Getting the Knack of NAC: N-Acetylcysteine in Acute Liver Injury

A presentation for HealthTrust Members

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Pharmacist & Nurse Objectives

- Recall the major types of acute liver injury and common etiologies
- Identify the mechanism of action and treatment recommendations for N-acetylcysteine (NAC) in acute liver injury
- Recognize evidence-based recommendations for the use of NAC in non-acetaminophen induced liver injury

Pharmacy Technician Objectives

- Recall the indication for use of N-Acetylcysteine (NAC) in acute liver injury patients
- Recognize the appropriate dosing schedules and preparations of NAC
- Identify storage and compounding considerations for NAC therapy in the context of non-acetaminophen related liver injury

Abbreviations

- AJG: American Journal of Gastroenterology
- AASLD: American Association for the Study of Liver Diseases
- ALT: alanine transaminase
- APAP: Acetaminophen
- AST: aspartate aminotransferase
- ALI: Acute liver injury
- ALF: Acute liver failure
- CE: Cerebral edema
- CT: Computed tomography
- DILI: Drug-induced liver injury
- EASL: European Association for the Study of the Liver
- HE: Hepatic encephalopathy
- HELLP: Hemolysis, elevated liver enzymes, low platelet count
- ICP: intracranial pressure
- INR: international normalized ratio
- LFT: liver function test
- MELD: Model for End-Stage Liver Disease
- NAC: N-acetylcysteine
- NAPQI: N-acetyl-p-benzoquinone imine
- NSAIDs: non-steroidal anti-inflammatory drugs
- TIPS: Transjugular intrahepatic portosystemic shunt
- ULN: upper limit of normal

Liver Physiology

- Storage
  - Blood, iron, vitamins
- Filtration
- Metabolism
  - Protein, medications
- Synthesis
  - Cholesterol, phospholipids, lipoproteins, fat
- Production of coagulation factors
- Bile secretion

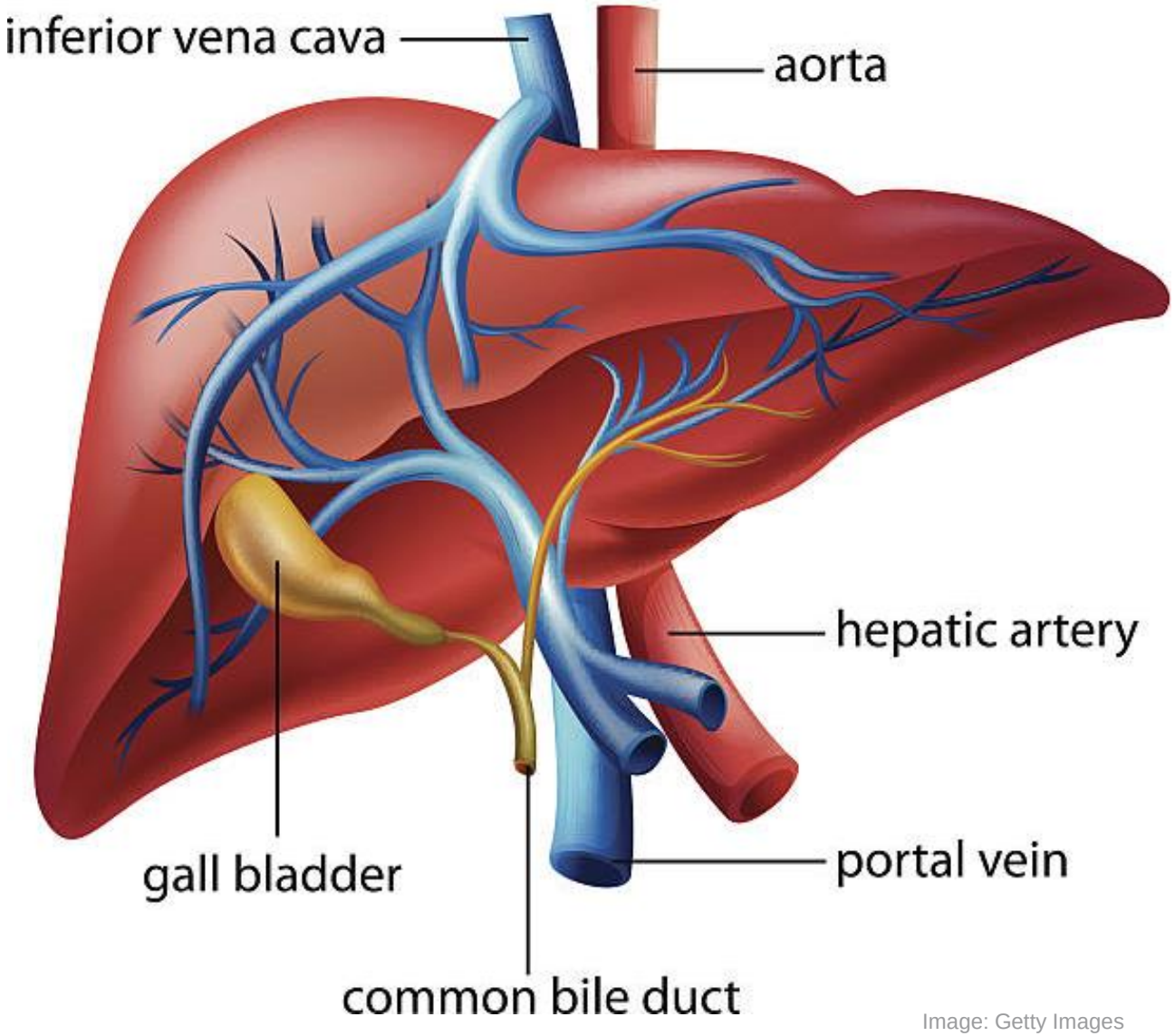
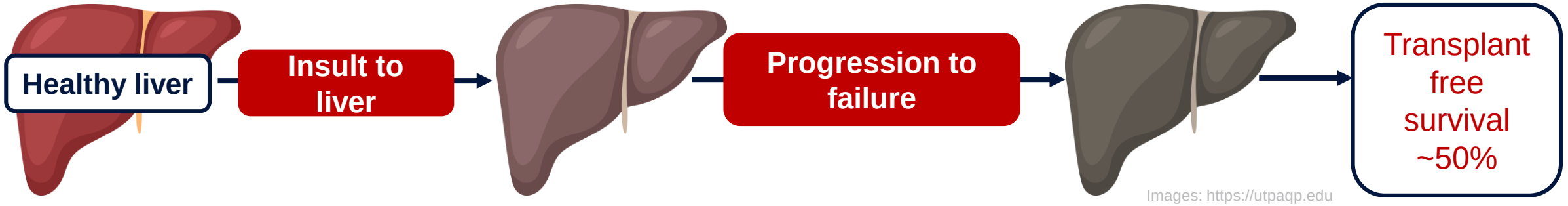


Image: Getty Images

Source: Trefts E, et al. *Curr Biol.* 2017;27(21):R1147-51.

Acute Liver Injury vs. Failure



Acute Liver Injury (ALI)

- No preexisting liver disease
- **No altered level of consciousness**
- Transaminitis (> 2-3x ULN)

Acute Liver Failure (ALF)

- No preexisting liver disease
- **Any degree of hepatic encephalopathy (HE)**
- Coagulopathy (INR ≥1.5)
- **Duration < 26 weeks; rapid onset**

ULN: upper limit of normal; INR: international normalized ratio

Sources: Wendon J, et al. *J Hepatol*. 2017;66(5):1047-81.
Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53.

Acute Liver Failure

- First described in 1970
- 1–6 cases per million population in developed countries
  - 2,000–3,000 cases per year in the United States
- True incidence is likely underestimated
- Most commonly caused by acetaminophen (APAP) toxicity
  - 28% mortality rate – one-third requiring liver transplantation
- Acute decompensated cirrhosis or acute on chronic liver failure are not included in definition

Sources: Trey C, et al. *Prog Liver Dis*. 1970;3:282-298
Bernal W, et al. *N Engl J Med.2013;369(26)*:2525-34.
Stravitz RT, et al. *Lancet*. 2019;394(10201):869-81.
Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53.

Etiologies of Acute Liver Injury and Failure

Viral
Hepatitis, herpes, cytomegalovirus, Epstein-Barr

Vascular
Budd-Chiari, ischemia, thrombosis, hepatic veno-occlusive disease

Drug-induced
Acetaminophen, antimicrobials, NSAIDs, statins, amiodarone, antineoplastics, supplements

Metabolic
Hereditary hemochromatosis, alpha-I antitrypsin deficiency, Wilson disease, acute fatty liver of pregnancy, HELLP syndrome

Toxins
Alcohol, amanita mushroom, kava, green tea extract

Other
Autoimmune, malignancy, heatstroke, indeterminate cause

NSAIDs: non-steroidal anti-inflammatory drugs, HELLP: hemolysis, elevated liver enzymes, low platelet count

Source: Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53.

