid resuscitation (12 hours)
  - Phosphate > 3.75 mg/dL (at 48-96 hours)

O'Grady JG, et al. Gastroenterology. 1989. 97(2):439-445.

# Two guys walk into a pub…

- Barry Rumack & Henry Matthew



# Nomogram Use Rules

- Single acute ingestion
- Single (known) time
- Single drug
- Immediate release

- USA: middle line (150 line)
- Check units
- Check time

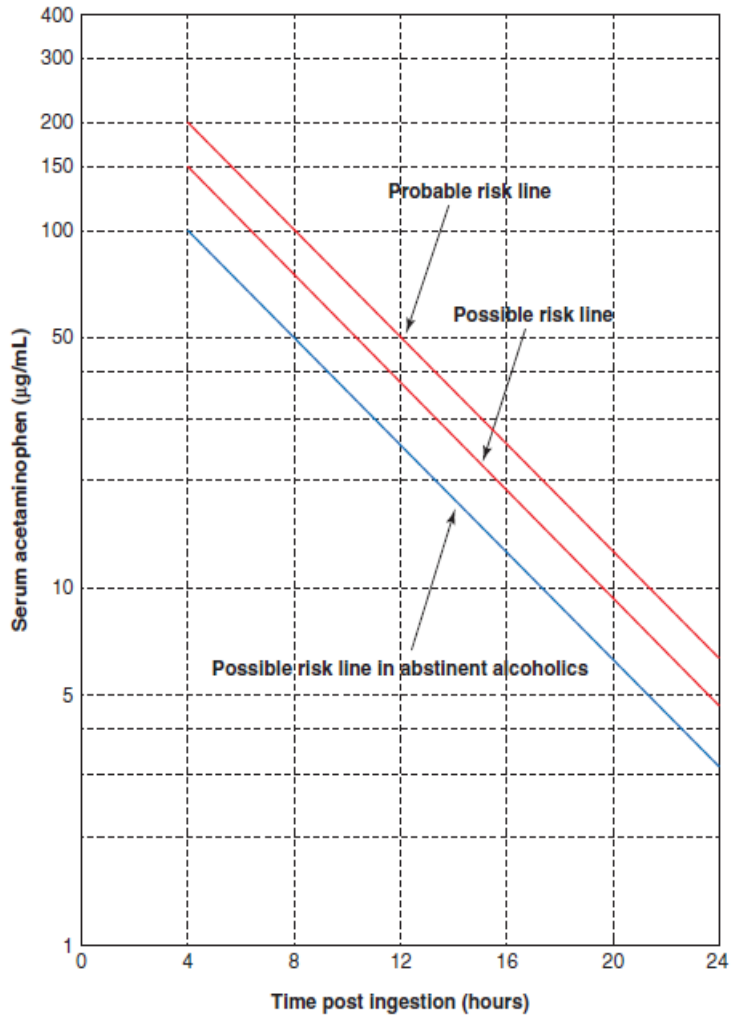



**Figure 1.** Rumack-Matthew nomogram including a line of 100 mcg/mL at 4 hours line and 25 mcg/mL at 12 hours, for abstinent alcoholic patients after an acute acetaminophen overdose.

Reprinted with permission from: Ali FM, Boyer EW, Bird SB. Estimated risk of hepatotoxicity after an acute acetaminophen overdose in alcoholics. Alcohol 2008;42:213-8.

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

# N-Acetylcysteine (NAC)

- Initiate therapy within 8-10 hours of ingestion

Standard Regimens (FDA Approved)

- 21 hour **IV** regimen or '3 bag method': (300mg/kg total dose)
  - Loading dose: 150mg/kg infused over 1 hour (max dose 15g)
  - Second dose: 50mg/kg infused over 4 hours (max dose 5g)
  - Third dose: 100mg/kg infused over 16 hours (max dose 10g)
- 72 hour **oral** regimen: (1330mg/kg total dose)
  - Loading dose: 140mg/kg
  - Subsequent dosing: 70mg/kg every 4 hours

CUMBERLAND® PHARMACEUTICALS

**FDA APPROVES ACETADOTE® sNDA**

**- New Dosing Regimen Simplifies Administration -**

**NASHVILLE, Tenn. (December 9, 2024) - Cumberland Pharmaceuticals Inc. (Nasdaq: CPIX)**, a specialty pharmaceutical company focused on delivering high-quality products to improve patient care, announced today the FDA has approved a supplemental New Drug Application (sNDA) for its Acetadote® (N-acetylcysteine for injection) product. Acetadote is an intravenous (IV) formulation of N-acetylcysteine (NAC) indicated to prevent or lessen liver injury after ingestion of potentially toxic quantities of acetaminophen[1].

