

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

Emergency Department

[See Moderate-severe
hepatotoxicity algorithm](#)

[Signs, Symptoms
&
Mechanism of Toxicity](#)

Ill appearing or encephalopathic and concern
for acetaminophen (APAP) ingestion?

Yes

No

Ingestion of extended release APAP?

Yes

Off Pathway
Call Poison Control

No

See Acute Acetaminophen
(APAP) Ingestion/
Overdose Algorithm

Yes

Did all ingestion of APAP occur within an 8
hour period?

No

Any of the following?

≥ 10 grams or ≥ 200 mg/kg (whichever is less) over a single 24-hour period
Or
≥ 12 grams 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

No

Off
Pathway

Call Poison Control

Place IV
Obtain:

- APAP level
- AST & ALT

Yes

Any of the following:

- Elevation of AST or ALT
- APAP ≥ 10mg/L

No

Yes

[Start N-Acetylcysteine \(NAC\)](#)

Admit to Hospital Pediatrics
for supportive care and
laboratory monitoring

Discharge home if no other
indications for admission

Provide education on:

- Avoiding APAP for at least 2 months
- [Safe APAP Dosing](#)
- [APAP Toxicity Risk Factors](#)

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.

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Supratherapeutic Ingestion
Algorithm](#)

Concern for Moderate-Severe Hepatotoxicity

III appearing or encephalopathic in with concern for Acetaminophen (APAP) ingestion

Call Poison Control

- **Cardiac Monitors**
- **Place IV**
- **Obtain**
 - iSTAT
 - Complete metabolic panel
 - Lactate
 - Ammonia
 - PT/INR

Admit to PICU with early consultation with Hepatology team

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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

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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 $\geq$ 60 kg: 3250 mg/day
- FDA
 - “Severe liver damage may occur if you take more than 4000 mg in 24 hours”

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

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**NATIONWIDE
CHILDREN'S**

When your child needs a hospital, everything matters.

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)

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

[Oral NAC Therapy](#)

Transfer to Main Campus
Emergency Department if at
BHP/PCD

No

IV NAC Therapy Use ED Order Panel

(Continue [3-bag NAC Therapy](#) if initiated at outside facility)

Loading

- 200 mg/kg (max 20 grams) IV over 4 hours

Second

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

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

Admit to Hospital Pediatrics

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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 & PT/INR 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

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[Patient at BHP/PCD](#)

3-Bag NAC Therapy

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 if GI symptoms **or** previously elevated AST

[**Return to NAC
Therapy Algorithm**](#)

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

- Hendrickson RG, McKeown NJ. Acetaminophen. In: Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. eds. Goldfrank's Toxicologic Emergencies, 11e. McGraw-Hill Education; 2019. Accessed September 25, 2025. <https://accesspharmacy.mhmedical.com/content.aspx?bookid=2569§ionid=210270383>
- Hendrickson RG, Howland M. N-Acetylcysteine. In: Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. eds. Goldfrank's Toxicologic Emergencies, 11e. McGraw-Hill Education; 2019. Accessed September 25, 2025. <https://accesspharmacy.mhmedical.com/content.aspx?bookid=2569§ionid=210261914>
- Smollin C. Acetaminophen. In: Olson K, Smollin C, eds. Poisoning & Drug overdose, 8e. McGraw-Hill Education; 2022.
- Dart RC, Mullins ME, Matoushek T, et al. Management of Acetaminophen Poisoning in the US and Canada: A Consensus Statement. *JAMA Netw Open*. 2023;6(8):e2327739. doi:10.1001/jamanetworkopen.2023.27739
- 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
- 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
- Prescott LF, Illingworth RN, Critchley JA, Stewart MJ, Adam RD, Proudfoot AT. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *Br Med J*. 1979;2(6198):1097-1100. doi:10.1136/bmj.2.6198.1097
- 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
- Dart RC, Mullins ME, Matoushek T, et al. Management of Acetaminophen Poisoning in the US and Canada: A Consensus Statement. *JAMA Netw Open*. 2023;6(8):e2327739. doi:10.1001/jamanetworkopen.2023.27739

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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 associated 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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