Clinical Presentation

- Fatigue
- Right upper quadrant pain
- Nausea and vomiting
- Jaundice
- Hypoglycemia
- Abnormal liver function tests (LFTs)
- Coagulopathy
- Altered mental status
- Cerebral edema (CE)
- Multiorgan failure
- Shock

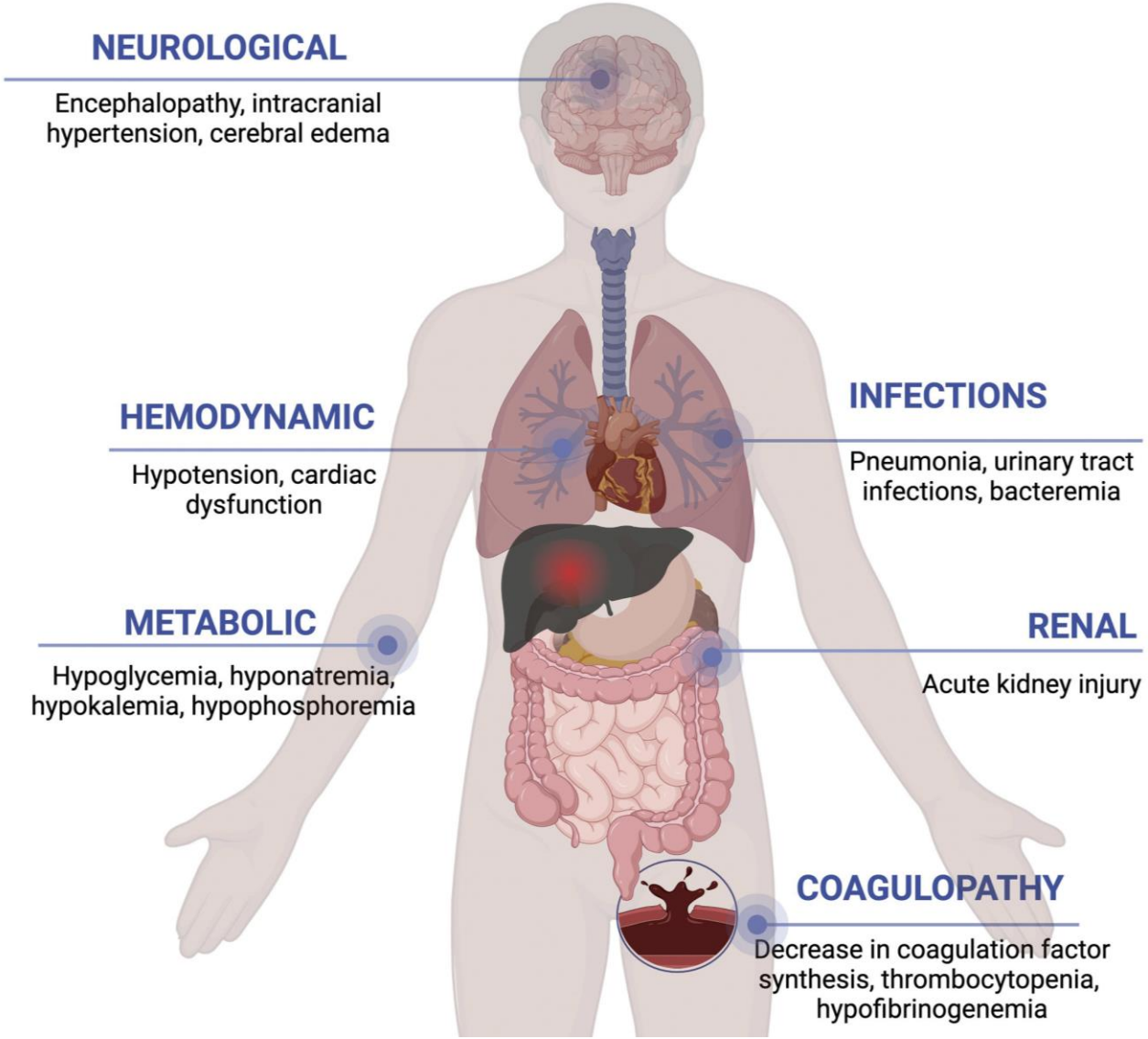


Image: *Rev Gastroenterol Mex (Engl Ed)*. 2024;89(3):404-17

Sources: Lee WM, et al. *Hepatology*. 2012;55(3):965-967
Martínez-Martínez LM, et al. *Rev Gastroenterol Mex (Engl Ed)*. 2024;89(3):404-417

Acute Liver Failure Classification

O'Grady Classification

Classifies patients based on the time between the presentation of jaundice and the onset of hepatic encephalopathy

Hyperacute

- Onset < 7 days
- Hepatitis A and E
- Acetaminophen toxicity, ischemic injury
- High risk of cerebral edema (CE)
- Best prognosis without transplantation

Acute

- Onset 7-21 days
- Hepatitis B infection
- Intermediate risk of CE

Subacute

- Onset >21 days
- Non-acetaminophen DILI
- Low risk of CE

Sources: Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53
O'Grady JG, et al. *Lancet*. 1993;342(8866):273-5.

West-Haven Criteria for Hepatic Encephalopathy

Grade	Symptoms	Management
0	No clinical evidence of altered mentation	• Observation
1	Diminished awareness, short attention span, altered sleep	• Baseline CT head • Initiate transfer to transplant center
2	Lethargy, disoriented to time, inappropriate behavior, dyspraxia, asterixis	• Transfer to intensive care unit • Hourly neuro checks
3	Somnolence, confusion, gross disorientation, bizarre behavior	• Intubation • Repeat CT head • Avoid benzodiazepines and opioids
4	Coma	• Repeat CT head • Consider intracranial pressure (ICP) monitoring • Treat cerebral edema

Source: Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53

Acute Liver Failure Classification

King's College Criteria

Predicts risk of mortality and need for liver transplantation in both acetaminophen and non-acetaminophen induced acute liver failure

Acetaminophen-induced

- **Arterial pH < 7.3** after resuscitation and >24 h since ingestion
- Lactate >3 mmol/L *OR* the following criteria:
  - HE > Grade 3
  - SCr > 3.4 mg/dL
  - INR > 6.5

Non-acetaminophen-induced

- INR > 6.5 *OR* 3 out of 5 criteria:
  - Unfavorable etiology
  - Age < 10 years or > 40 years
  - **Duration of jaundice to encephalopathy > 7 days**
  - Bilirubin > 17.4 mg/dL
  - INR > 3.5

Source: Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53

Model for End-Stage Liver Disease (MELD)

- Originally developed to predict three-month mortality in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedures
- Validated as a prognostic tool in ALF
- Includes bilirubin, sodium, INR, serum creatinine, and dialysis status

MELD Score	Mortality
≤9	1.9 %
10-19	6.0 %
20-29	19.6 %
30-39	52.6 %
≥40	71.3 %

Patients presenting with **MELD >25** are at high risk of **poor outcomes**

Sources: Jamil Z, et al. *J Clin Med.* 2022;11(22):6654
Malinchoc M, et al. *Hepatology*. 2000;(4):864-71

Pharmacist/RN Assessment Question #1:

- Which of the following is the most common drug-induced etiology of acute liver failure in the US?

A. Steroids
B. Acetaminophen
C. Non-steroidal anti-inflammatory drugs
D. Beta blockers

Pharmacist/RN Question #1: Correct Response

- Which of the following is the most common drug-induced etiology of acute liver failure in the US?

A. Steroids
B. Acetaminophen
C. Non-steroidal anti-inflammatory drugs
D. Beta blockers

Acetaminophen Toxicity

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Epidemiology

- Most acetaminophen (APAP) overdoses result in limited toxicity and very low mortality rates
- Leading cause of acute hepatic failure in United States
  - Mortality rates up to 30%

Single Ingestion

- Usually intentional
- Single dose >10-15 g

Chronic Ingestion

- Usually unintentional
- Large quantities (>10 g) over several days

Source: Ostapowicz G, et al. *Ann Intern Med*. 2002;137(12):947-954

Acetaminophen Basics

- Most widely used analgesic-antipyretic worldwide
- Available in many combination products and formulations
  - Analgesics, opioids, sedatives, antihistamines, decongestants, expectorants
- Common dosing
  - Adult: 650-1,000 mg every 4-6 h
  - Maximum: 3,000-4,000 mg/day
- Pharmacology
  - Centrally acting
  - Indirect COX inhibition
  - Modulation of serotonin and cannabinoid receptors