Acetaminophen, a common over-the-counter pain reliever and ver reducer, is the leading cause of acute liver failure in the United States. Each year, thousand individuals experience accidental or intentiona etaminophen poisoning, ding to seriou damage.

The newly appro ng regimen si the ad on of Acetadote by combining the first two bags of the regimen reamlined approach has been implemented strated to reduce the frequency of medication lactoid reactions (NAARs) the dosing regimen, hea more efficiently, potentially improv

Two-Bag Method now FDA approved!

2 Bag Method
- Loading Dose: 200mg/kg over 4 hours
- Second Dose: 100mg/kg over 16 hours

…more on this later

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

# NAC: Dilution & Preparation

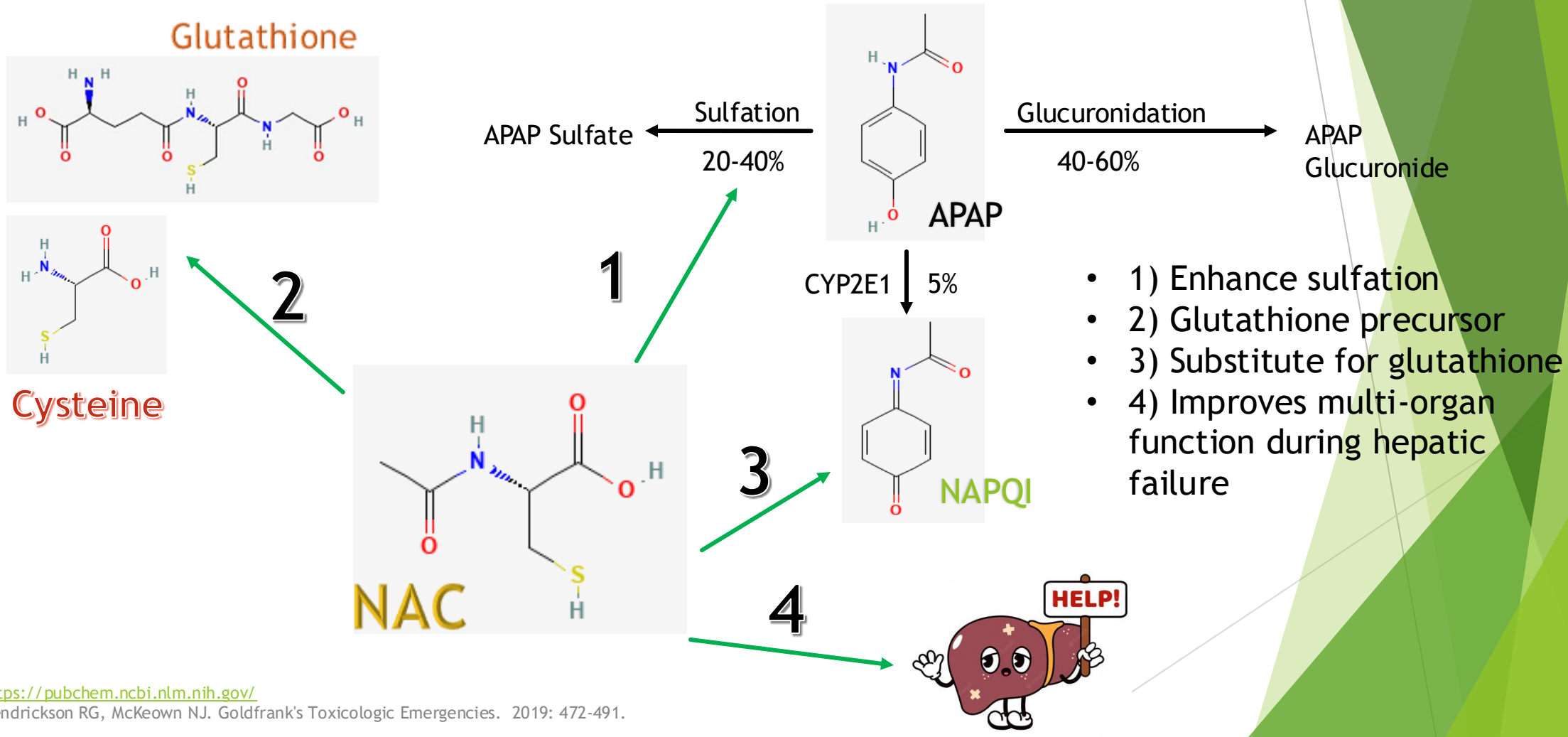
**Table 2. Three-Bag Recommended ACETADOTE Dosage and Dilution for Patients 5 kg or greater**

