ACETAMINOPHEN (APAP) TOXICITY

CLINICAL PATHWAYS

BACKGROUND:

- Acetaminophen (APAP) is the leading cause of acute liver failure in the United States.
- N-acetylcysteine (NAC) is an effective antidote for APAP toxicity because of its multiple mechanisms of action, primarily serving as a glutathione substitute. Published literature in the last 20 years has demonstrated additional anti-oxidant mechanisms resulting in favorable effects on the acutely injured liver, improving systemic hemodynamics and tissue oxygen delivery.
- In assessing the risk of toxicity of APAP ingestion and hence the need to administer NAC, it is useful to separate different categories of APAP exposure: acute single exposures, repeated supratherapeutic ingestions (or chronic overdose), ingestion of extended-release APAP, massive ingestions, and unknown time of APAP ingestion
- The Rumack-Matthew Nomogram can only be used to determine the risk of toxicity when the time of ingestion is known for acute single ingestions based on its original development and validation. Thus, there is a need to understand risk determination of toxicity of other APAP exposure scenarios.
- Stated timing and dose of APAP ingestion are often unreliable which needs to be taken into consideration in deciding whether to initiate treatment with NAC.
- The majority of unintentional acute single pediatric APAP exploratory ingestions will not require treatment.
- All ingestions with intent for self-harm require evaluation in a healthcare facility.
- Repeated supratherapeutic ingestions- unintentional, misuse, or abuse—will likely need evaluation in a healthcare facility. Call the Arkansas Poison and Drug Information 1-800-222-1222 for triage assistance.
- Certain patients may be at higher risk for hepatoxicity when taking therapeutic or supratherapeutic APAP doses depending on co-morbid medical conditions and/or use of Cytochrome P450 CYP2E1 drugs/substances which increase the conversion of APAP to its toxic metabolite NAPQI.
- This guideline **does not address IV acetaminophen** medication errors/overdose. Consult the Clinical Pharmacology/Toxicology attending for further recommendations

ADVERSE REACTIONS TO NAC

Pathways

Acute Single Ingestion	Massive Ingestion (>25g)	Prolonged or Repeated Supratherapeutic Ingestion	Extended Release or Co-Formulation	Unknown Ingestion Time / Delayed Presentation

Last Updated
2-14-22

Acetaminophen (APAP) Toxicity Pathway
Acute Single Immediate-Release Ingestion - Known Time

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Labs/Diagnostics

- Acetaminophen concentration
- CMP
- PT/INR
- Salicylate concentration
- Urine HCG
- ECG
- Urine drug screen

Acetaminophen ingested**

YES

- Administer activated charcoal if within **2 hours** of ingestion, and no contraindications*
- Check APAP level and other labs
- Check APAP level as soon as possible after 4 hours post-ingestion (Refer to Nomogram)

APAP Level below Standard Treatment Line

No treatment needed

APAP Level between standard and higher dose treatment lines

Start standard NAC dose IV or PO

APAP Level above Higher Dose Treatment Line

Start Higher NAC dose (IV only) and consult Clinical Pharmacology/Toxicology

*Contraindications to Charcoal:

- Inability to protect airway
- Altered mental status
- Seizure
- Multiple episodes of vomiting
- Caustic ingestion

Repeat APAP, CMP, PT/INR at:

- Hour 19 of 20 during Standard Dose NAC infusion
- Hour 23 of 24 hour infusion of Higher NAC Dose infusion
- After 24 hours of Oral NAC

(Follow **Continuation/Discontinuation Pathway**)

NAC Dosing

Standard (IV and PO)
Higher (IV only)

**Accidental/exploratory single ingestions of < 200 mg/kg in children < 6 years of age
OR
Unintentional ingestions in older children ≥ 6 years of age of < 200 mg/kg
OR
< 10 grams, whichever is more, usually do not require referral and evaluation in a healthcare facility or treatment

Acetaminophen (APAP) Toxicity Pathway – Massive Ingestion

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Labs/Diagnostics

- Acetaminophen concentration
- CMP
- PT/INR
- Salicylate concentration
- Urine HCG
- ECG
- Urine drug screen

≥ 25 grams Acetaminophen ingested

Within < 8 hours of ingestion time?

