Acute Acetaminophen (APAP) Ingestion/Overdose

Inpatient

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

Center for Clinical Excellence

Verify that patient is appropriate for this pathway

Ingestion of ≥ 10g or ≥ 200 mg/kg APAP (whichever is less) **or dose unknown or intentional ingestion**?

- No → **Off Pathway**
- Yes ↓

BHP/PCD APAP ingestion/overdose process

Did all ingestion/overdose occur within an 8 hour period? (Does NOT need to occur within 8 hours of presentation)

- No → Go to **APAP Non-Acute Supratherapeutic Ingestion Clinical Pathway**
- Yes ↓

- If **time of ingestion** is unknown, discuss with Toxicology
- If **APAP level** not available within 8 hours of initiation of ingestion, give loading dose of NAC.
- If N-Acetylcysteine (NAC) is running, complete bag

Send Ingestion Labs if not already obtained

Was last APAP level at or above treat line on Rumack-Matthew Nomogram?

- 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

IV access unavailable or pt preference → 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 Center 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.

Pathway Inclusion Criteria

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

Pathway Exclusion Criteria

- **Non-Acute supratherapeutic ingestion (i.e.** APAP ingested over ≥8-hour)
- 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
- LFT 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

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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

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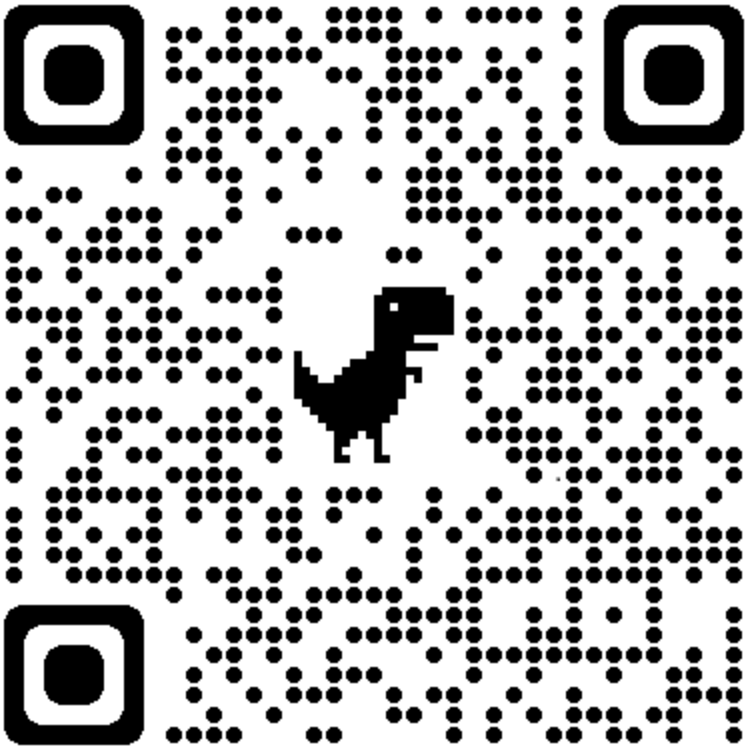
Severity Assessment

Plot APAP level on Rumack-Matthews nomogram



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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.

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Ingestion Labs

All patients with APAP ingestion:

- AST/ALT
- APAP (obtained 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 /encephalopathic (moderate/severe hepatotoxicity) also include:

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

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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, lactate, ammonia, INR & alkaline phosphatase (AP) if GI symptoms or previously-elevated AST

- Continue maintenance NAC if APAP >10 mg/L or 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

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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 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

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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

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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

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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

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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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