| Body Weight | Bag 1 (Loading Dose) | | | Bag 2 (Second Dose) | | | Bag 3 (Third Dose) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Loading Dose | Diluent Volume* | Infusion time | Second Dose | Diluent Volume* | Infusion time | Third Dose | Diluent Volume* | Infusion time |
| 5 kg** to 20 kg | 150 mg/kg | 3 mL/kg | Infused over 1 hour | 50 mg/kg | 7 mL/kg | Infused over 4 hours | 100 mg/kg | 14 mL/kg | Infused over 16 hours |
| 21 kg to 40 kg | 150 mg/kg | 100 mL | | 50 mg/kg | 250 mL | | 100 mg/kg | 500 mL | |
| 41 kg to 99 kg | 150 mg/kg | 200 mL | | 50 mg/kg | 500 mL | | 100 mg/kg | 1,000 mL | |
| 100 kg or greater*** | 15,000 mg | 200 mL | | 5,000 mg | 500 mL | | 10,000 mg | 1,000 mL | |

- Solutions
  - 5% dextrose in water (D5W)
  - Sterile water for injection (SW)
  - 0.45% sodium chloride (1/2 NS)

Cumberland Pharmaceuticals Inc. *Acetadote (acetylcysteine) Injection Package Insert*. 2024. Retrieved from FDA.

# NAC: Mechanism of Action




- 1) Enhance sulfation
- 2) Glutathione precursor
- 3) Substitute for glutathione
- 4) Improves multi-organ function during hepatic failure

https://pubchem.ncbi.nlm.nih.gov/

Hendrickson RG, McKeown NJ. Goldfrank's Toxicologic Emergencies. 2019: 472-491.

# Non-Allergic Anaphylactoid Reactions (NAARS)

- Most associated with IV administration
  - Highest incidence during first hour of therapy
- Mild to severe
  - Rashes, flushing / erythema, hives
  - Angioedema, bronchospasm, hypotension
- Patients presenting with higher serum acetaminophen levels at lower risk of developing anaphylactoid reactions

Acetylcysteine. Lexi-Drugs. Lexicomp.
Schult, RF, Acquisto NM. Acetaminophen and salicylates. Toxicology/Practice Issues. ACCP. 2018: 7-30.

# Non-Allergic Anaphylactoid Reactions (NAARS)

- Stop NAC in patients who develop: hypotension, dyspnea, wheezing, flushing, or erythema
  - Continue NAC if limited to flushing and erythema with close monitoring
- Diphenhydramine may be beneficial if history of atopy or histamine-mediated reactions

- If NAC stopped: restart after 1 hr
  - During loading dose: administer remainder of load at ½ the rate
  - After loading dose: continue to next bag without adjustments
- For persistent / worsening NAAR: switch to PO NAC

# NAC Discontinuation Criteria

After completion of acetylcysteine course, evaluate the following:

- APAP level < 10 mCg/mL
- AST / ALT remains normal or, if elevated, has down-trended by 25-50%
- INR < 2 (if indicated)
- Clinically well-appearing

If above criteria NOT met:

- Continue acetylcysteine at 6.25mg/kg/hr
  - If 2 bag method, repeat bag 2
  - If 3 bag method, repeat bag 3

*Note: practice variation still exists depending on poison center / toxicologist

Dart RC, et al. JAMA. 2023;6(8):e2327739.

