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

Inpatient

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

Center for Clinical Excellence

APAP Dose and Symptoms with risk for liver injury

≥ 10g or ≥ 200 mg/kg over 8-24hrs (whichever dose is less)
≥ 12 g or ≥ 300 mg/kg over <48hrs
Or
≥ a daily therapeutic dose per day
for more than 48 hours
in patients who **also** have **abdominal pain or nausea or vomiting**

APAP Dose and/or Symptoms concerning for liver injury

Definitions, Diagnosis Inclusion&Exclusion Criteria

Ingestion/overdose occurred over **<8hrs**?

Yes → Go to **Acute Acetaminophen (APAP) Ingestion/Overdose Clinical Pathway**

No

Send **Ingestion Labs** if not already obtained

If **time of ingestion** is unknown, discuss with Toxicology

BHP/PCD APAP ingestion/overdose process

Any elevation of AST or APAP ≥ 10 mcg/mL?

No → **Off Pathway** NAC treatment not required.

Yes

- Review ED treatment course to determine stage and route of NAC therapy
- **If arriving with NAC infusion, have next bag NAC ready prior to finishing current bag**
- Call Poison Center **800-222-1222,** to confirm treatment plan
- Notify on call "**GI Liver/Hepatology**" if elevated AST or ALT

If no IV access or pt prefer → **Oral NAC Protocol**

Continue Intravenous

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, PT/INR & alkaline phosphatase (AP) if GI symptoms **or** previously elevated AST

Signs of Deterioration
- Monitor for signs and symptoms of:
  - **APAP Toxicity**
  - **Anaphylactoid reaction (NAC)**

- Call Poison Center

Toxicity:
- Consult Toxicology; Consider Hepatology consult

Anaphylactoid reaction:
- Pause NAC. Consider treatment with IM epi, H1/H2 blockade, and/or steroids.

Call Poison Control with results and discuss further management

*Notify on call "GI Liver/Hepatology" for management input if AST or ALT are elevated

AST normal or declining
and
Acetaminophen level <10 mg/L or "None Detected"
and
Well appearing patient?

No →
- Repeat NAC 100 mg/kg over 16 hours
- Also Call Poison Center for guidance

Yes

- If intentional ingestion: Patient is medically cleared for psychiatric management and disposition.
- If psychiatric assessment not indicated: Discharge
- Avoid taking APAP for next 2 months

Pre-Pathway Validation

Is this Acetaminophen poisoning?

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.

Inclusion Criteria

- **Non-acute, supratherapeutic ingestion**
  - **Non-Acute/Chronic timeline**
    - APAP ingested over ≥ 8-hour period (regardless of timing prior to presentation)
  - **Supratherapeutic dose:**
    - ≥ 10 g or ≥ 200 mg/kg (whichever is less) over a single 24-hour period

      OR
    - ≥ 12 g or ≥ 300 mg/kg (whichever is less) over a single 48-hour period

      OR
    - ≥ a daily therapeutic dose per day for more than 48 hours in patients who also have abdominal pain or nausea or vomiting

Exclusion Criteria

- **Acute APAP Ingestion**
  - ≥ 10g or ≥ 200 mg/kg (whichever is less) over < 8hrs
- Ingestion of extended release APAP

Diagnostic Timeout

Red Flags

- Nausea or vomiting or abdominal pain in patient with dehydration who has been taking recurrent doses of acetaminophen for fever
- AST/ALT elevation and a history of acute or chronic acetaminophen use

Diagnostic Timeout

Differential Diagnosis

- Include acetaminophen toxicity in the Differential Diagnosis for:
- Unexplained AST/ALT elevation
- Right upper quadrant abdominal pain
- Nausea and vomiting
- Encephalopathy

Return to Algorithm

Daily Therapeutic APAP Dose

Lexicomp®

- **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**

Return to Algorithm

Return to Pre-Pathway Validation

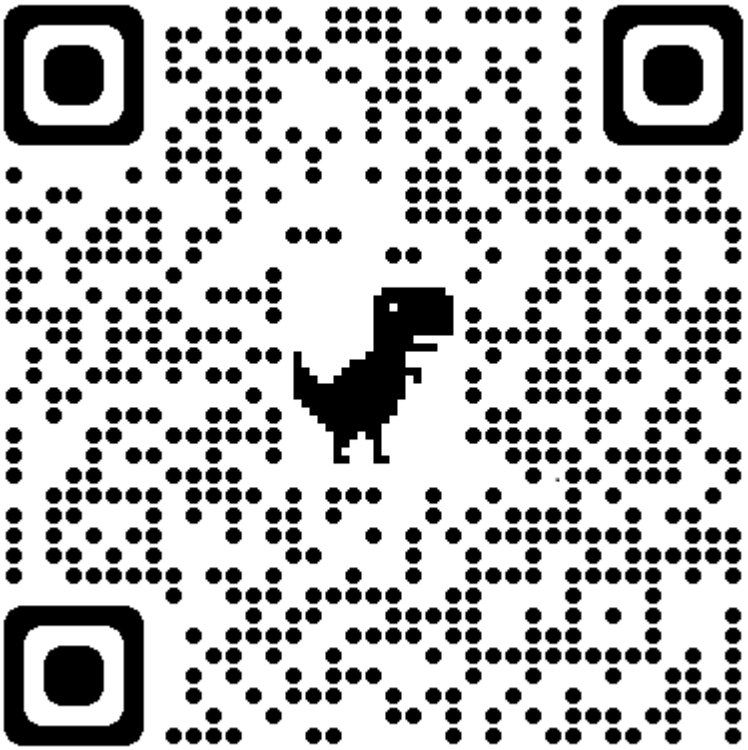
Admission Criteria

- **Acute Ingestion:** APAP level at or above treatment line on nomogram
- **Non-Acute supratherapeutic ingestion:** APAP level > 10 mcg/mL **or** elevation in AST indicating treatment with NAC
- Intentional overdose not ruled out
- Unable to medically clear beyond presenting symptoms

Return to Algorithm

Severity Assessment

Plot APAP level on Rumack-Matthews nomogram



Return to Algorithm

Signs of Deterioration

Acetaminophen toxicity: Four clinical stages of, 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.