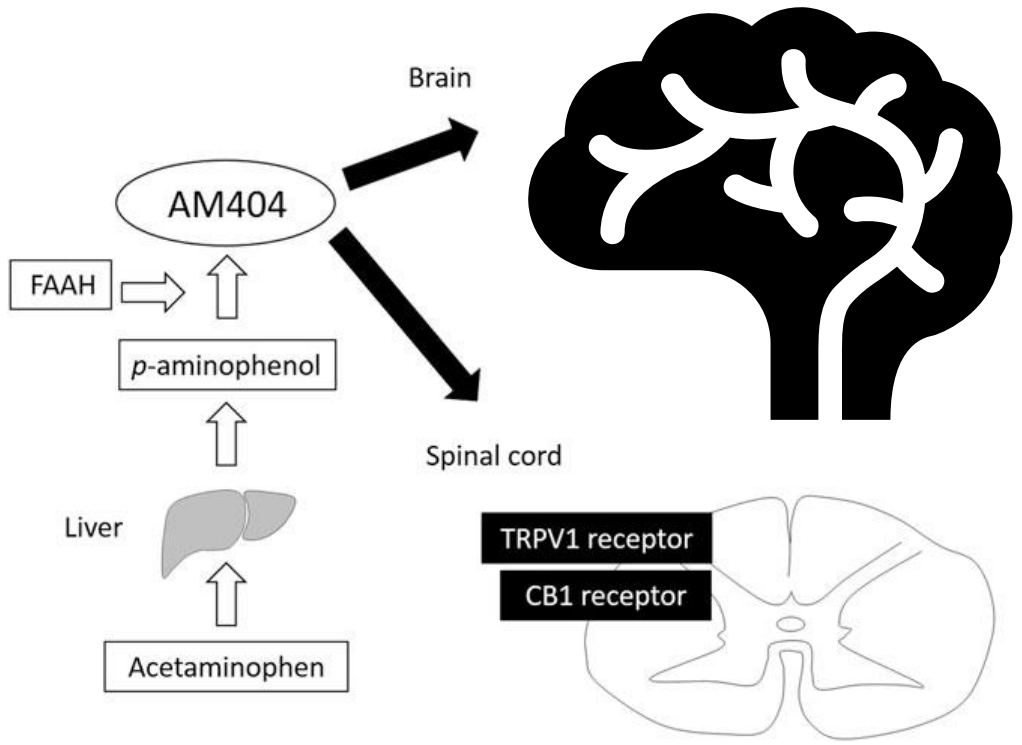


Image: *Front Pharmacol*. 2020;11:580289

Sources: Jóźwiak-Bebenista M, et al. *Acta Pol Pharm*. 2014;71(1):11-23
Ohashi N, et al. *Front Pharmacol*. 2020;11:580289

Acetaminophen Metabolism

- 90% via hepatic conjugation to inactive metabolites
- 50-60% via glucuronidation
- 25-35% via sulfation
- 5% oxidized via CYP
  - Neutralized by glutathione

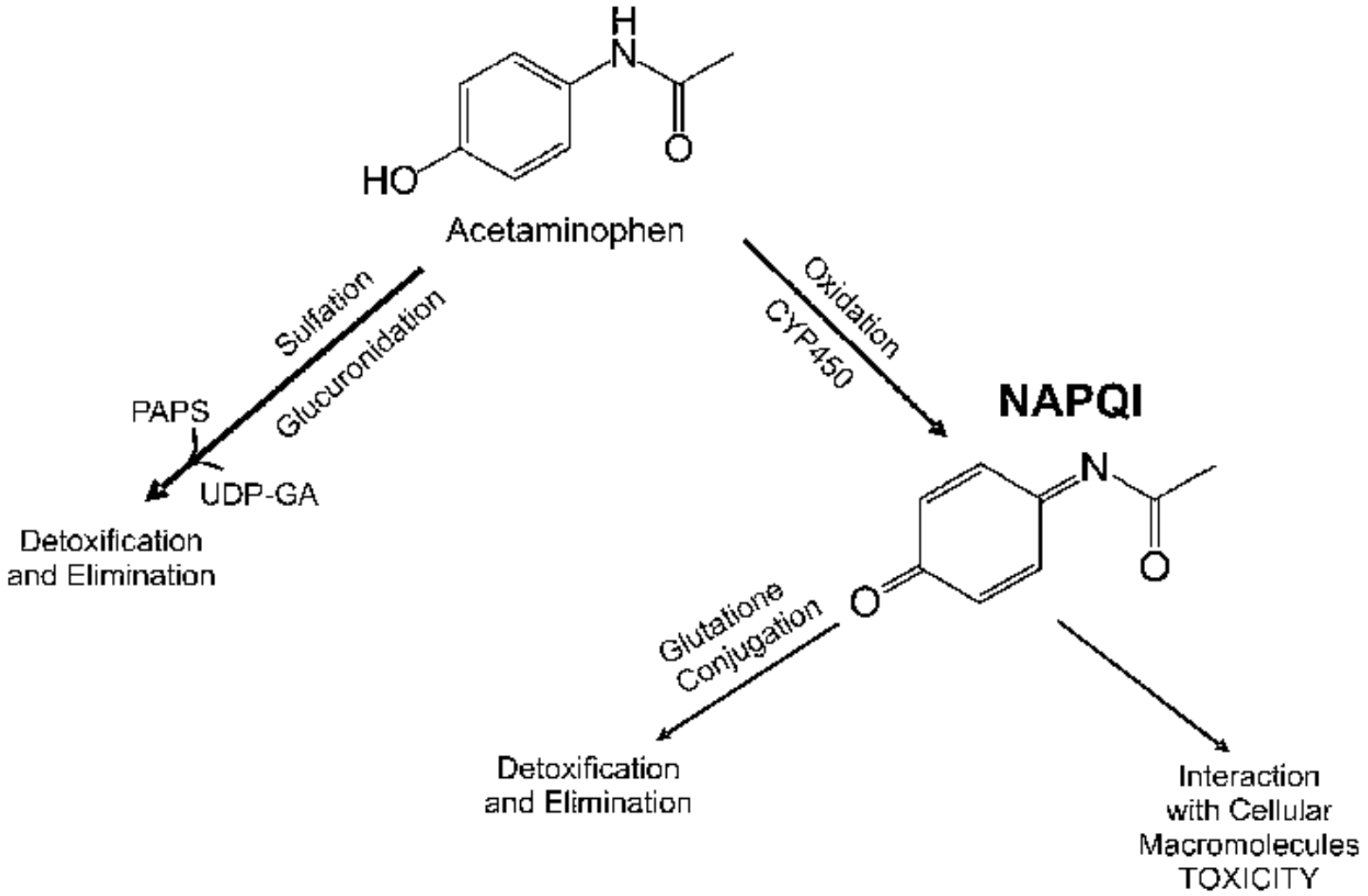


Image: *Toxicol Sci*. 2011;120(1):33-41.

Source: Moyer AM, et al. *Toxicol Sci*. 2011;120(1):33-41.

Acetaminophen Toxicity

- Dose-related toxicity
  - Single intentional overdose of >10-15 g
  - Unintentional overdose of >10 g over several days
- Fasting or ingestion of alcohol may contribute to toxicity
- Acute vs. chronic toxicity