# Alternate NAC Administration Protocols

# Wong et al, 2016

RESEARCH ARTICLE

## Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions

Anselm Wong[a,b,c,d] and Andis Graudins[a,b,d]

[a]Emergency Physician and Clinical Toxicologist, Monash Health Toxicology Service, Monash Health, Victoria, Australia; [b]School of Clinical Sciences, Faculty of Medicine, Nursing and Health Sciences, Monash University, Victoria, Australia; [c]Austin Toxicology Service, Austin Hospital, Victoria, Australia; [d]Victorian Poisons Information Centre, Austin Hospital, Victoria, Australia

CLINICAL TOXICOLOGY, 2016
VOL. 54, NO. 2, 115–119
http://dx.doi.org/10.3109/15563650.2015.1115055

| | |
|---|---|
| Study Design | Pre-post data analysis |
| Methods | • Prospectively identified patients administered 20 hour two-bag regimen from February 2014 - June 2015<br>• Compared to historical cohort of patients treated with 21 hour three-bag regimen from October 2009 - October 2013 |
| Patients | N = 599; three-bag (389) vs two-bag (210) |
| Results | Primary Endpoints<br>• Incidence of non-allergic anaphylactoid reactions<br>  • 10% vs 4.3%; p=0.02<br>• Incidence of GI reactions:<br>  • 39% vs 41%; p=0.38 |

# Schmidt et al, 2018

CLINICAL RESEARCH

## Fewer adverse effects associated with a modified two-bag intravenous acetylcysteine protocol compared to traditional three-bag regimen in paracetamol overdose

Lars E. Schmidt[a], Ditlev N. Rasmussen[b], Tonny S. Petersen[c], Ines M. Macias-Perez[d], Leo Pavliv[d], Byron Kaelin[d], Richard C. Dart[e] and Kim Dalhoff[c]

[a]Rigshospitalet and Glostrup University Hospital, Copenhagen, Denmark; [b]Hvidovre and Amager University Hospital, Copenhagen, Denmark; [c]Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark; [d]Cumberland Pharmaceuticals Inc., Nashville, Tennessee; [e]Rocky Mountain Poison and Drug Center, Denver, CO, USA

CLINICAL TOXICOLOGY
2018, VOL. 56, NO. 11, 1128–1134
https://doi.org/10.1080/15563650.2018.1475672

| | |
|---|---|
| Study Design | Retrospective chart review |
| Methods | Conducted chart review in three Danish medical centers from January 2012 – December 2014 comparing safety and efficacy data |
| Patients | N = 767; three-bag (274), two-bag (493) |
| Results | • Overall incidence non-allergic anaphylactoid reactions: 9%<br>  • 17% vs 4%, $p < 0.001$<br>• No difference in hepatotoxicity rates (4% incidence overall)<br>• Interruptions or delays: 12% vs 5% |

# Wong et al, 2020

EClinicalMedicine. 2020 Mar; 20: 100288.
Published online 2020 Mar 19. doi: 10.1016/j.eclinm.2020.100288
PMCID: PMC7082646
PMID: 32211597

**Efficacy of a two bag acetylcysteine regimen to treat paracetamol overdose (2NAC study)**

Anselm Wong,[a,b,c,*] Geoff Isbister,[d,e] Richard McNulty,[f,g] Katherine Isoardi,[h,i] Keith Harris,[j,k] Angela Chiew,[l,m] Shaun Greene,[a,b,n,o] Naren Gunja,[g,p,q] Nicholas Buckley,[r,s] Colin Page,[j,k] and Andis Graudins[c,t]

| | |
|---|---|
| **Study Design** | Multi-center observational study with non-inferiority analysis |
| **Methods** | • Reviewed patients presenting with paracetamol overdose from 2009 – 2019 who were referred to inpatient toxicology units from ED<br>• Primary non-inferiority analysis:<br>  • Included single, acute ingestions with serum paracetamol concentration performed at four to eight hours post ingestion |
| **Patients** | Reviewed 6419 paracetamol overdose cases<br>• N = 2763 received acetylcysteine; 783 (three-bag) vs 1003 (two-bag) |
| **Results** | Primary Outcome: development of acute liver injury<br>• 4-8hr APAP lvls: 16 (2.9%) vs 21 (3.1%)<br>• 8-24hr APAP lvls: 46 (23%) vs 70 (21%)<br>Secondary Outcome: incidence of adverse reactions<br>• 65 (7.1%) vs 17 (1.3%); $p < 0.0001$ |