> 8 hours of ingestion time?

Administer activated charcoal 1g/kg if no *contraindications

*Contraindications to Charcoal:

- Inability to protect airway
- Altered mental status
- Seizure
- Multiple episodes of vomiting
- Caustic ingestion

- Obtain APAP and other labs
- Check APAP level as soon as possible after 4 hours post-ingestion (refer to Nomogram)

APAP ≥ 800 mcg/mL with metabolic acidosis and elevated lactate, Hemodialysis may be warranted

Consult Clinical Pharmacology/ Toxicology & Nephrology

If Hemodialysis started, administer Higher NAC Dose infusion (IV only)

> 300 mcg/mL @ 4 hours
OR
> 150 mcg/mL @ 8 hours
OR
> 75 mcg/mL @ 12 hours

- Start Higher NAC dose (IV only)
- Consult Clinical Pharmacology/ Toxicology

Repeat APAP at 6 hours after initiation of NAC

Repeat APAP, CMP, PT/INR at:

- Hour 19 of 20 during Standard Dose NAC infusion
- Hour 23 of 24 hour infusion of Higher NAC Dose in
- After 24 hours of Oral NAC

(Follow **Continuation/Discontinuation Pathway**)

NAC Dosing

Standard (IV and PO)
Higher (IV only)

Acetaminophen (APAP) Toxicity Pathway – Prolonged/Repeated Supratherapeutic Ingestion

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Labs/Diagnostics

- Acetaminophen concentration
- CMP
- PT/INR
- Salicylate concentration
- Urine HCG
- ECG
- Urine drug screen

- ≥ 200 mg/kg OR ≥ 10 grams over 24 hour period
- > 150 mg/kg/day OR > 6 grams/day over 48 hour period
- > 100 mg/kg/day OR > 4 grams/day over 72 hour period

Obtain APAP level
+
Obtain labs

APAP < 20 mcg/mL + AST < 50

No treatment needed

APAP 20 – 150mcg/mL or AST ≥ 50

Start Standard NAC dose (IV or PO)

APAP ≥ 150 mcg/mL

- **Consult Clinical Pharmacology / Toxicology**
- **Standard or Higher NAC dose may be needed depending on multiple factors**

Repeat APAP, CMP, PT/INR at:

- Hour 19 of 20 during Standard Dose NAC infusion
- Hour 23 of 24 hour infusion of Higher NAC Dose in
- After 24 hours of Oral NAC

(Follow **Continuation/Discontinuation Pathway**)

NAC Dosing

Standard (IV and PO)
Higher (IV only)

Acetaminophen (APAP) Toxicity Pathway – Extended Release or Co-Formulation with Opioid/ Diphenhydramine/Doxylamine

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Labs/Diagnostics

- Acetaminophen concentration
- CMP
- PT/INR
- Salicylate concentration
- Urine HCG
- ECG
- Urine drug screen

*Contraindications to Charcoal:

- Inability to protect airway
- Altered mental status
- Seizure
- Multiple episodes of vomiting
- Caustic ingestion

Acetaminophen ingested**

- Activated charcoal if under 4 hours if no *contraindications
- Check APAP level x2: as soon as possible 4 hours post-ingestion and 4 hours apart
- Obtain other labs

If both APAP levels are below Standard Treatment Line

No treatment needed

If either APAP level between standard and higher dose treatment lines

Start standard NAC dose IV or PO

If either APAP level above Higher Dose Treatment Line

Start Higher NAC dose (IV only) and consult Clinical Pharmacology/Toxicology

Repeat APAP, CMP, PT/INR at:

- Hour 19 of 20 during Standard Dose NAC infusion
- Hour 23 of 24 hour infusion of Higher NAC Dose in
- After 24 hours of Oral NAC

(Follow **Continuation/Discontinuation Pathway**)

NAC Dosing

Standard (IV and PO)
Higher (IV only)