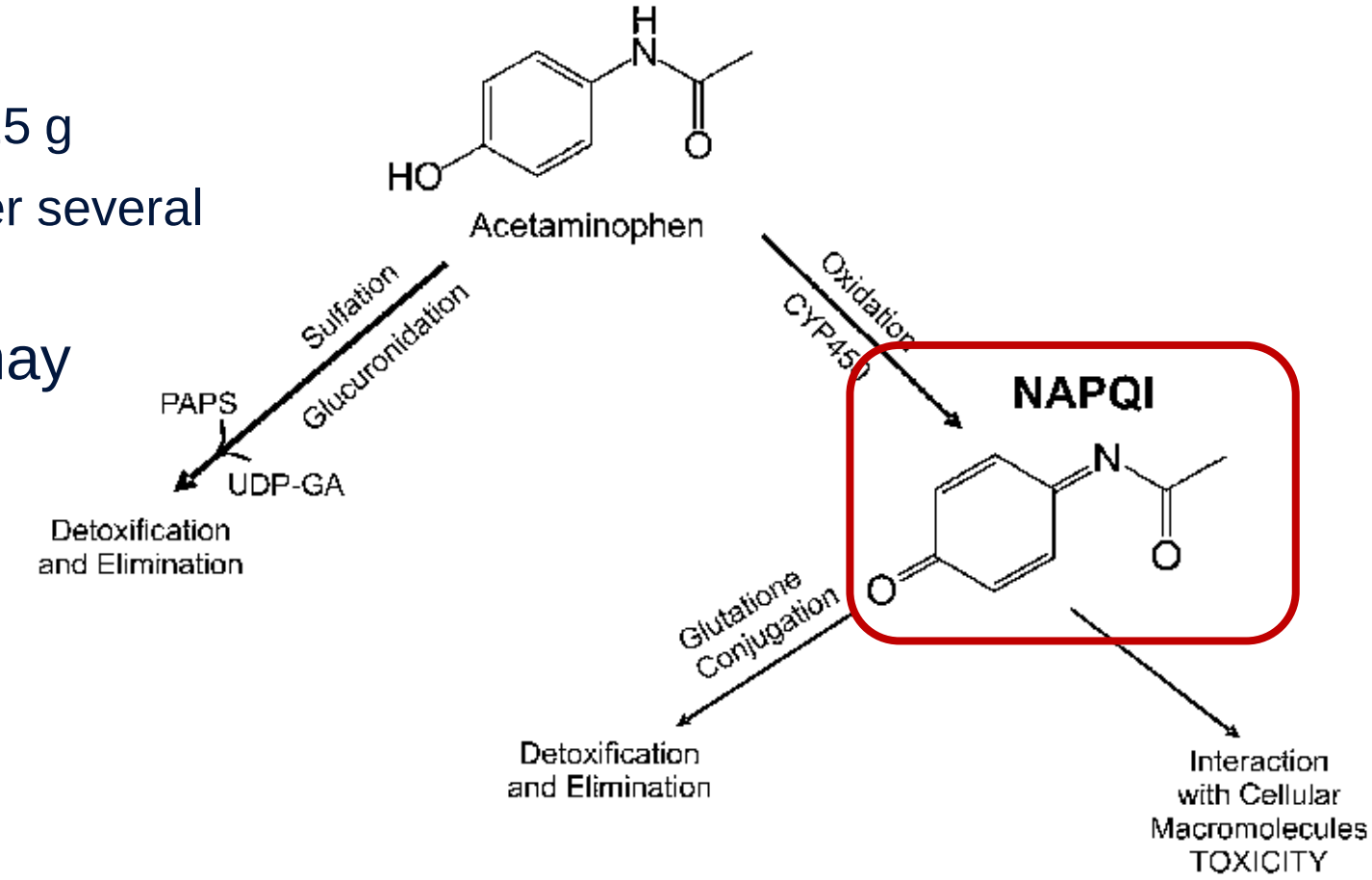
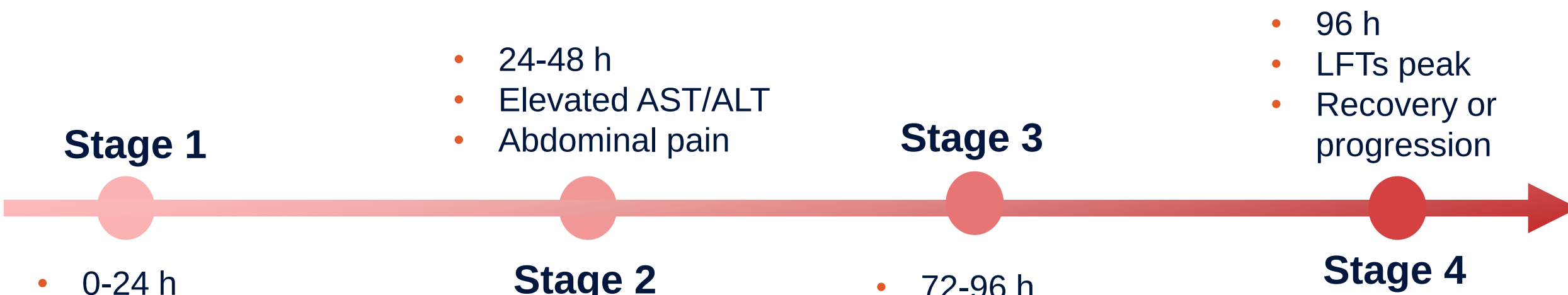


Image: *Toxicol Sci*. 2011;120(1):33-41.

Source: Moyer AM, et al. *Toxicol Sci*. 2011;120(1):33-41.

NAPQI: N-acetyl-p-benzoquinone imine

Clinical Stages of Acetaminophen Toxicity



Source: Saccomano SJ. *Nurse Pract*. 2019;44(11):42-47

Management of Acetaminophen Toxicity

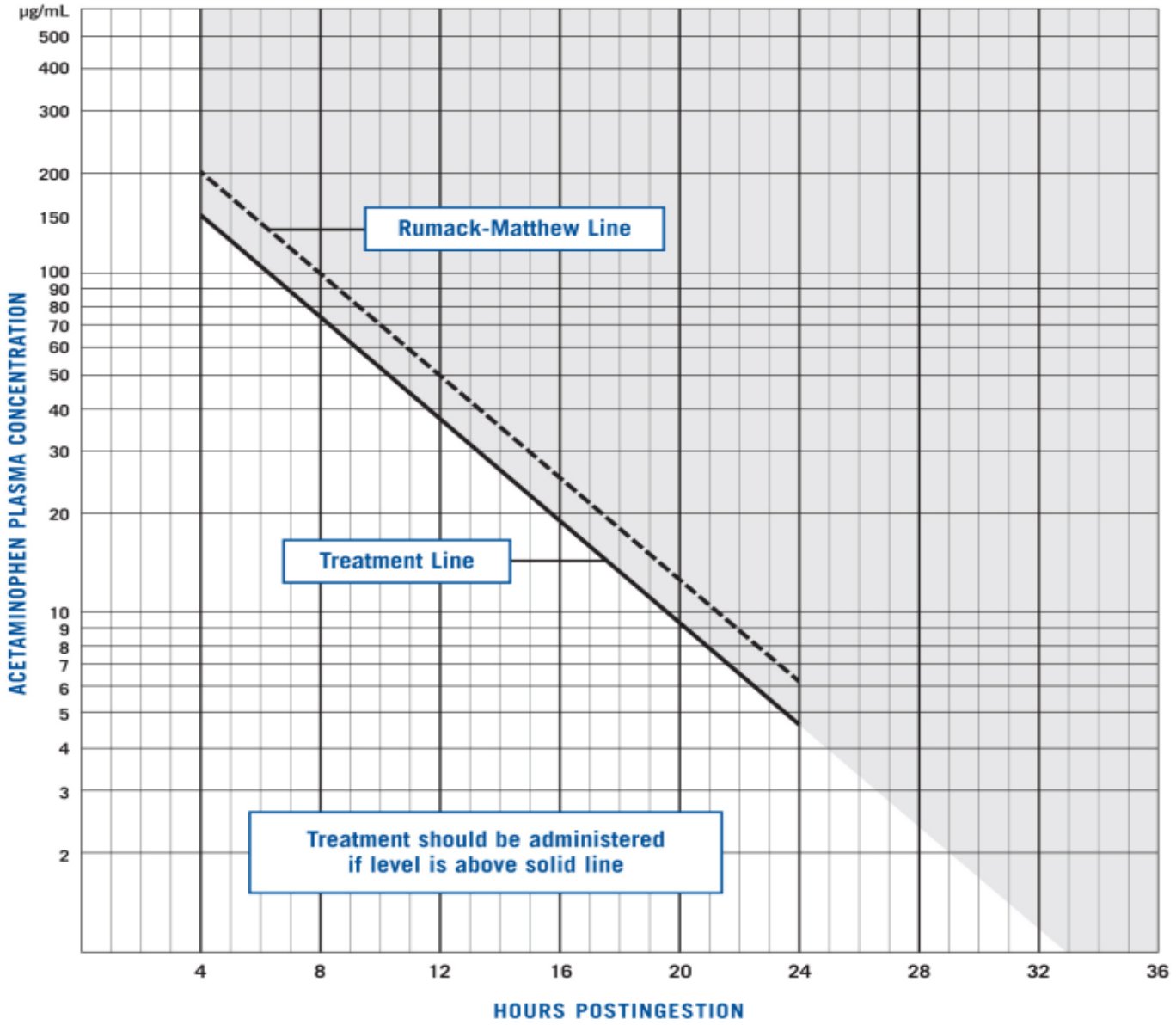
- Poison control consultation
- Early gastric decontamination if ingestion < 4 h
  - 1-2 g/kg single dose of activated charcoal
- N-acetylcysteine (NAC)
  - Guideline recommendation if positive APAP level or evidence of liver injury even if time of ingestion is unknown
  - Rumack-Matthew nomogram
- Fomepizole
- Dialysis
- Liver transplantation

Image: *America's Poison Centers*

Sources: Lee WM, et al. *Hepatology*. 2012;55(3):965-967
Wendon J, et al. *J Hepatol*. 2017;66(5):1047-81.
Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53.