# 2-bag Method: Advantages

- Non-inferior efficacy when compared to 3-bag method
- Less incidence of NAARs
- Less incidence of gastrointestinal reactions
- Reduced infusion administration errors
- Reduced burden on central pharmacy / IV room compounding time

# Management of Massive Acetaminophen Overdose

# Massive Overdose – Definition

- No single definition

- Ingestion of > 50g APAP, > 40g APAP
- Ingestion of > 30g APAP with co-ingested opioid or antimuscarinic agent
- Extremely high serum concentrations: > 300 mCg/mL, > 500 mCg/mL

- 2023 Consensus Statement: referred to as High-Risk APAP Ingestion
  - At least 30g of APAP ingested OR
  - APAP concentration above the high-risk line on nomogram (> 300 mCg/mL)

Dart RC, et al. JAMA. 2023;6(8):e2327739.
Hendrickson RG, et al. J Med Toxicol. 2010;6:337-344.
Chiew AL, et al. Clin Toxicol. 2017;55:1055-1065.
Marks DJB, et al. Br J Clin Pharmacol. 2017;83:1263-1272.

# Hendrickson 2019

CLINICAL TOXICOLOGY
2019, VOL. 57, NO. 8, 686–691
https://doi.org/10.1080/15563650.2019.1579914

Taylor & Francis
Taylor & Francis Group

Check for updates

REVIEW

## What is the most appropriate dose of *N*-acetylcysteine after massive acetaminophen overdose?

Robert G. Hendrickson

Department of Emergency Medicine, Oregon Health and Science University, Portland, OR, USA

# Risk of Hepatotoxicity

- Dose-dependent relationship with initial APAP level and hepatotoxicity *despite prompt administration of NAC*

Table 2. The risk of hepatotoxicity by initial acetaminophen concentration in patients treated with an IV NAC 6.25 mg/kg/h final infusion and with NAC started within 8 h of their ingestion [4,6].

| 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% |

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

# NAC Dosing Comparison

Table 1. Comparison of NAC infusion rate and total dose per day for traditional IV NAC, PO NAC and potential altered IV NAC protocols.

| Protocol | Initial infusion | "Second bag" | Total NAC in first 5h | NAC continuous infusion rate | Total NAC in first 24h | Total NAC per day all additional days |
|---|---|---|---|---|---|---|
| FDA IV NAC (Prescott protocol) | 150 mg/kg IV | 12.5 mg/kg/h IV over 4 h | 200 mg/kg | 6.25 mg/kg IV | 300 mg/kg (319 mg/kg if continued at 6.25 mg/kg/h) | 150 mg/kg |
| Oral NAC | 140 mg/kg PO | 70 mg/kg every 4 h | 210 mg/kg | 17.5 mg/kg PO* | 560 mg/kg | 420 mg/kg |
| SNAP protocol | 100 mg/kg IV over 2 h | 20 mg/kg/h IV over 10 h | 160 mg/kg | 20 mg/kg/h (×10h) | 300 mg/kg (540 mg/kg if continued at 20 mg/kg/h rate) | N/A |
| IV NAC with "double dose" continuous infusion | 150 mg/kg IV | 12.5 mg/kg/h IV over 4 h | 200 mg/kg | 12.5 mg/kg IV | 438 mg/kg | 300 mg/kg |
| IV NAC with "triple dose" continuous infusion | 150 mg/kg IV | 12.5 mg/kg/h IV over 4 h | 200 mg/kg | 18.75 mg/kg IV | 556 mg/kg | 450 mg/kg |
| IV NAC with "quadruple dose" continuous infusion | 150 mg/kg IV | 12.5 mg/kg/h IV over 4 h | 200 mg/kg | 25 mg/kg IV | 675 mg/kg | 600 mg/kg |

*PO NAC is dosed at 70 mg/kg every 4 h. The reference to 17.5 mg/kg/h "continuous infusion" is not meant to suggest that PO NAC be given as a continual infusion, but as a way to compare the dose per hour of IV and PO NAC. Additional differences in bioavailability, etc, exist between PO and IV NAC and should not be considered an exact comparison.

