DRAFT APH Acetaminophen Toxicity Clinical Pathway DRAFT

- Acetaminophen (APAP) is the leading cause of acute liver failure in the United States.

- N-acetylcysteine (NAC) is an effective antidote for APAP toxicity through 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 indications for administering 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 revised Rumack-Matthew Nomogram can be used to determine the risk of toxicity when the time of ingestion is known for acute single ingestions.

- Stated timing and dose of APAP ingestion are often unreliable and should be taken into consideration when making management decisions.

- The majority of unintentional/accidental acute single pediatric APAP ingestions will not require treatment.

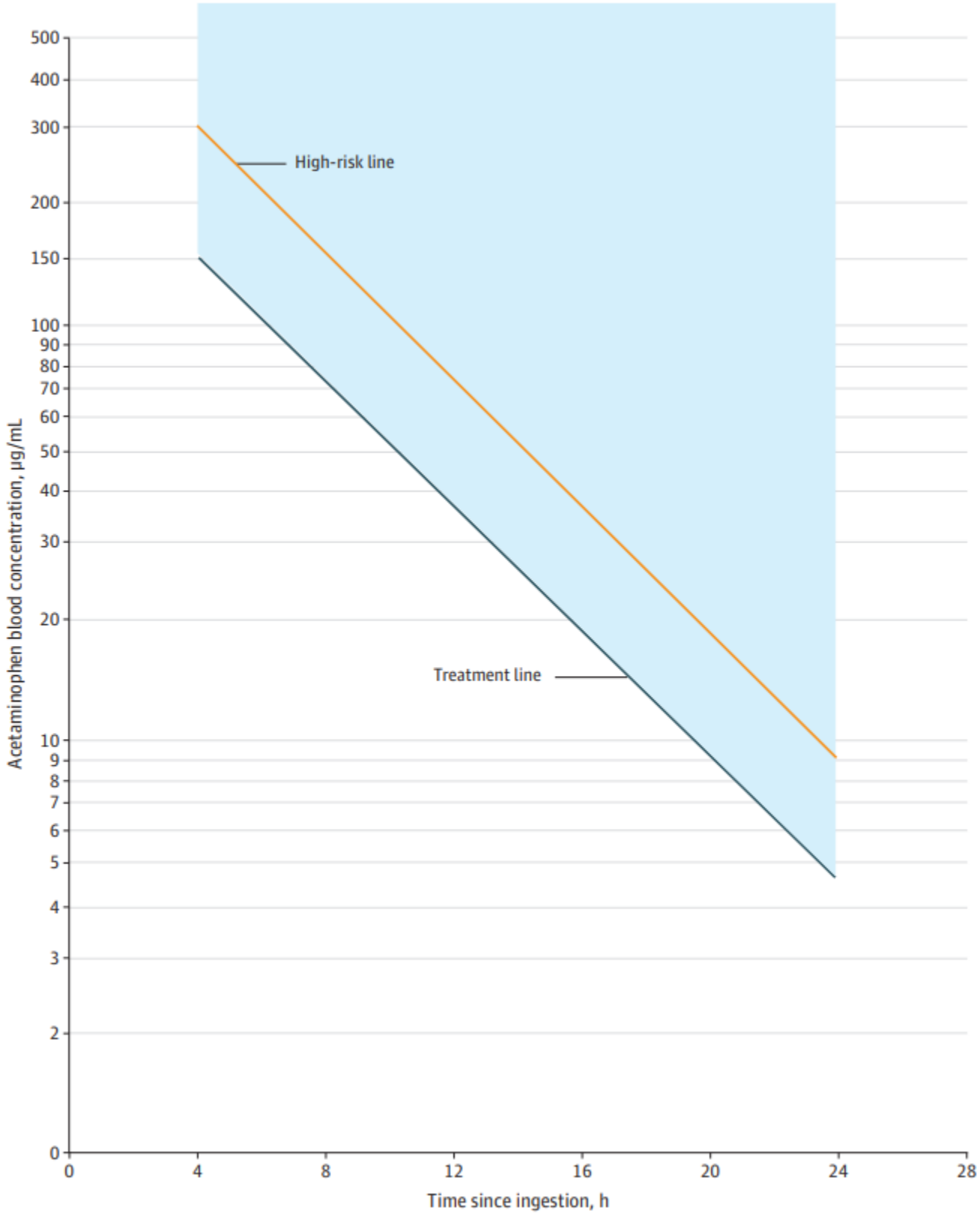
- Certain patients may be at higher risk for hepatoxicity when taking therapeutic or supratherapeutic APAP doses depending on co-morbid medical conditions and/or use of Cytochrome P450 CYP2E1 drugs/substances, which increase the conversion of APAP to its toxic metabolite NAPQI.