Rumack-Matthew Nomogram

- Used for acute ingestions only
- Based on exposures to 325 mg immediate release tablets
- Cannot plot on graph until 4 h post ingestion
  - Serum levels drawn prior may not reflect peak levels
- Treatment warranted for values above black solid line



Source: Ostapowicz G, et al. *Ann Intern Med*. 2002;137(12):947-954

N-acetylcysteine Mechanism of Action

Restores glutathione reserves

↓

Increases capacity to detoxify NAPQI

↓

Limits formation of NAPQI

↓

Reactive oxygen species scavenger

↓

Preservation of multiorgan function

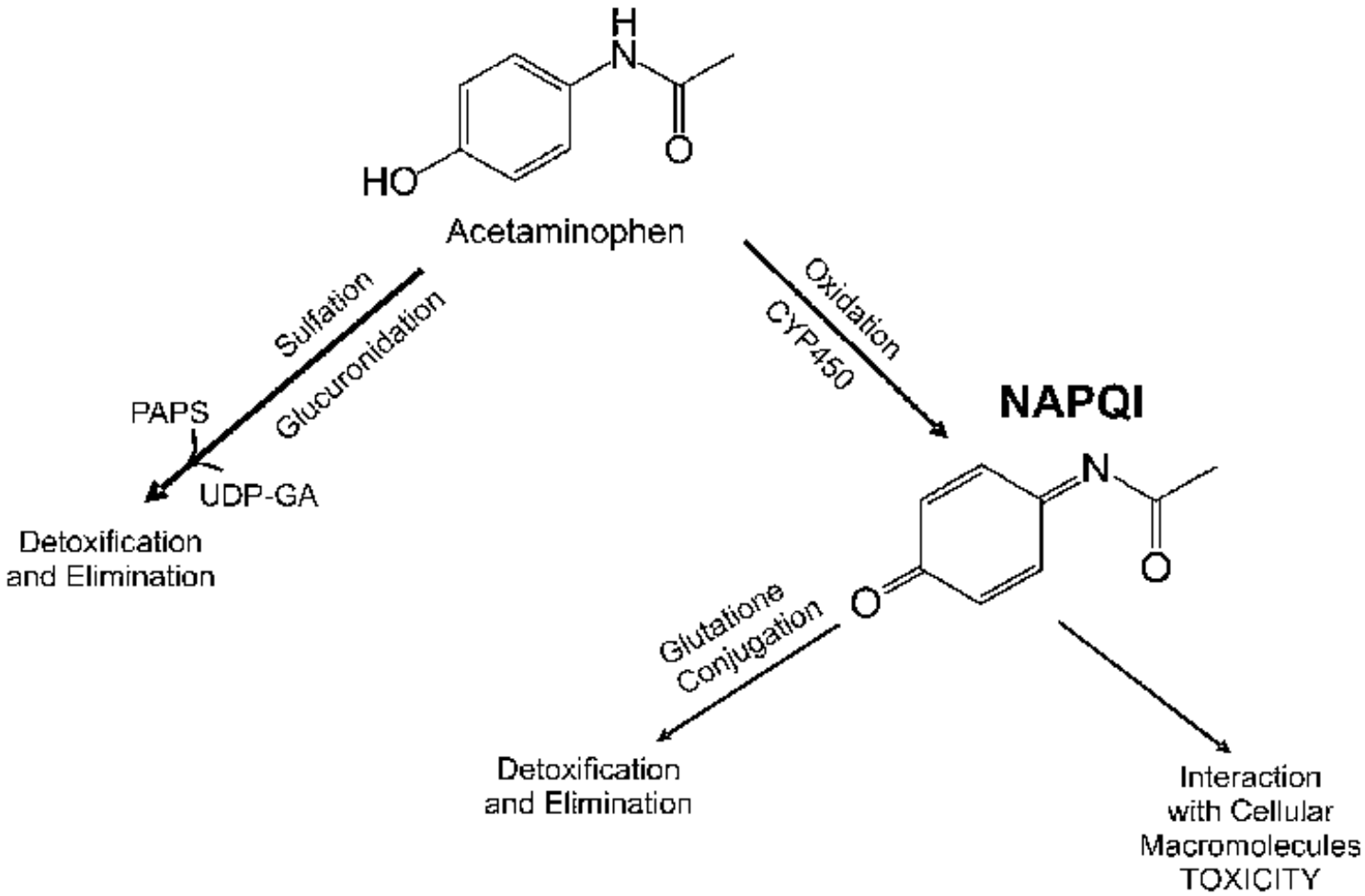


Image: *Toxicol Sci*. 2011;120(1):33-41.

Source: Moyer AM, et al. *Toxicol Sci*. 2011;120(1):33-41.

NAC Dosing

Oral Administration

- 140 mg/kg once → 70 mg/kg q4h for 17 doses

Intravenous Administration

- 3 Bag Regimen → 1st dose: 150 mg/kg over 1 h; 2nd dose: 50 mg/kg over 4 h; 3rd dose: 100 mg/kg over 16 h
- 2 Bag Regimen → 1st dose: 200 mg/kg over 4 h; 2nd dose: 100 mg/kg over 16 h

Source: Acetaminophen. *Lexi-Drugs*. UpToDate Lexidrug. Accessed February 2, 2025.

NAC Treatment

- Adverse effects
  - Oral – emesis; repeat dose if vomiting within 1 h of administration
  - IV – flushing; anaphylactoid reaction
- Studies have demonstrated oral and IV are equally effective
- Repeat APAP level and liver enzymes after 12-20 h of treatment
- NAC can be discontinued if APAP level is undetectable and transaminases are improving
  - May continue treatment after 21 h based on APAP level
  - Continuing treatment beyond the initial protocol may be based on elevated APAP level, persistent coagulopathy (INR>1.5), or encephalopathy

Sources: Lee WM, et al. *Hepatology*. 2012;55(3):965-967
Wendon J, et al. *J Hepatol*. 2017;66(5):1047-81.
Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53.

Technician Assessment Question #1

- Which of the following is the most common indication for using NAC in acute liver injury patients?
  A. Mushroom toxicity
  B. Viral hepatitis
  C. Acetylsalicylic acid toxicity
  D. Acetaminophen toxicity

Technician Assessment Question #1: Correct Response

- Which of the following is the most common indication for using NAC in acute liver injury patients?
  - A. Mushroom toxicity
  - B. Viral hepatitis
  - C. Acetylsalicylic acid toxicity
  - **D. Acetaminophen toxicity**

Fomepizole

- Off-label use as **adjunctive** therapy in acetaminophen toxicity
  - Consider in patients with delayed presentation/identification, evidence of hepatotoxicity despite adequate NAC therapy, or in massive acetaminophen ingestion
  - Massive ingestion: >30 g, serum APAP concentration >300 mcg/mL at any time, or a multiplication product (serum APAP x ALT) of ≥ 10,000
- Proposed mechanism
  - Blunt oxidative metabolism of acetaminophen to NAPQI via CYP 2E1 inhibition
- Dosing
  - 15 mg/kg IV over 30 mins, followed by 10 mg/kg IV every 12 hours
  - Dose adjustments required in renal replacement therapy
- Cost remains limiting factor

Source: Link SL, et al. *Clin Toxicol (Phila)*. 2022;60(4):472-477

Fomepizole Case Studies

Case Report	Initial Labs	Management	Result
33 y/o M with history of alcohol abuse; ingested 25,000 mg APAP over 2 days	APAP: 337 mg/L AST: 137 IU/L ALT: 194 IU/L INR: 2.2 Lactate 4.1 mmol/L	NAC Fomepizole 15 mg/kg x1	INR normalized in 3 days, peak LFTs <1000 IU/L, medically cleared for discharge at 3 days
47 y/o F; ingested 6,000 mg over 2-3 days	APAP: 10 APAP*AT: 26,322 Lactate 12.1 mmol/L	NAC Fomepizole 15 mg/kg x1	Full recovery with no signs of liver failure at discharge
45 y/o M with history of epilepsy and alcohol abuse; unknown ingestion	APAP: >377 mg/L AST: 14 U/L ALT 47 U/L	NAC Fomepizole 15 mg/kg CRRT NAC boluses and fomepizole 10 mg/kg x2 doses	CRRT stopped after 12 hours Full recovery with no significant liver injury Discharged to inpatient psych day 8

Sources: Link SL, et al. *Clin Toxicol (Phila)*. 2022;60(4):472-477
Shah KR, et al. *Am J Emerg Msed.* 2020;38(2):410.e5-410.e6

Pharmacist/RN Assessment Question #2

- Which of the follow is a mechanism of action associated with NAC in the treatment of acetaminophen-induced acute liver failure?

A. Restores glutathione reserves
B. Decreases capacity to detoxify NAPQI
C. Promotes formation of NAPQI
D. Directly removes acetaminophen from the body

Pharmacist/RN Assessment Question #2: Correct Response

- Which of the follow is a mechanism of action associated with NAC in the treatment of acetaminophen-induced acute liver failure?

A. **Restores glutathione reserves**
B. Decreases capacity to detoxify NAPQI
C. Promotes formation of NAPQI
D. Directly removes acetaminophen from the body

Technician Assessment Question #2

- Which formulation of NAC is most commonly used for acetaminophen toxicity?

A. Oral NAC
B. IV 3 bag method
C. IV 2 bag method
D. IV 1 bag method

Technician Assessment Question #2: Correct Response

- Which formulation of NAC is most commonly used for acetaminophen toxicity?

A. Oral NAC
B. IV 3 bag method
C. IV 2 bag method
D. IV 1 bag method

Non-Acetaminophen Toxicity

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Management of Non-APAP Toxicity

- **Determining etiology is paramount in order to guide treatment and provide prognostic information**
- Supportive strategies for all patients
  - Hemodynamic support
  - Hepatic encephalopathy correction
    - Intracranial pressure monitoring and adjunctive agents
  - Coagulopathy
    - Correction is recommended in patients with active bleeding
  - Nutritional and metabolic support

Sources: Lee WM, et al. *Hepatology*. 2012;55(3):965-967
Wendon J, et al. *J Hepatol*. 2017;66(5):1047-81.
Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53.