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

# 300/450/600 Treatment lines

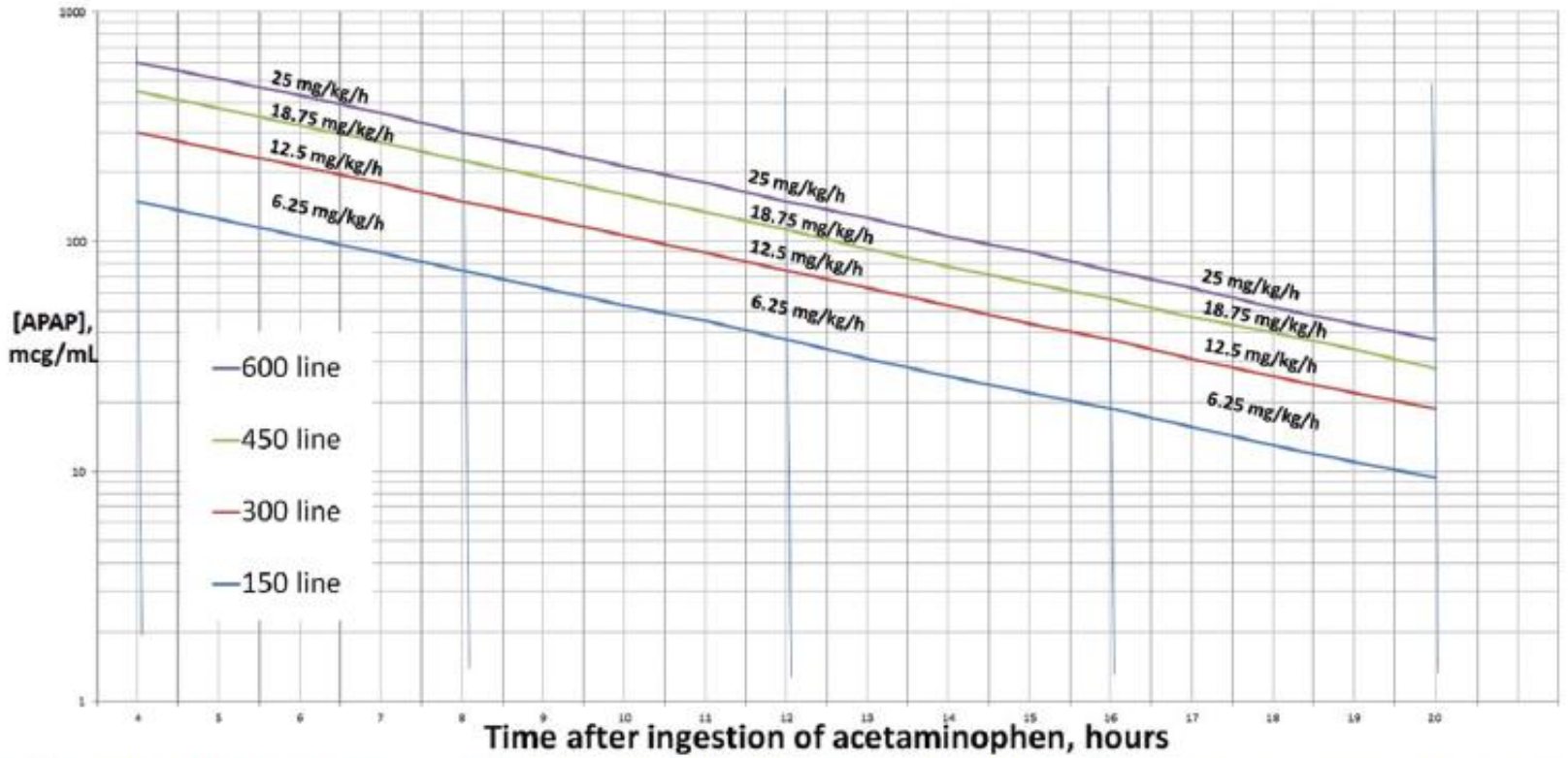



Figure 1. NAC dose adjustment for massive acetaminophen overdoses. Plot the time and concentration of acetaminophen after massive overdose to determine the continuous NAC infusion rate.

