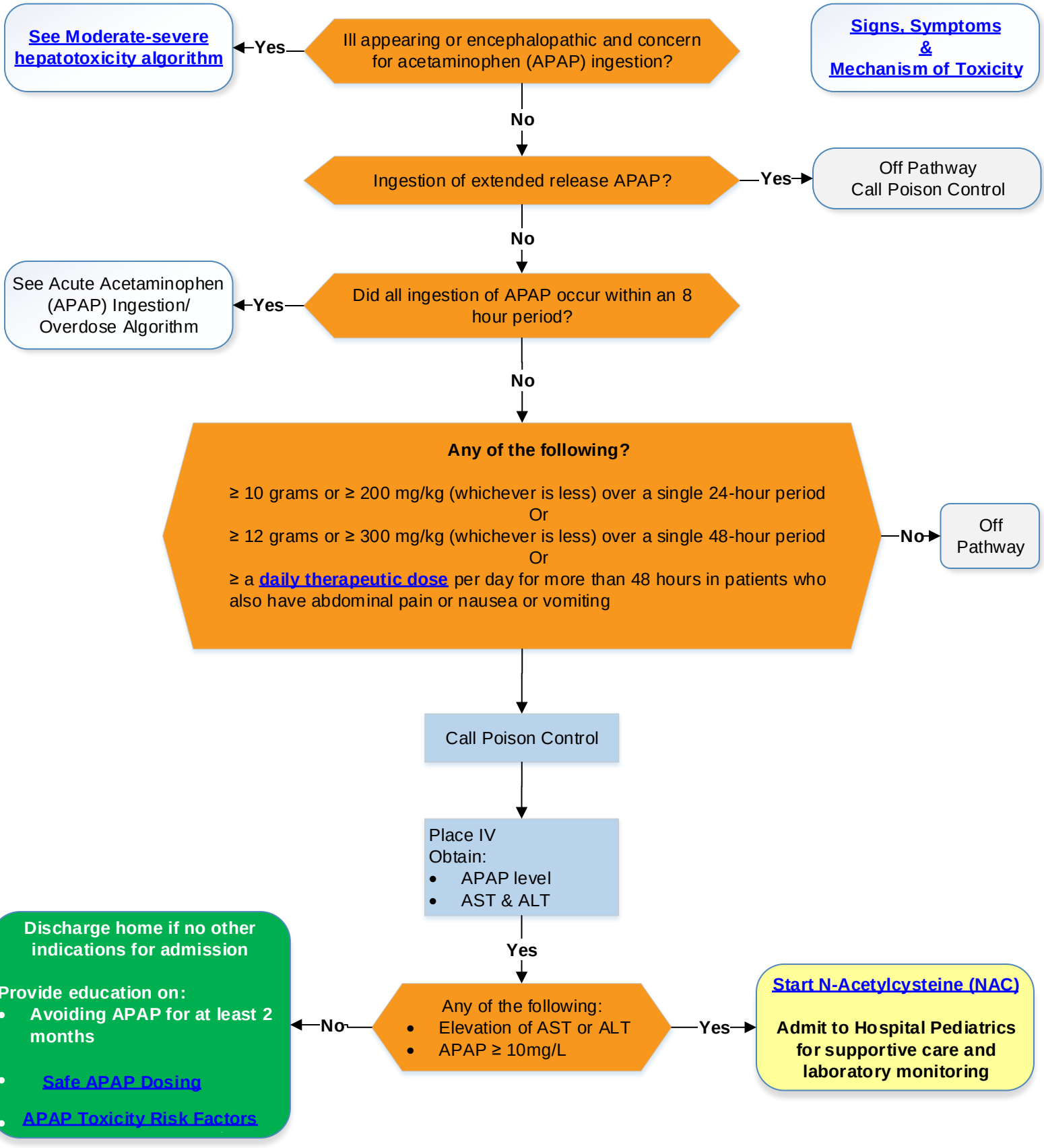
Acetaminophen (APAP) Poisoning due to Non-Acute/ Supratherapeutic Ingestion

Nationwide Children's — When your child needs a hospital, everything matters.

Emergency Department

Center for Clinical Excellence



Signs, Symptoms & Mechanism of Toxicity

Acetaminophen toxicity can occur after one ingested overdose (acute ingestion) or as a result of repeated, supratherapeutic doses (chronic ingestion)

Typical presentation:
Clinical manifestations of acetaminophen overdose can be **gradual and nonspecific.**
Four clinical stages of acetaminophen toxicity, based on time after ingestion::

- **Stage 1: 12 to 24 hours** - anorexia, malaise, diaphoresis, nausea, and vomiting.
- **Stage 2: 36 to 48 hours** – variable clinical presentation, may include elevation of liver enzyme levels, liver enlargement, or right upper quadrant abdominal pain. Patients also may be asymptomatic.
- **Stage 3: 3 to 5 days** - recurrence of anorexia, nausea, vomiting, and malaise. Liver enzyme levels may worsen and be accompanied by signs of liver failure, including jaundice, hypoglycemia, coagulopathy, and encephalopathy.
- **Stage 4:** Complete recovery ***or*** progression to liver failure.