Signs of NAC Anaphylactoid Reaction:

- Urticaria, pruritus, facial flushing, wheezing, dyspnea, and hypotension.

Return to Algorithm

Ingestion Labs

All patients with APAP ingestion:

- AST/ALT
- APAP (at least 4 hours from start of ingestion time)

Intentional ingestion/self harm:

- Salicylate level
- Ethanol level
- EKG
- Beta HCG(if applicable)
- Chem 7
- Urine drug abuse screen if concerned for street drugs
- Send out urine drug screen if concern for other medication overdose

If ill appearing or encephalopathic (moderate/severe hepatotoxicity) include:

- iSTAT
- Comprehensive Metabolic Panel (CMP)
- Lactate
- Ammonia
- PT/INR

Return to Algorithm | Return to Oral NAC Therapy | Return to Pre-Pathway Validation

Oral NAC Therapy

Loading

- 140mg/kg (max 15 grams) PO

Maintenance

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

- Obtain repeat labs 24 hours AFTER starting NAC:
  - APAP level and AST/ALT
  - Add total and direct bilirubin, INR, ammonia & 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
- No need to repeat dose if emesis > 1 hour later & does not smell like NAC

Return to Algorithm

Return to Pre-Pathway Validation

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 Algorithm

Return to Oral NAC Therapy

Discharge Criteria & Planning

- Down trending or normal AST
- Acetaminophen level <10 mg/L or “None Detected”
- Well appearing
- Cleared by psychiatry for discharge (if applicable)

Notify on call “GI Liver/Hepatology” for management input if **ANY** AST or ALT elevation.

If AST elevation,
Two levels showing significant decline
and
AST < 1000 U/L
are required before discontinuing NAC

[Return to Algorithm] [Return to Oral NAC Therapy] [Return to Pre-Pathway Validation]

Quality Measures

Process Measure:

- Order set use
- Time from AST level *or* APAP level to start of NAC treatment

Outcome Measure:

- AST normal ***or*** <1000 U/L with 2 declining levels, prior to discharge

Balancing Measure:

- LOS

[Return to Algorithm] [Return to Oral NAC Therapy] [Return to Pre-Pathway Validation]

References

1. Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. *Goldfrank's Toxicologic Emergencies*, Ch 35 – Acetaminophen. 2015

2. Olson K. *Poisoning & Drug Overdose, Sixth Edition*. 6th ed. McGraw Hill; 2012:69-72.

3. Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. *Crit Care Clin*. 2012;28(4):499-516. doi:10.1016/j.ccc.2012.07.006

4. Spiller HA, Winter ML, Klein-Schwartz W, Bangh SA. Efficacy of activated charcoal administered more than four hours after acetaminophen overdose. J Emerg Med. 2006;30(1):1-5. doi:10.1016/j.jemermed.2005.02.019

5. Prescott LF, Illingworth RN, Critchley JA, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcystine: the treatment of choice for paracetamol poisoning. *Br Med J*. 1979;2(6198):1097-1100. doi:10.1136/bmj.2.6198.1097

6. 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(4):606-614. doi:10.1016/j.annemergmed.2009.05.010

7. Chiew AL, Reith D, Pomerleau A, et al. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. *Med J Aust*. 2020;212(4):175-183. doi:10.5694/mja2.50428

Return to Algorithm | **Return to Oral NAC Therapy** | **Return to Pre-Pathway Validation**

Team & Process

Content Development Team

Hospital Pediatrics:
Gerd McGwire MD, PhD

Toxicology:
Marcel J. Casavant, MD
Hannah Hays, MD

Hepatology:
Carol Potter, MD

ED:
Berkeley Bennett, MD

Resident:
Meghan Fennell, MD

Clinical Pathways Program:

Medical Director – Emergency Medicine:
Berkeley Bennett, MD, MS

Medical Director – Hospital Pediatrics:
Gerd McGwire, MD, PhD

Medical Director – Clinical Informatics & Emergency Medicine:
Laura Rust, MD, MPH

Business & Development Manager:
Rekha Voruganti, MBOE, LSSBB

Program Coordinators:
Tara Dinh, BS

Clinical Pathway Approved

Medical Director – Associate Chief Quality Officer, Center for Clinical Excellence:
Ryan Bode, MD, MBOE

Advisory Committee Date: *June, 2023*

Origination Date: *Dec, 2021*

Last Revision Date: *June, 2023*

Next Revision Date: *June, 2026*

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.

For more information about our pathways and program please contact:
ClinicalPathways@NationwideChildrens.org

Return to Algorithm | Return to Oral NAC Therapy | Return to Pre-Pathway Validation