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

# Dosing Rationale

Table 3. Correlation of ingested dose of acetaminophen with the predicted 4-hour [APAP] [16], the approximate "Treatment line", and predicted dose of NAC [15].

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

Column 2 (Predicted $[APAP]_{4h}$) is the predicted 4 h acetaminophen concentration that is produced from the ingested dose in column 1. Column 3 (APAP "line") is the treatment line that correlates most closely with the value in column 2 – note that these are not exact matches, simply approximations. Column 4 is the predicted dose of NAC needed with an acetaminophen concentration above the treatment line in column 3 – details of this approximation are in the text.

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

# Hendrickson Protocol: Safety

Table 4. NAC concentration and osmolarity of alternative dosing strategies for NAC in massive overdoses.

| Dosing formulation | Dose of NAC | Min-Max dose of NAC | Diluent/solution | Max concentration | Max osmolarity |
|---|---|---|---|---|---|
| "1st bag" | 150 mg/kg | 6–15 g | 200 mL D5W | 75 mg/mL | 603–890 mOsm/L |
| "2nd bag" | 50 mg/kg | 2–5 g | 500 mL D5W | 10 mg/mL | 297–368 mOsm/L |
| "3rd bag" | 100 mg/kg | 4–10 g | 1000 mL D5W | 10 mg/mL | 297–368 mOsm/L |
| Double 3rd bag | 200 mg/kg | 8–20 g | 1000 mL D5W | 20 mg/mL | 344–485 mOsm/L |
| Triple 3rd bag | 300 mg/kg | 12–30 g | 1000 mL D5W or sterile $H_20$ | 30 mg/mL | 156–390 mOsm/L (sterile $H_20$)<br>391–603 mOsm/L (D5W) |
| Quadruple 3rd bag | 400 mg/kg | 16–40 g | 1000 mL D5W or sterile $H_20$ | 40 mg/mL | 208–520 mOsm/L (sterile $H_20$)<br>438–720 mOsm/L (D5W) |

All formulations are for patients between 40 and 100 kg.
Calculations assume the following: 20% NAC = 2.6 mOsm/mL, D5W = 0.25 mOsm/mL, 1/2NS = 0.154 mOsm/mL. Solutions are reduced by the amount of NAC volume added. For example, if 150 mL of NAC is in 1000 mL D5W, calculations are based on 150 mL of NAC and 850 mL of D5W, since 150 mL of D5W would be removed prior to mixing. All calculations are for patients 40–100 kg.

Hendrickson RG. Clin Toxicol (Phila). 2019;57(8):686-691.

# Hendrickson Protocol aka High Dose NAC

So, should we use it?

- Can be considered for high-risk APAP ingestions
- Use varies throughout the medical toxicology community

2023 Consensus Statement: increased dosage of acetylcysteine may be warranted in consultation with a poison center or toxicologist

Dart RC, et al. JAMA. 2023;6(8):e2327739.

# Hemodialysis


**Blood Purification in Toxicology:** *Reviewing the Evidence and Providing Recommendations*

- Perform systematic reviews on the use of extracorporeal treatments (ECTRs)
- Provide clinical recommendations on the use of ECTRs in poisoning, including criteria for indication / cessation / modality of ECTR
- Publish guidelines for prospective data collection, calculations, and data reporting to assist clinicians, authors and reviewers
- Offer tools and collaboration for multicenter research opportunities

# Hemodialysis

EX-TRIP Recommendations

- Consider ECTR when:
  - APAP level > 1000 mCg/mL and NAC is NOT administered
  - Patient with AMS, metabolic acidosis, elevated lactate and APAP level > 700 mCg/mL and NAC is NOT administered
  - Patient with AMS, metabolic acidosis, elevated lactate and APAP level > 900 mCg/mL despite NAC administration
- ECTR Modality
  - Intermittent hemodialysis preferred
    - Can consider CRRT, intermittent HP, exchange transfusion (neonates)
  - Continue NAC therapy at increased rate

2023 Consensus Guideline

- Hemodialysis recommended (in addition to treatment with NAC)
  - APAP level ≥ 900 mCg/mL with acidosis or altered consciousness
- NAC dosing adjustments:
  - IV NAC: 12.5 mg/kg/hr during hemodialysis
  - PO NAC: no adjustment required

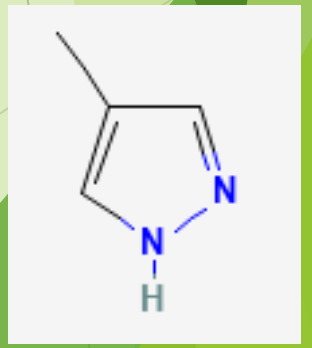
Dart RC, et al. JAMA. 2023;6(8):e2327739.
Gosselin S, et al. Clin Toxicol (Phila). 2014;52:856-867.