NAC in the Management of Non-APAP Toxicity

- N-acetylcysteine
  - 2023 American Journal of Gastroenterology (AJG) Acute Liver Failure Guidelines: “In patients with non-APAP ALF, we suggest the initiation of intravenous NAC”
- Populations studied largely consist of viral hepatitis followed by drug-induced liver injury
- Other potential indications
  - Amanita phalloides poisoning
  - Ischemic liver injury (due to congestive heart failure, sepsis, traumatic injury, or major surgery)
  - Indeterminate cases

Sources: Lee WM, et al. *Hepatology*. 2012;55(3):965-967
Wendon J, et al. *J Hepatol*. 2017;66(5):1047-81.
Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53.

Proposed Mechanisms of NAC in Non-APAP ALF

Replenishes glutathione stores

Anti-inflammatory effects blunt cytokine response

Precursor for glutathione synthesis

Antioxidant effects decrease free radical damage

Microcirculatory vasodilation via nitric oxide and cyclic guanosine monophosphate (cGMP) regeneration

Source: Chertoff J. *J Intensive Care Med*. 2018;33(2):87-96

Current Evidence of NAC in Non-APAP Liver Injury

2011 AASLD position paper on ALF: "N-acetylcysteine may be beneficial for acute liver failure due to drug-induced liver injury" outside of acetaminophen toxicity

2017 European Association for the Study of the Liver (EASL) guidelines: "NAC may improve outcomes in non-paracetamol induced liver injury"

2023 AJG Acute Liver Failure Guidelines: "In patients with non-APAP ALF, we suggest the initiation of intravenous NAC"

AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver; AJG: American Journal of Gastroenterology

Sources: Lee WM, et al. *Hepatology*. 2012;55(3):965-967
Wendon J, et al. *J Hepatol*. 2017;66(5):1047-81.
Shingina A, et al. *Am J Gastroenterol*. 2023;118(7):1128-53.

Intravenous N-acetylcysteine Improves Transplant-free Survival in Early Stage Non-acetaminophen Acute Liver Failure

Lee WM, et al. Gastroenterology. 2009;137(3):856-64, 864.e1.

Study Design	• Prospective, randomized, double blind placebo controlled trial
Population	• Adults, evidence of ALF (encephalopathy and INR ≥1.5, onset <24 weeks • Excluded patients with acetaminophen overdose, **shock liver**, previously received NAC • DILI (n=45), autoimmune hepatitis (n=26), HBV (n=37), unknown (n=41)
Intervention	• **NAC:** 150 mg/kg/h for 1 h → 12.5 mg/kg/h for 4 h → 6.25 mg/kg for 67 h • **Placebo:** dextrose 5%
Outcomes	• **Primary:** overall survival at 21 days • **Secondary:** transplant-free survival at 21 days, transplant rate, hospital length of stay, number of organ systems failing

Source: Lee WM, et al. *Gastroenterology*. 2009;137(3):856-864.e1

Intravenous N-acetylcysteine Improves Transplant-free Survival in Early Stage Non-acetaminophen Acute Liver Failure

Baseline Characteristics	NAC (n=81)	Placebo (n=92)
Age, years	42 (17-69)	40.5 (18-71)
Hepatic encephalopathy grade I-II*	73% (63-83)	62% (51-72)
Symptoms to coma, days	15 (0-1170	17 (0-69)
Jaundice to coma, days	7 (0-153)	12 (0-65)
Bilirubin, mg/dL	22.3 (0.7-51)	20.3 (0.7-62)
INR	2.4 (1.4-20.1)	2.9 (1.1-14)
ALT, IU/L	999 (13-10,153)	756.5 (31-13,000)
MELD	32 (12-57)	33 (19-49)

Results presented as median (range)
*Hepatic encephalopathy grade I-II presented as % (95% CI)

Source: Lee WM, et al. *Gastroenterology*. 2009;137(3):856-864.e1

Intravenous N-acetylcysteine Improves Transplant-free Survival in Early Stage Non-acetaminophen Acute Liver Failure

Outcome	NAC (n=81)	Placebo (n=92)	P value
Primary Outcome			
Overall survival	70% (60-81)	66% (56-77)	0.283
Secondary Outcomes			
Transplant-free survival	40% (28-51)	27% (18-37)	0.043
Transplantation rate	32% (21-43)	45% (34-55)	0.093
Hospital length of stay, days	9	13	0.056
Number of organ system failures	No difference between groups		0.923

Results presented as % with 95% CI or average

- Similar safety profile with the exception of nausea and vomiting (NAC: 14%, placebo: 4%; p=0.031)
- Patients with DILI or HBV showed improved outcomes with NAC compared with those with autoimmune hepatitis or indeterminate etiologies

Source: Lee WM, et al. *Gastroenterology*. 2009;137(3):856-864.e1

Intravenous N-acetylcysteine Improves Transplant-free Survival in Early Stage Non-acetaminophen Acute Liver Failure

- Conclusion
  - NAC improves transplant-free survival in patients with non-APAP induced acute liver injury, with no significant differences in overall survival
    - Improvement in transplant-free survival primarily observed in Grade I-II HE on admission
- Interpretation
  - First to demonstrate advantages to NAC in non-APAP induced acute liver injury
  - Included a variety of etiologies of acute liver injury; excluded patients with shock liver
  - Majority of patients in both groups did not complete full NAC treatment (NAC: 63% vs placebo: 59%)
  - Serious adverse events and long term outcomes at one year were not reported, although the trial reported that they were collected
  - Patients who received liver transplants could have confounded survival results

Source: Lee WM, et al. *Gastroenterology*. 2009;137(3):856-864.e1

Pharmacist/RN Assessment Question #3:

- What were the findings of Lee et al trial that supports the use of NAC in non-acetaminophen induced acute liver failure?
  A. Improved mortality
  B. Improved transplant free survival
  C. Decreased hospital length of stay
  D. Increased hospital length of stay

Pharmacist/RN Question #3: Correct Response

- What were the findings of Lee et al trial that supports the use of NAC in non-acetaminophen induced acute liver failure?
  A. Improved mortality
  B. Improved transplant free survival
  C. Decreased hospital length of stay
  D. Increased hospital length of stay

Role of N-acetylcysteine Treatment in Non-acetaminophen-induced Acute Liver Failure: A Prospective Study

Nabi T, et al. *Gastroenterol*. 2017;23(3):169-175.

Study Design	• Prospective, randomized case control trial
Population	• Adults, evidence of ALF (encephalopathy and INR ≥1.5, onset <8 weeks) • Excluded patients with acetaminophen overdose, **shock liver**, previously received NAC, acute on chronic liver failure • Viral hepatitis (n=30), DILI (n =15), undetermined (n=30), others (n=5)
Intervention	• **NAC**: 150 mg/kg/h for 1 h → 12.5 mg/kg/h for 4 h → 6.25 mg/kg for 67 h • **Placebo:** dextrose 5%
Outcomes	• Hospital length of stay • Overall survival

Source: Nabi T, et al. *Saudi J Gastroenterol*. 2017;23(3):169-175

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Baseline Characteristics	NAC (n=40)	Placebo (n=40)	P value
Hepatic Encephalopathy Grade I Grade II Grade III Grade IV	 10 (25) 13 (33) 7 (18) 10 (25)	 21 (53) 8 (20) 7 (18) 4 (10)	0.054
Age, years	31 ± 12	38 ± 20	0.035
INR	2.9 ± 1.2	2.5 ± 0.8	0.114
Bilirubin, mg/dL	21 ± 9	21 ± 10	0.827
AST, mg/dL	1,726 ± 983	1,462 ± 679	0.166
ALT, mg/dL	1,051 ± 717	1,056 ± 569	0.972
Jaundice to encephalopathy, days	22 ± 11	28 ± 18	0.081
MELD	32 ± 7	30 ± 5	0.313

Results presented as n,% or average ± SD

Source: Nabi T, et al. *Saudi J Gastroenterol*. 2017;23(3):169-175

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Outcome	NAC (n=40)	Placebo (n=40)	P value
Hospital length of stay, days	8 ± 2	11 ± 3	0.002
Overall survival	29 (72.5)	19 (47.5)	0.025

Results presented as n (%) or average ± SD

- Patients in the control group had higher incidence of seizures (p=0.156) and significantly more mannitol administration (p=0.037) when compared to NAC
- Subgroup analysis of ALF etiology found significant improved in survival in the DILI group (p=0.049) when compared to other etiologies

Source: Nabi T, et al. *Saudi J Gastroenterol*. 2017;23(3):169-175

Role of N-acetylcysteine Treatment in Non-acetaminophen-induced Acute Liver Failure: A Prospective Study

- Conclusion
  - NAC is useful and has advantages in the treatment of non-APAP induced acute liver injury with improved hospital admission duration and improved survival during admission
    - Improved outcomes primarily seen in the DILI subgroup
- Interpretation
  - This trial further supported the use of NAC in non-APAP induced acute liver injury
  - Showed significant results in reduced hospital stay along with improved survival
  - ALF definition and etiologies consistent with Lee trial
  - Lee et al. found improved transplant-free survival primarily in the viral hepatitis and DILI subgroups
    - This trial only found significant reductions in the DILI subgroup

Source: Nabi T, et al. *Saudi J Gastroenterol*. 2017;23(3):169-175

Effect of N-Acetylcysteine on Mortality and Liver Transplantation Rate in Non-Acetaminophen-Induced Acute Liver Failure: A Multicenter Study

Darweesh et al. Clin Drug Investig. 2017;37(5):473-482.