**Accidental/exploratory single ingestions of < 200 mg/kg in children < 6 years of age
OR
Unintentional ingestions in older children ≥ 6 years of age of < 200 mg/kg
OR
< 10 grams, whichever is more, usually do not require referral and evaluation in a healthcare facility or treatment

Acetaminophen (APAP) Toxicity Pathway – Unknown Ingestion Time/Delayed Presentation (>24 hours)

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Labs/Diagnostics

- Acetaminophen concentration
- CMP
- PT/INR
- Salicylate concentration
- Urine HCG
- ECG
- Urine drug screen

Symptoms

- Nausea
- Vomiting
- Clinical or lab evidence of hepatotoxicity or liver failure

- NAC 150mg/kg loading dose
- Obtain APAP level
- Obtain other labs

APAP < 10 mcg/mL *and* AST < 50	APAP < 10 *and* Elevated AST, prolonged PT/INR	APAP 11-150 mcg/mL	APAP > 150 mcg/mL
No treatment needed	Consult Clinical Pharmacology/ Toxicology to determine whether to start NAC	Start Standard NAC dose IV or PO	• Consult Clinical Pharmacology / Toxicology • Start Standard or Higher NAC dose depending on multiple factors

Repeat APAP, CMP, PT/INR at:

- Hour 19 of 20 during Standard Dose NAC infusion
- Hour 23 of 24 hour infusion of Higher NAC Dose in
- After 24 hours of Oral NAC

(Follow **Continuation/Discontinuation Pathway**)

NAC Dosing

Standard (IV and PO)
Higher (IV only)

Acetaminophen (APAP) Toxicity Pathway – Continuation/Discontinuation

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End of maintenance NAC infusion

Re-evaluate

Repeat APAP, CMP, PT/INR at:

- Hour 19 of 20 during Standard Dose NAC infusion
- Hour 23 of 24 hour infusion of Higher NAC Dose infusion
- After 24 hours of Oral NAC

Discontinuation Criteria

(all criteria must be met)

- APAP < 10 mcg/mL
- AST decreasing value for 2 consecutive measurements (AST < 1000)
- INR < 2
- No evidence of liver failure OR improving prognostic markers if acute liver injury/failure initially present (e.g. creatinine, lactate, pH, phosphate, encephalopathy, metabolic acidosis)
- Clinical improvement

Stop treatment

Continuation Criteria

- APAP > 10 mcg/mL
- AST > 100 and increasing*
- INR > 2
- Evidence of acute liver failure

Continue Standard NAC 200mg/kg/20 hours dose IV including patients given 24 hours of Higher NAC Dose

* Small fluctuations in AST (e.g. +/- 20 IU/L or +/- 10% of previous measured value) are common and do not on their own indicate the need for ongoing NAC

NAC Dosing

Standard (IV and PO)
Higher (IV only)