- All ingestions with intent for self-harm require timely psychiatric evaluation.

- Repeated supratherapeutic ingestions - unintentional, misuse, or abuse – will likely need evaluation in a healthcare facility. Call the Florida Poison Control Centers (1-800-222-1222) for triage assistance.

- This guideline does not address IV acetaminophen medication errors/overdose.

Figure 2. Revised Rumack-Matthew Nomogram for the Acute Ingestion of Acetaminophen



Acute, single APAP ingestion with known time of ingestion

Updated 1/30/25

Acetaminophen (APAP) ingested*

- Consider administration of activated charcoal if within 4 hours of ingestion and no contraindications*
- Collect APAP level asap (must be at least 4hrs post-ingestion for use on nomogram)
- Collect other recommended labs**
- Contact FL Poison Control Centers (800-222-1222) as needed.

APAP level below treatment line

NAC treatment not indicated

APAP level at/above treatment line

Start IV NAC per Appendix A

- Repeat APAP level, CMP, lactate, and coags 18-20 hrs after start of NAC treatment.
- More frequent and/or add'l labs may be indicated based on case severity. Consider adding blood gas in severe cases.
- Follow Discontinuation Criteria.

Consider admission/transfer to PSCU/PICU if:

- Unstable vital signs or altered mental status.
- Known or suspected co-ingestion requiring CR monitoring.
- Evidence of acute liver damage or coagulopathy.
- Reaction to NAC infusion requiring higher level of care.
- Other medical complexity requiring higher level of care.

All ingestions with intent for self-harm require timely psychiatric evaluation.

** Recommended labs:

- APAP level
- Salicylate level
- UDP
- CMP
- Coags
- Lactate
- Lipase
- bHCG
- EKG

* Contraindications to activated charcoal

- Inability to protect airway
- AMS/Seizure
- Intractable vomiting
- Caustic ingestion

Updated 1/30/25

APAP ingestion with unknown ingestion time or delayed presentation

Acetaminophen (APAP) ingested*

- Collect APAP level asap (must be at least 4hrs post-ingestion for use on nomogram)
- Collect other recommended labs*
- Contact FL Poison Control Centers (800-222-1222) as needed.

APAP level <10mcg/mL,

and other labs normal,

and patient asymptomatic.

NAC treatment not indicated

Start IV NAC per Appendix A if:

APAP is at/above 150 mcg/mL, or

APAP is >20mcg/mL and delayed presentation suspected

- Repeat APAP level, CMP, lactate, and coags 18-20 hrs after start of NAC treatment.
- More frequent and/or add'l labs may be indicated based on case severity. Consider adding blood gas in severe cases.
- Follow Discontinuation Criteria.

For cases that fall between the above criteria or are ambiguous, use clinical judgement in consultation with FL Poison Control to triage case (E.g., APAP level <20 but lab evidence of hepatotoxicity or N/V is present).

Consider admission/transfer to PSCU/PICU if:

- Unstable vital signs or altered mental status.
- Known or suspected co-ingestion requiring CR monitoring.
- Evidence of acute liver damage or coagulopathy.
- Reaction to NAC infusion requiring higher level of care.
- Other medical complexity requiring higher level of care.

All ingestions with intent for self-harm require timely psychiatric evaluation.

* Recommended labs:

- APAP level
- Salicylate level
- UDP
- CMP
- Coags
- Lactate
- Lipase
- bHCG
- EKG

Updated 1/30/25

Extended-release acetaminophen or co-formulation with opioid, diphenhydramine, or doxylamine

(these drugs may delay gastric emptying)

Acetaminophen (APAP) ingested*

- Consider administering activated charcoal if within 4 hours of ingestion and no contraindications*
- Collect APAP level x 2 (asap and again 4hrs later) and other recommended labs**
- Contact FL Poison Control Centers (800-222-1222) as needed.

Both APAP levels below treatment line

NAC treatment not indicated. Repeat level in 4-6 hrs.

All APAP levels below treatment line – treatment not indicated.

APAP level above treatment line

Start IV NAC per Appendix A

- Repeat APAP level, CMP, lactate, and coags 18-20 hrs after start of NAC treatment.
- More frequent and/or add'l labs may be indicated based on case severity. Consider adding blood gas in severe cases.
- Follow Discontinuation Criteria.

Consider admission/transfer to PSCU/PCIU if:

- Unstable vital signs or altered mental status.
- Known or suspected co-ingestion requiring CR monitoring.
- Evidence of acute liver damage or coagulopathy.
- Reaction to NAC infusion requiring higher level of care.
- Other medical complexity requiring higher level of care.

All ingestions with intent for self-harm require timely psychiatric evaluation.