Study Design	• Prospective, multicenter, observational study
Population	• Adults with ALF (jaundice (bilirubin >25 mmol/L) and coagulopathy (INR >1.5) **with or without encephalopathy** • Excluded clinical or historical evidence of acetaminophen overdose or prior liver disease
Intervention	• **NAC**: 150 mg/kg IV over 0.5 h → 70 mg/kg IV over 4 h → 70 mg/kg IV over 16 h → 600mg/day PO NAC 2-3 days prior to discharge • **Placebo**
Outcomes	• **Primary:** reduction in mortality or liver transplantation • **Secondary:** length of hospital stay, ICU admission, hepatic encephalopathy incidence, safety profile

Source: Darweesh SK, et al. *Clin Drug Investig*. 2017;37(5):473-482

Effect of N-Acetylcysteine on Mortality and Liver Transplantation Rate in Non-Acetaminophen-Induced Acute Liver Failure: A Multicenter Study

Baseline Characteristic	NAC (n=85)	Placebo (n=70)	P value
Age, years	33.5 ± 11	34.8 ± 9	n/a
INR	2.4 ± 0.5	2.3 ± 0.5	0.283
AST, IU/L	3951 ± 1630	3956 ± 1386	0.990
ALT, IU/L	3144 ± 1748	2993 ± 1295	0.706
Bili, mg/dL	1.0 ± 0.5	1.1 ± 0.4	0.314
Encephalopathy grade 0 I-II III-IV	 61 (72) 20 (24) 4 (5)	 45 (64) 19 (27) 6 (9)	0.7

Results presented as n,% or average ± SD

Source: Darweesh SK, et al. *Clin Drug Investig*. 2017;37(5):473-482

Effect of N-Acetylcysteine on Mortality and Liver Transplantation Rate in Non-Acetaminophen-Induced Acute Liver Failure: A Multicenter Study

Outcome	NAC (n=85)	Placebo (n=70)	P value
Primary Outcome			
Recovered	82 (96)	17 (23)	< 0.01
Died	1	16	
Liver transplant	2	37	
Secondary Outcomes			
Hospital stay, days	10 ± 4	28 ± 5	<0.001
ICU admission	28 (33)	47 (67)	0.01
Bleeding	20 (23)	47 (67)	0.002
Encephalopathy	28 (33)	44 (63)	0.02

Results presented as n,% or average ± SD

Source: Darweesh SK, et al. *Clin Drug Investig*. 2017;37(5):473-482

Effect of N-Acetylcysteine on Mortality and Liver Transplantation Rate in Non-Acetaminophen-Induced Acute Liver Failure: A Multicenter Study

LFT	NAC (n=85)	Placebo (n=70)	P value
Bili, mg/dL(before)	1.0 ± 0.5	1.1 ± 0.4	0.314
Bili, mg/dL (after)	**0.9 ± 0.4**	**1.3 ± 0.6**	**0.02**
ALT, IU/L (before)	3144 ± 1748	2993 ± 1295	0.706
ALT, IU/L (after	1931 ± 1286	2113 ± 1106	0.558
AST IU/L (before)	3951 ± 1630	3956 ± 1386	0.990
AST IU/L (after)	**1155 ± 539**	**2850 ± 1321**	**<0.001**
INR (before)	2.4 ± 0.5	2.3 ± 0.5	0.283
INR (after)	**2.0 ± 1.0**	**3.0 ± 1.1**	**<0.001**

Results presented as average ± SD
Before = before NAC administration, after = after NAC administration

Source: Darweesh SK, et al. *Clin Drug Investig*. 2017;37(5):473-482

Effect of N-Acetylcysteine on Mortality and Liver Transplantation Rate in Non-Acetaminophen-Induced Acute Liver Failure: A Multicenter Study

- Conclusion
  - NAC can improve mortality and reduce the need of liver transplant in patients with non-acetaminophen induced acute liver failure
- Interpretation
  - Definition of ALF inconsistent with similar studies
    - Less severe ALF when compared to similar studies
    - Majority of patients had grade 0 HE
    - Did not document MELD score
  - Collected LFTs pre and post NAC administration to observe the effect on levels
  - Included oral NAC dosing prior to discharge
  - Mortality benefit has not been replicated in other studies

Source: Darweesh SK, et al. *Clin Drug Investig*. 2017;37(5):473-482

N-acetylcysteine in non-acetaminophen-induced acute liver failure: a systematic review and meta-analysis of prospective studies

Amjad et al Prz Gastroenterol. 2022;17(1):9-16

Study Design	• Systemic review and meta-analysis
Population	• Adult patients with non-acetaminophen ALF who received NAC • Excluded patients with underlying chronic disease • **Viral hepatitis** (46% vs. 33%), **DILI (**25% vs. 28%), indeterminate cause, autoimmune hepatitis
Intervention	• **NAC**: dependent on trial protocol • **Placebo**
Outcomes	• **Primary:** overall mortality • **Secondary:** transplant-free survival, safety, hospital length of stay

Source: Amjad W, et al. *Prz Gastroenterol*. 2022;17(1):9-16

N-acetylcysteine in non-acetaminophen-induced acute liver failure: a systematic review and meta-analysis of prospective studies

- The overall survival was 70.1% (237/334) in the NAC group and 59.8% (202/338) in the control group (RR = 0.73; 95% CI: 0.48–1.09)

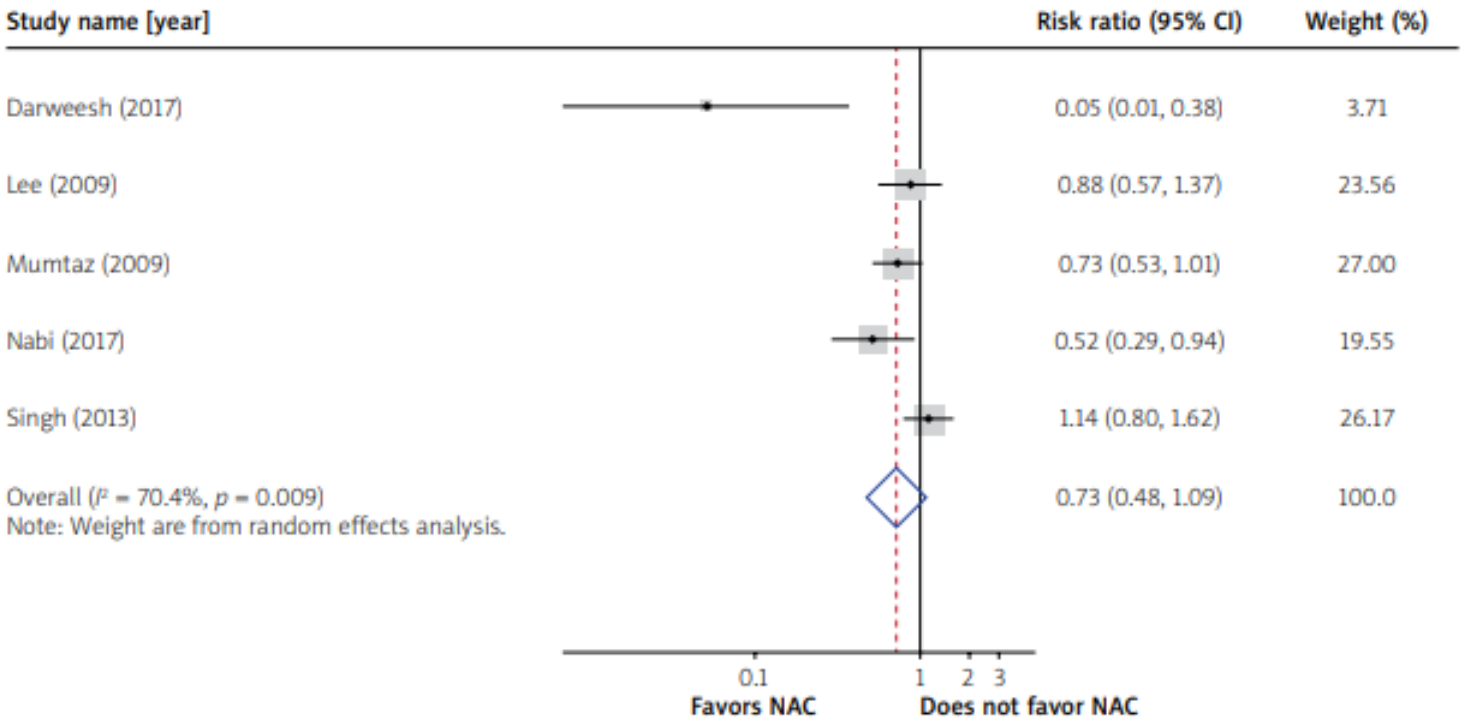

Figure 2. Forest plot of overall mortality in N-acetylcysteine and control group

Source: Amjad W, et al. *Prz Gastroenterol*. 2022;17(1):9-16

N-acetylcysteine in non-acetaminophen-induced acute liver failure: a systematic review and meta-analysis of prospective studies