Modified APAP-NAC Nomogram for ACUTE APAP Ingestion within 4-24 hours

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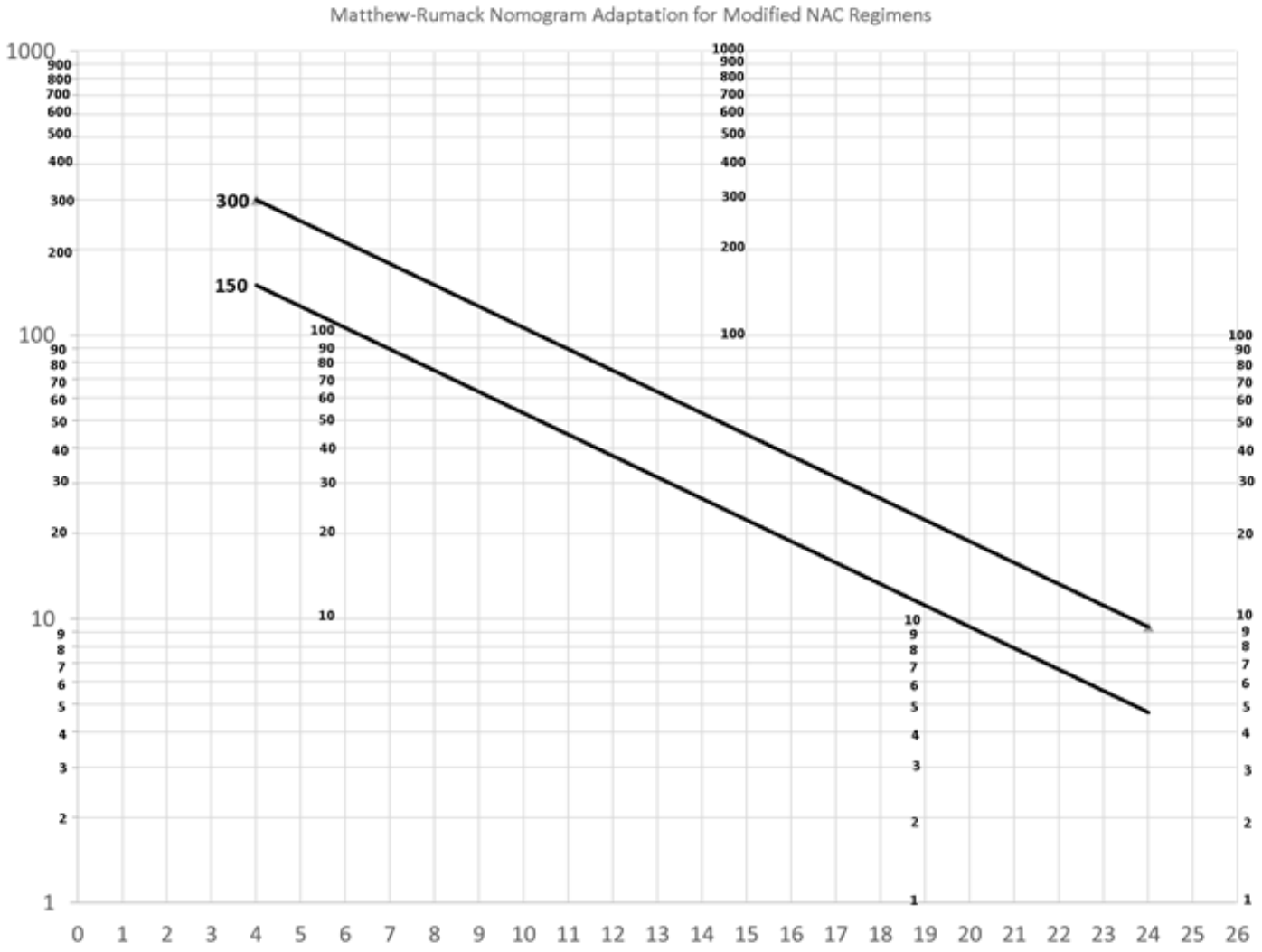

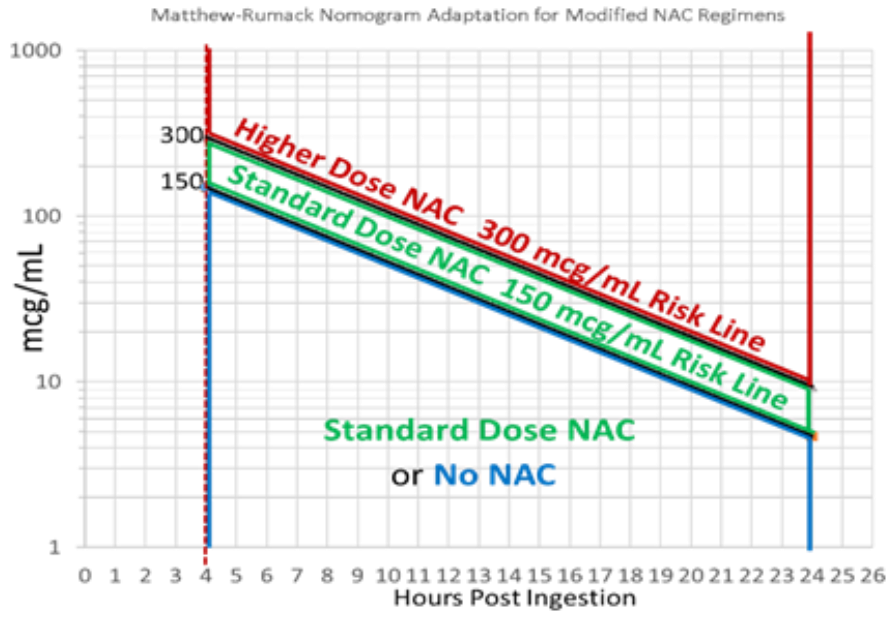

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Intravenous NAC:

Standard NAC Dose Infusion:

Loading Dose: 150mg/kg (max 15 grams) over 1 hour

then

Maintenance Dose: continuous infusion of 200mg/kg/over 20 hours (max 20grams in 20 hours)

Total Dose: (in 21 hours) 350mg/kg

Higher NAC Dose Infusion:

***RESTRICTED** – Must get Pharmacology / Toxicology approval before ordering

Loading dose: 150mg/kg (max 15 grams) over 1 hour

then

Maintenance Dose: continuous Infusion of 480mg/kg/ over 24 hours (max 48 grams in 24 hours)

Total dose: (in 25 hours) 630mg/kg

Oral NAC:

Standard Oral NAC Dosing:

Loading dose: 140 mg/kg (max 15 grams)

Maintenance Dose: 70mg/kg/dose (max 7 grams) every 4 hours for 12 doses

The maintenance dose course may be shortened depending on APAP concentration and AST measurements after 24 hours.

ADVERSE REACTIONS TO NAC:

- Anaphylactoid or hypersensitivity reactions may occur in up to 18% of patients with the Loading Dose and can include flushing, itching, hives, or *rarely* bronchospasm and hypotension.
- Anaphylactoid reactions are attributed to both the dose and concentration of NAC and are caused by non-IgE-mediated release of histamine.
- If not self-limited, then stop the infusion and administer antihistamine (diphenhydramine: 1-1.25mg/kg/dose).
- Once symptoms resolve, **re-start the IV NAC at a slower rate**. Rarely severe intolerance will require a switch to oral NAC therapy.
- If there is a history of atopy or moderate-severe asthma, then consider a slower Loading Dose Rate over 2-3 hours.

DEFINITIONS OF APAP INGESTIONS THAT MAY BE ASSOCIATED WITH HEPATOTOXICITY

Acute Single Immediate-Release Ingestions: the entire ingestion occurs within a single 4-hour period.

- Accidental/exploratory single ingestions of < 200 mg/kg in children < 6 years of age or unintentional ingestions in older children ≥ 6 years of age < 200 mg/kg or < 10 grams, whichever is more, usually do not require referral and evaluation in a healthcare facility or treatment.

Massive APAP Ingestion: History of ingestion ≥ 25 grams

Repeated supra-therapeutic ingestions: ≥ 10 grams or ≥ 200 mg/kg (whichever is less) over a single 24-hour period OR >150 mg/kg/day or 6 grams/day (whichever is less) in a 48 hour period OR > 100 mg/kg/day or 4 grams/day (whichever is less) during a 72 hour period or longer when there are risk factors: alcohol use disorder, isoniazid therapy, underlying liver disease, prolonged fasting, malnutrition, catabolic states (e.g. anorexia, post-surgical), febrile illnesses in infants and young children, and/or concomitant use of CYP2E1 inducing medications.

Extended-release APAP ingestions: Formulations of APAP that contain both 325 mg of immediate release and an additional 325 mg dose designed for delayed dissolution. Based on multiple studies, utilization of the treatment nomogram is possible for acute, single substance extended-release preparation ingestions, although measurement of at least 2 APAP concentrations is recommended. "Nomogram crossing" due to delayed peak absorption from the formulation was found in very few patients and did not correlate with worse clinical outcome.