** Recommended labs:

- APAP level
- Salicylate level
- UDP
- CMP
- Coags
- Lactate
- Lipase
- bHCG
- EKG

* Contraindications to activated charcoal

- Inability to protect airway
- AMS
- Seizure
- Intractable vomiting
- Caustic ingestion

Updated 1/30/25

APPENDIX A: N-acetylcysteine (NAC) Administration

The current approach to administering N-acetylcysteine (NAC) at APH is via a 3 dose regimen. In the near future, Orlando Health will be changing to a 2-bag regimen. Both regimens are outlined below.

3-BAG REGIMEN (Current OH/APH practice)

NOTE: If APAP level is above the high-risk line, consider higher NAC dosing and discuss with pharmacy

Loading Dose: 150mg/kg over 1hr

then,

Second Dose: 50mg/kg over 4 hrs (12.5mg/kg/hr x 4hrs),

then,

Third Dose: 100mg/kg over 16hrs (6.25mg/kg/hr x 16hrs)

- Total dose (20 hrs): 300 mg/kg [max total dose 30g]
- Follow with continuous infusion of 6.25mg/kg/hr until discontinuation criteria met.

The Epic orders for the 3-bag regimen is “Acetylcysteine IV for Acetaminophen related liver toxicity”. If continuing NAC beyond the 3-bag regimen, then use the order in the order set entitled “Additional dosing for extended toxicity”.

2-BAG REGIMEN (Not Yet Available; Coming Soon)

Standard NAC Infusion (APAP level between treatment line and high-risk line)

Loading Dose: 200mg/kg over 4h (50mg/kg/hr x 4hrs) [max 20g/dose; 5g/hr]

then,

Second Dose: 100mg/kg over 16h (6.25mg/kg/hr x 16 hrs) [max 10g/dose; 625mg/hr]

- Total dose (20 hrs): 300 mg/kg [max total dose 30g]
- Follow with continuous infusion of 6.25mg/kg/hr until discontinuation criteria met.

NAC Infusion for high-risk ingestion (APAP level above high-risk line)

Loading Dose: Same as standard infusion - 200mg/kg over 4 h (50 mg/kg/hr x 4hrs) [max 20g/dose; 5g/hr]

then,

Second dose: 200mg/kg over 16h (12.5mg/kg/hr x 16hrs) [max dose: 20g/dose; 1250mg/hr]

- Total dose (20 hrs): 400 mg/kg [max dose 40g]
- Hemodialysis may be recommended. Consult with Pharmacy and Poison Control for NAC dosing if starting hemodialysis.
- Follow with continuous infusion of 12.5mg/kg/hr until discontinuation criteria met.

***Note for patients started on a 3-bag regimen at an outside facility:**

- If the first bag (150 mg/kg over 1 hour) is still running when the patient arrives, stop the current 150 mg/kg bag and begin 2-bag-regimen starting with 200 mg/kg over 4 hours followed by 100 mg/kg over 16 hours.
- If the second bag (50 mg/kg over 4 hours) is still running when the patient arrives let it finish, then start the "second" dose of 100 mg/kg over 16 hours.

Adverse Reactions to N-acetylcysteine (NAC)

- Non-immune anaphylaxis or hypersensitivity reactions may occur in up to ~15% of patients with the loading dose and can include flushing, itching, hives, or rarely bronchospasm and hypotension.
- Non-immune anaphylactic 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 diphenhydramine IV or PO 1-1.25mg/kg/dose (max dose 50mg/dose).
- Once symptoms resolve, restart the IV NAC at half rate.

NAC Discontinuation

NAC may be discontinued if **all** the following criteria are met:

- APAP level <10mcg/mL
- AST is normal or, if elevated, has decreasing value for 2 consecutive measurements
- INR <2
- Clinical improvement, with resolution of abdominal pain, N/V.
- No evidence of liver failure or serial improvement in prognostic markers if acute liver injury/failure is suspected*.
- FL Poison Control concurs with plan to discontinue NAC

If above criteria are not met, then:

- continue NAC, and
- Order follow-up labs, and
- Consider Pediatric GI consultation (if not already done), and
- Review discontinuation criteria when next set of lab result available.

*King's College Criteria:

- Arterial lactate >3.5 mmol/L after early fluid resuscitation (i.e., at least 1 L), **or**
- Arterial lactate >3.0 mmol/L after adequate fluid resuscitation (i.e., tissue perfusion restored), **or**

- Arterial pH <7.3 (irrespective of grade of encephalopathy), **or**
- Grade III or IV encephalopathy with **both** a prothrombin time (PT) greater than 100 secs and a serum creatinine greater than 3.4 mg/dL (300 micromol/L).