- The transplant-free survival was improved by 44% in the NAC group (RR = 0.56; 95% CI: 0.33–0.94)

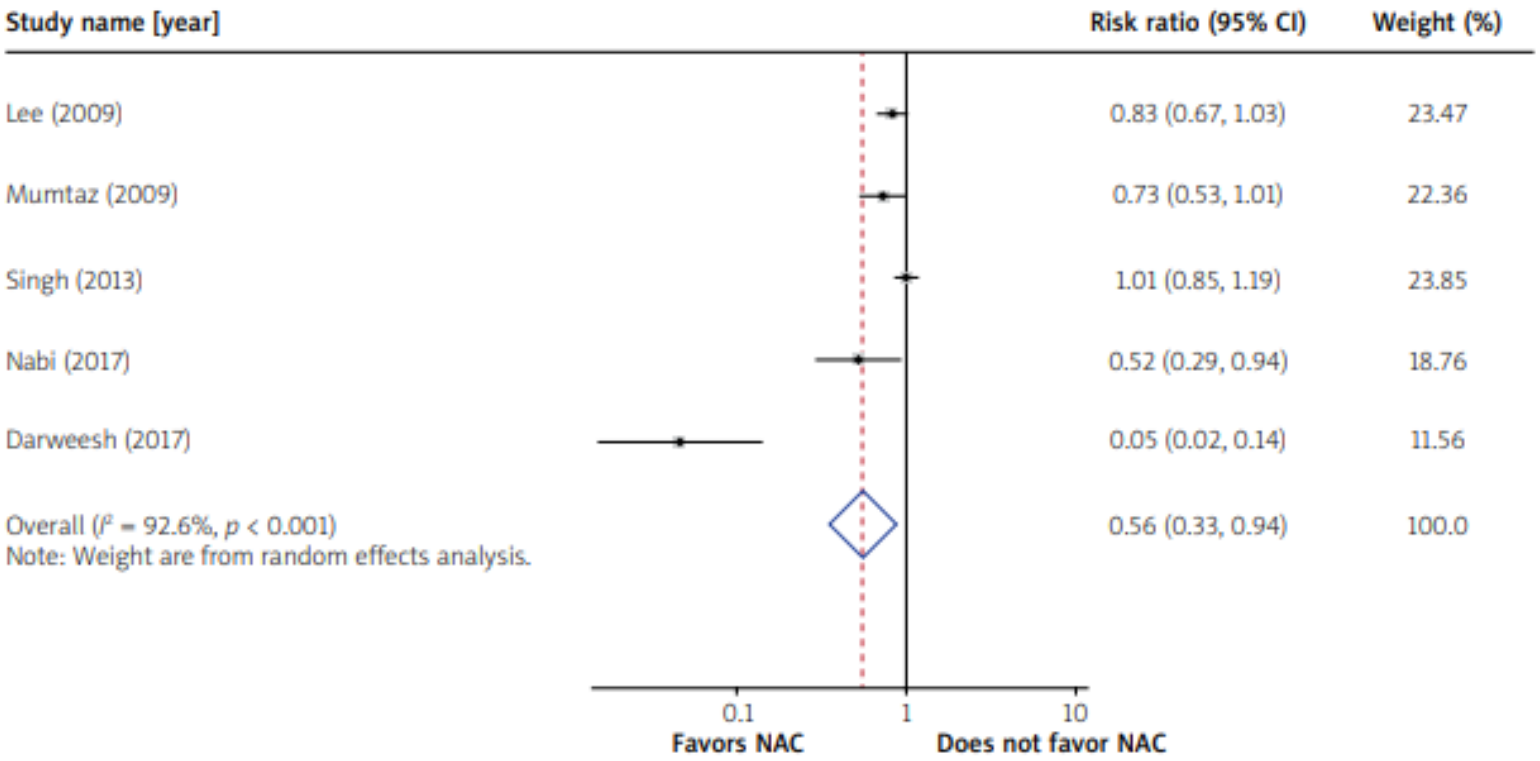

Figure 3. Forest plot of transplant-free survival in N-acetylcysteine and control group

Source: Amjad W, et al. *Prz Gastroenterol*. 2022;17(1):9-16

N-acetylcysteine in non-acetaminophen-induced acute liver failure: a systematic review and meta-analysis of prospective studies

Hospital Length of Stay

- NAC significantly reduced the duration of hospital stay by ~1.6 days
  - SMD -1.62; 95% CI (-1.84 to -1.4); $p < 0.001$

Safety

- Most common adverse events in the NAC group were nausea, vomiting, dyspepsia, fever, rash, infections, arrhythmias and rarely bronchospasms
- No statistically significant difference when compared to the control group

SMD: standard difference in means

Source: Amjad W, et al. *Prz Gastroenterol*. 2022;17(1):9-16

N-acetylcysteine in non-acetaminophen-induced acute liver failure: a systematic review and meta-analysis of prospective studies

- Conclusion
  - N-acetylcysteine improved transplant-free survival and hospital length of stay with no significant differences observed in mortality rates
- Interpretation
  - Meta-analysis confirmed the improved transplant-free survival and hospital length of stay with NAC in non-APAP induced ALF
  - More studies are needed to determine NAC benefit on mortality due to conflicting data

Source: Amjad W, et al. *Prz Gastroenterol*. 2022;17(1):9-16

NAC Evidence in Shock Liver

Case Report	Initial Labs	Management	Result
79 y/o M with acute liver failure secondary to severe sepsis	APAP: < 5 mg/dL AST: 1216 IU/L ALT: 736 IU/L INR: 1.93 Lactate 9.4 mmol/L	NAC	Peak LFTs > 5000 IU, improved over 72 h; did not require vasopressors
32 y/o M with history of pericarditis; ingested 32.4 mg colchicine	Colchicine: 9.6 ng/mL AST: 286 IU/L ALT: 58 IU/L INR: .331 Lactate 7.1 mmol/L	NAC Activated charcoal Bicarbonate infusion Vasopressors Hemodialysis	Peak LFTs > 2000 IU, normalized on day 7; patient expired due to worsening metabolic acidosis and progressive pancytopenia

- Minimal clinical evidence – limited randomized controlled trials
- Outcomes primarily evaluating surrogate outcomes

Sources: Parvataneni S, et al. *Cureus*. 2020;12(2):e7149
Cozza J, et al. *Journal of Investigative Medicine High Impact Case Reports*. 2021;9

Conclusions

- Improved transplant-free survival has been demonstrated in literature with the use of NAC in non-acetaminophen induced ALF
  - Benefits primarily seen in viral hepatitis and drug-induced ALF and if administered with HE Grade I or II prior to progression to Grade III-IV
  - Limited evidence in shock liver
- Volume content in NAC should be considered prior to initiation of NAC on a patient-specific evaluation
  - 3 bag method of NAC (without extension) in adults results in 1700 ml of fluid being administered

Technician Assessment Question #3:

- How much fluid is required for the traditional 3 bag method of NAC to be administered to a patient without extension of therapy?
  A. 1000 mL
  B. 1250 mL
  C. 1700 mL
  D. 2000 mL

Technician Assessment Question #3: Correct Response

- How much fluid is required for the traditional 3 bag method of NAC to be administered to a patient without extension of therapy?
  - A. 1000 mL
  - B. 1250 mL
  - **C. 1700 mL**
  - D. 2000 mL

Conclusions

Benefits Seen	Consider Risks vs Benefits
Viral hepatitis induced ALF	Shock liver
Non-acetaminophen DILI	Volume overload
Acetaminophen-induced ALF	High aspiration risk
ALF with HE Grade 1-2	Indeterminate

- The use of NAC can be considered in other indications based on risk vs. benefit
- IV NAC is relatively inexpensive and has a favorable safety profile
  - Supplied as 200 mg/mL vials ~$1.00/mL
  - Ex: 60 kg patient requiring full therapeutic dosing utilizing traditional 3 bag method: < $100

Source: N-acetylcysteine. *Lexi-Drugs*. UpToDate Lexidrug. UpToDate Inc. Accessed April 25, 2025.

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Thank You!!!

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