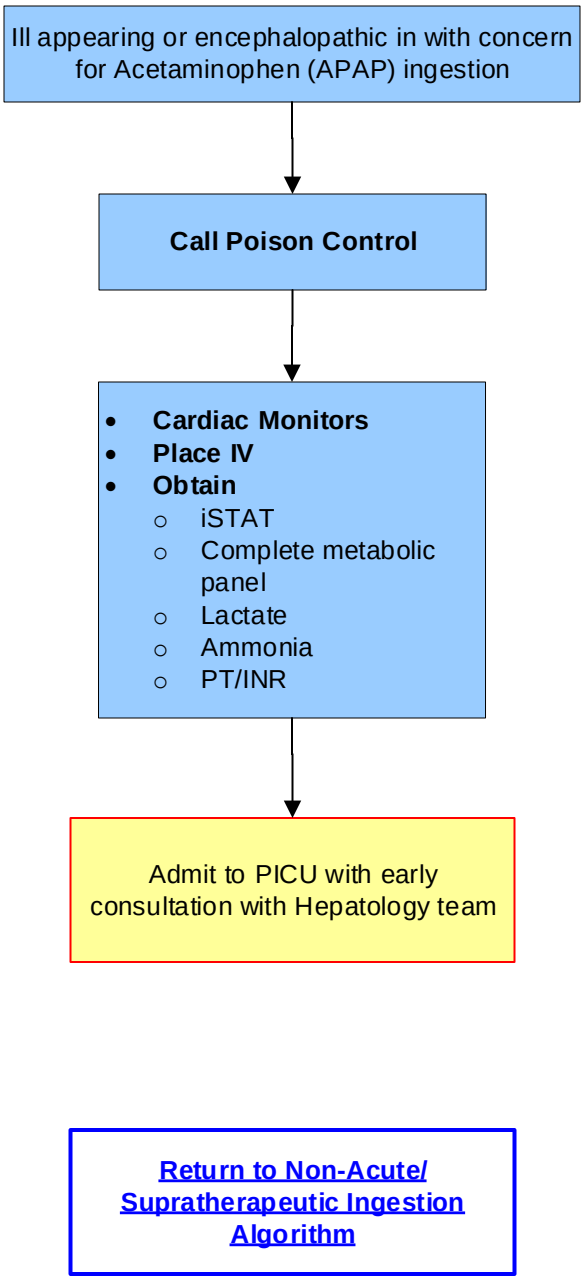
Mechanism of toxicity:

- Acetaminophen is metabolized mainly in the liver by conjugation with sulfate and glucuronide.
- When an excessive amount of acetaminophen is present, it overwhelms the normal conjugation pathway, and metabolism is channeled to the cytochrome P-450 pathway, which produces the **toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI)**.
- **NAPQI is detoxified by glutathione; however, when glutathione becomes depleted, NAPQI binds directly to hepatocytes, causing cellular necrosis.**

Argentieri J, Morrone K, Pollack Y. Acetaminophen and Ibuprofen overdosage. Pediatr Rev. 2012 Apr;33(4):188-9. doi: 10.1542/pir.33-4-188. PMID: 22474118.

Return to Non-Acute/ Supratherapeutic Ingestion Algorithm

Concern for Moderate-Severe Hepatotoxicity



Risk Factors for Acetaminophen Toxicity

- Underlying liver disease
  - Non-alcoholic steatohepatitis
  - Hepatitis B or C infection
  - Chronic transaminitis
  - Chronic alcoholism
- Acute and chronic malnutrition
- Dehydration
- Catabolic post-surgical patients
- Acute febrile illness
- Young age
- Genetic polymorphism
- Repeat exposure
- Ethanol exposure
- Drug interactions
  - Anti-Epileptics
    - Carbamazepine
    - Phenobarbital
    - Phenytoin
  - Miscellaneous
    - Dasatinib
    - Isoniazid
    - Probenacid
    - Rifampin

Return to Non-Acute/ Supratherapeutic Ingestion Algorithm

Safe APAP Dosing

How Much is Safe?

- Lexi-Comp
  - 75 mg/kg/day or 4000 mg/day (whichever is less)
- Micromedex
  - Infants: 75 mg/kg/day
  - Children: 100 mg/kg/day or 1625 mg/day (whichever is less)
  - Adolescents ≥ 60 kg: 3250 mg/day
- FDA
  - “Severe liver damage may occur if you take more that 4000 mg in 24 hours”

Current resources focus on total administration per day and not cumulative prolonged exposure

Return to Non-Acute/ Supratherapeutic Ingestion Algorithm

N-Acetylcysteine (NAC) Therapy

Emergency Department

Center for Clinical Excellence

Indications for NAC Therapy
Patients that meet criteria by:
Non-Acute/Supratherapeutic Ingestion Algorithm