Ingestion of APAP co-formulations that delay gastric emptying Formulations of APAP that contain diphenhydramine, doxylamine or an opioid that may delay gastric emptying and cause a delay in peak absorption may require multiple APAP concentrations to determine toxicity risk and decision to initiate NAC therapy

"Delayed Presenters": Patients who present more than 24 hours after either single acute ingestion or repeated supra-therapeutic ingestions may present with evidence of hepatotoxicity or acute liver failure. NAC therapy may be indicated in these patients based on evidence of its additional mechanisms resulting in favorable effects on the acutely injured liver, improving systemic hemodynamics and tissue oxygen delivery.

Acute liver failure: Severe acute liver injury with impaired synthetic function (prolonged Prothrombin time) and encephalopathy.

Metrics

1. Time to medical clearance (Time to transfer – end of IV NAC infusion)
2. Type and length of infusion: Standard NAC, Standard NAC + continuation, Higher NAC, Higher NAC + continuation
3. Were IV NAC continuation metrics met?
4. Peak AST and ALT
5. Order set utilization

Contributing Members

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REFERENCES

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1. American College of Medical Toxicology. ACMT position statement: duration of intravenous acetylcysteine therapy following acetaminophen overdose. J Med Toxicol2017;13:126-127.
2. Bateman DN Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomized controlled trial. Lancet 2014;383:697-704.
3. Baum RA, Woolum JA, Bailey AM et al. Evaluation of dosing strategies of N-acetylcysteine for acetaminophen toxicity in patients greater than 100 kilograms: should the dosage cap be used? J Med Toxicol 2021;17:241-249.
4. Chiew AL, Isbister GK, Kirby KA et al. Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2). Clin Toxicol 2017;55 (10); 1055-1065.
5. Dart RC, Erdman AR, Olson KR et al. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol 2006;44 (1);1-18. DOI: 10.1080/15563650500394571
6. Gosselin S, Juurlink DN, Kielstein JT, Ghannoum M, Lavergne V, Nolin TD, Hoffman RS; EXTRIP Workgroup. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. Clin Toxicol (Phila). 2014 Sep-Oct;52(8):856-67.
7. Graudins A. Overdose with modified-release paracetamol (Panadol Osteo®) presenting to a metropolitan emergency medicine network: a case series. Emerg Med Australas 2014;26(4): 398-402.
8. Hendrickson RG, McKeown NJ. "Acetaminophen" in Goldfrank's Toxicologic Emergencies 11th edition. Nelson LS, Howland MA, Lewis NA et al (editors). McGraw Hill (New York) 2019.
9. Isbister GK, Downes MA, Mcnamara K et al. A prospective observational study of a novel 2-phase infusion protocol for the administration of acetylcysteine in paracetamol poisoning. Clin Toxicol 2016;54:2, 120-126.
10. Pettie JM, Caparrotta TM, Hunter RW et al. Safety and efficacy of the SNAP 12-hour Acetylcysteine regimen for the treatment of paracetamol overdose. EClinicalMedicine 2019; 11:11-17.
11. Prescott L. Oral or intravenous N-acetylcysteine for acetaminophen poisoning? Ann Emerg Med 2005;45:409-413.
12. Wong A, Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. Clin Toxicol 2016;54:2, 115-119.
13. Yoon E, Baber A, Choudhary M et al. Acetaminophen-induced hepatotoxicity: a comprehensive update. J Clinical and Translational Hepatology 2016;4:121-142.

Massive APAP OD:

1. Hendrickson RG. What is the most appropriate dose of N-acetylcysteine after massive acetaminophen overdose? Clin Toxicol 2019;57 (8): 686-691.
2. Marks DJB, Dargan PI, Archer JRH et al. Outcomes from massive paracetamol overdose: a retrospective observational study. Br J Clin Pharmacol 2017;83:1263-1272.
3. Schwartz EA, Hayes BD, Sarmiento KF. Development of hepatic failure despite use of intravenous acetylcysteine after a massive ingestion of acetaminophen and diphenhydramine. Ann Emerg Med 2009;54:421-423.
4. Wang GS, Monte A, Bagdure D, et al. Hepatic failure despite early acetylcysteine following large acetaminophen-diphenhydramine overdose. Pediatrics 2011;127:e1077-1080.