# Fomepizole

- 4-methylpyrazole (4-MP)

- Antidote: ethylene glycol and methanol toxicity
- Competitive inhibitor of alcohol dehydrogenase
  - Prevents formation of toxic metabolites

- Inducer & inhibitor of cytochrome P450 enzymes
  - Use in APAP toxicity?
  - CYP 2E1 inhibition




Howland MA. Goldfrank's Toxicologic Emergencies. 2019: 1435-1439.

# Fomepizole

*Hum Exp Toxicol.* 2018 December ; 37(12): 1310–1322. doi:10.1177/0960327118774902.

## 4-Methylpyrazole Protects against Acetaminophen Hepatotoxicity in Mice and in Primary Human Hepatocytes

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## Fomepizole as an Adjunctive Treatment in Severe Acetaminophen Toxicity

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# Fomepizole

Journal of Medical Toxicology (2020) 16:169–176
https://doi.org/10.1007/s13181-019-00740-z

ORIGINAL ARTICLE

## The Effect of 4-Methylpyrazole on Oxidative Metabolism of Acetaminophen in Human Volunteers

A. Min Kang[1,2] · Angela Padilla-Jones[2] · Erik S. Fisher[2] · Jephte Y. Akakpo[3] · Hartmut Jaeschke[3] · Barry H. Rumack[4] · Richard D. Gerkin[2] · Steven C. Curry[1,2]

Received: 12 July 2019 / Revised: 12 September 2019 / Accepted: 15 September 2019 / Published online: 25 November 2019
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# Fomepizole

- Consider in patients who meet criteria for hemodialysis
  - APAP level > 900 mCg/mL
  - Metabolic acidosis
  - Altered consciousness
- Dose: single dose of 15mg/kg IV

- Controlled trials are lacking → discuss with poison center or toxicologist
- 2023 Consensus Statement: does not include standard recommendation for use of fomepizole given lack of data

Dart RC, et al. JAMA. 2023;6(8):e2327739.

# Other Elimination Techniques

- Plasmapheresis: removes small amounts of APAP (5%) with therapeutic dosing
  - Limited data available to assess utility in overdose
  - May be useful in correcting coagulopathy
- Exchange transfusion: has been used to eliminate a portion of total APAP
- Liver dialysis methods:

| Molecular adsorbent recirculation system (MARS) | Fractionated plasma separation and adsorption | Single pass albumin dialysis (SPAD) |
|---|---|---|
| Uses: bridge to transplant, hemodynamic stabilization before transplant, bridge to spontaneous recovery | | |
| Benefits: improves encephalopathy, cerebral blood flow, ICP, and hemodynamics. May improve APAP clearance<br><br>A meta-analysis failed to show mortality benefit | Benefits: higher $NH_3$ clearance than MARS<br><br>Does not improve hemodynamics. Relatively unstudied in APAP overdose. | Benefits: higher $NH_3$ clearance than MARS<br><br>Does not improve hemodynamics or encephalopathy |

# Summary

- Acetylcysteine has nearly 100% prevention of hepatotoxicity and death when initiated in 8-10hrs
  - Best to wait for 4 hour levels
- Many regimens of acetylcysteine used: 1 bag / 2 bag / 3 bag methods
  - Aim to decrease medication errors and adverse events
- Massive overdoses have increased risk of bad outcome despite early intervention with antidote
  - Consider: activated charcoal, increased doses of NAC, hemodialysis, fomepizole
- Consult a poison center or toxicologist for any complicated or serious APAP poisoning

# Poison Control

- Specially trained nurses & pharmacists
- Staffed 24/7/365
- Professional callers: consultation with board-certified medical toxicologist
- National phone number – routed by caller's location

# Questions

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