Call Poison Control 1-800-222-1222 to confirm treatment plan

Transfers from outside hospitals:
- Complete bag of NAC that is already running
- Order subsequent doses (consult pharmacy)

If **APAP level ≥ 300 mcg/mL** or if twice as high as treatment level at any point:
Consult Poison Control Immediately

IV access unavailable (and/or patient at Behavioral Health Pavilion/Psychiatric Crisis (BHP/PCD) or patient preference for Oral NAC therapy?
(shared decision making recommended)

Yes

No

Oral NAC Therapy

Transfer to Main Campus Emergency Department if at BHP/PCD

Anaphylactoid Reaction
- Pause NAC and call Poison Control for any concerns of anaphylactoid reaction.
- Consider treatment with intramuscular epinephrine, H1/H2 blockade, and / or steroids, as indicated

IV NAC Therapy
Use ED Order Panel

Loading
- 150 mg/kg (max 15 grams) IV over 1 hour

Second
- 50 mg/kg (max 5 grams) IV over next 4 hours

Third
- 100 mg/kg (max 10 grams) IV over next 16 hours
- Draw APAP level and AST **2 hours prior** to completion of last bag of NAC
- Add ALT, total and direct bilirubin & alkaline phosphatase (AP) if GI symptoms **or** previously elevated AST

Admit to Hospital Pediatrics

Return to Non-Acute/ Supratherapeutic Ingestion Algorithm

Oral NAC Therapy

Loading

- 140 mg/kg (max 15 grams) PO

Maintenance

- 70 mg/kg (max 7.5 grams) PO 4 hours after loading dose and every 4 hours x 24 hours

- Obtain repeat labs 24 hours AFTER starting NAC:
  - APAP level and AST
  - Add ALT, total and direct bilirubin & alkaline phosphatase (AP) if GI symptoms or previously-elevated AST

To optimize tolerance of PO NAC

- Dilute to 5% solution in orange juice or soft drink
- Chilled/over ice
- Sip through straw poked in hole of saran wrap covering cup to reduce odor
- If normal QT on EKG, use ondansetron to prevent emesis
- No need to repeat dose if emesis > 1 hour later & does not smell like NAC

Return to NAC Therapy Algorithm

Patient at BHP/PCD

Patient at Behavioral Health Pavilion/ Psychiatric Crisis Department BHP/PCD

In the instances where transport or IV access is delayed, **initiation of oral NAC should be considered at the Behavioral Health Pavilion.** Studies have shown that oral NAC is as effective as IV NAC in reducing hepatotoxicity in acetaminophen toxicity, though some patients may not tolerate the oral product due to nausea/vomiting.

Acetylcysteine 20% oral solution is now stocked in the BH1A Pyxis Station located in the PCD medication room. *This product comes as an oral solution in glass vials and should be diluted prior to administration.*

Prior to ordering NAC, physicians should assess if oral NAC would be appropriate to start in patients with acetaminophen ingestion. As always, contact Poison Control Center (800-222-1222) with any questions/concerns.

- When to ***emergently*** transfer patients to MCED (via ambulance) for IV treatment:
  - Altered mental status
  - "Massive" ingestion
    - Definition of "massive" may vary; generally if
      - 4-hr acetaminophen serum concentration > 300 mcg/mL **or**
      - Ingestion of greater than 32 g of acetaminophen
  - Delay in safe car transportation to main campus and patient unable to tolerate oral product
  - Any other medical instability or if recommended by Poison Control Center

Return to NAC Therapy Algorithm

Return to Oral NAC Therapy

Key References

- Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. Acetaminophen. In: Goldfrank LR, ed. *Goldfrank's Toxicologic Emergencies*. 10th ed. New York, NY: McGraw-Hill; 2015.
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- Hodgeman MJ, Garrard AR. A review of acetaminophen poisoning. *Crit Care Clin*. 2012;28(4):499-516.
- Spiller H, Winter M, Klein-Schwartz W, Bangh S. Efficacy of activated charcoal administered more than 4 hours after acetaminophen overdose. J Emerg Med. 2005;30(1):1-5.
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- Yarema MC, Johnson DW, Berlin RJ, et al. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. *Ann Emerg Med*. 2009;54:606-614.
- Chiew AL, et al. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. 2019. AMPCo Ltd.

Return to Non-Acute/ Supratherapeutic Ingestion Algorithm

Pathway Team & Process

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Clinical Pathway Development

This clinical pathway was developed using the process described in the NCH Clinical Pathway Development Manual Version 6, 2022. Clinical Pathways at Nationwide Children's Hospital (NCH) are standards which provide general guidance to clinicians. Patient choice, clinician judgment, and other relevant factors in diagnosing and treating patients remain central to the selection of diagnostic tests and therapy. The ordering provider assumes all risks associates with care decisions. NCH assumes no responsibility for any adverse consequences, errors, or omissions that may arise from the use or reliance on these guidelines. NCH's clinical pathways are reviewed periodically for consistency with new evidence; however, new developments may not be represented, and NCH makes no guarantees, representations, or warranties with respect to the information provided in this clinical pathway.

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