ED GUIDELINE

Acetaminophen Poisoning Emergency Department Management

Exclusion guidelines:
- Signs of acute liver failure necessitating urgent transfer to a transplant facility
- Pre-existing liver disease
- Age <40 weeks CGA

Aim: to standardize the evaluation and management of patients presenting with acetaminophen poisoning

Definitions Box
- **Toxicology** = Toxicologist on call or Poison Center (1-800-222-1222)
- **APAP** = acetaminophen
- **NAC** = acetylcysteine or n-acetylcysteine

Suspected acetaminophen (APAP) **overdose** in a patient (see Note 1 for definitions)

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Obtain detailed history and exam including the patient's intent, timing, and volume of ingestion (Note 2)

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If concern for suicidal intent, consult Social Work for a Mental Health Evaluation and place patient on 1:1 Suicidal Precautions

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Time since ingestion?

← < 4 hours

If patient *may* have had an ingestion ≥ 10 g or ≥ 200 mg/kg, **discuss activated charcoal** with Toxicology (see Definitions Box) and administer Activated Charcoal if indicated (Note 3)

→ >4 hours since ingestion, unknown time, OR non-acute repeated supratherapeutic ingestion

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- **Work up:** ***draw serum APAP level 4 hrs post-ingestion or ASAP if ≥ 4 hrs***
  - If exploratory ingestion in child < 6 years old: discuss labs and timing with Toxicology (see Definitions Box) prior to drawing labs
  - If unknown time of ingestion or non-acute: add CMP, INR
  - If concern for intentional ingestion/self-harm: add CMP, INR, EKG, salicylate level, ethanol level, urine drug screen, pregnancy test (if patient has a uterus and is of childbearing age)
- **Consult Toxicology ASAP** (see Definitions Box)**, as they may advise activated charcoal (Note 3) or starting NAC before labs return in certain situations**
- Provide anti-nausea medication as needed (Note 4)

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If <24 hrs since ingestion: Plot serum APAP level on Rumack-Matthew Nomogram (Note 5)
Is the patient's APAP level above the "treatment line"?
Or
If unknown time of ingestion or non-acute: Is the APAP level ≥ 10 mcg/mL (if acute) or ≥ 20 mcg/mL (if non-acute), transaminases elevated, or INR >2?

→ Yes

Treat with Standard-Dose or High-Dose NAC (depending on whether the ingestion was high-risk and per toxicologist) (see Note 1, 5, 6) **and admit to hospital** (Note 7 for PICU considerations)

See page 2 for inpatient management.

← No

If < 24 hours since ingestion, is the APAP level >10 mcg/mL AND the patient ingested extended-release APAP or co-ingested an anticholinergic or opioid?

Possibly/ Yes →

Redraw APAP level after 4-6 hours and discuss with Toxicology. *See p. 2 for inpatient management if hospital admission advised by Toxicology.*

No →

If medically cleared (e.g. tolerating a regular diet, normal mentation), consider discharge to home (if accidental overdose) or inpatient psychiatric facility
Avoid APAP-containing products for at least 1 week

Disclaimer: This guideline is designed for general use with most patients; each clinician should use their own independent judgment to meet the needs of each individual patient. This guideline is not a substitute for professional medical advice, diagnosis or treatment.

CLINICAL GUIDELINE

Acetaminophen Poisoning Inpatient/ICU Management

Aim: to standardize the evaluation and management of patients presenting with acetaminophen poisoning

Exclusion guidelines:
- Signs of acute liver failure necessitating urgent transfer to a transplant facility
- Pre-existing liver disease
- Age <40 weeks CGA

Acute acetaminophen (APAP) overdose requiring admission for NAC Therapy (Note 5 and 6) or for trending labs

If concern for self-harm: ensure patient is admitted with "suicide precaution" orders and 1:1 monitoring

Is this a high-risk ingestion? (see Note 1)

No

- Consult Toxicology (see Definitions Box), if not already involved
- If patient's acetaminophen level is above the "treatment line" on the Rummack-Matthew Nomogram, administer **standard** NAC dosing (Note 5 and 6)

Yes

- Consult Toxicology (see Definitions Box) and administer their treatment recommendations, which may include activated charcoal (even if > 4 hours post-ingestion), **high-dose** NAC (Note 6), or possibly fomepizole

Labs:
- Draw AST, ALT, APAP level, and INR 1-2 hours prior to NAC (2nd bag) completion
- If AST or ALT >1000 IU/L: also monitor bilirubin, ammonia, serum pH, lactate, creatinine, and BUN
- Provide anti-nausea medication as needed (Note 4)

Are all the following NAC discontinuation criteria met?

1. Patient is clinically well
2. APAP level <10 mcg/mL
3. INR <2 (Note 10)
4. If AST normal for age OR AST down-trending criteria met:
   - If peak AST elevated and <1,000 IU/L, may stop NAC if AST decreasing
   - If peak AST ≥1,000 IU/L, may stop NAC once AST has decreased at least 25% from peak and ALT has decreased from peak

No

Continue NAC (Note 6) and draw labs (AST, ALT, INR and APAP level) every 12-24 hours (discuss timing with Toxicology) until NAC discontinuation criteria met.

If progressive increases in AST or ALT and coagulation abnormalities, PT>100 sec, encephalopathy, or multisystem failure despite NAC (e.g. SCr >3 mg/dL), consider transfer to a liver transplant center

Yes

If medically cleared (e.g. tolerating a regular diet, normal mentation and vitals), consider discharge to home (if unintentional overdose) or consult social work about transfer to an inpatient psychiatric facility

If AST and ALT <1,000 IU/L, avoid APAP for at least one week

If AST or ALT > 1,000 IU/L, trend ALT and AST every 2 weeks until normalized and avoid APAP until that time (Note 9)

Definitions Box
- **Toxicology** = Toxicologist on call or Poison Center (1-800-222-1222)
- **APAP** = acetaminophen
- **NAC** = acetylcysteine or n-acetylcysteine

CLINICAL GUIDELINE

Acetaminophen Poisoning Notes

Aim: to standardize the evaluation and management of patients presenting with acetaminophen poisoning

Note 1: Overdose Definitions

APAP Overdose = ingestion potentially ≥ 200 mg/kg or ≥ 10 g total of APAP (exact volume of an intentional ingestion may be unknown, so providers should generally err on the side of caution pending lab results).

- Considered "acute" if entirety of APAP ingestion taken within a 24-hour timeframe and patient presenting <24 hours after initial time of ingestion
- Considered "high risk" if >30 g ingestion OR APAP level falls above high-risk line in Note 5 OR patient has altered mental status (see Note 8 for evaluation of patients with altered mental status; see note 6 for high-risk dosing recommendations for NAC)

Note 2: Detailed history and physical should include:

- APAP ingestion: formulation of APAP, amount consumed, duration and pattern of ingestion, time of ingestion, any potential co-ingestions
    - Co-ingestions with anticholinergics or opioid agonists can delay/prolong APAP absorption and these patients may need additional lab monitoring, even if their serum APAP level falls below the nomogram "treatment line"
- Mental health evaluation: inquire about history of mental health concerns and treatment, and assess patient's current state of mental health
- Sign/symptoms of APAP toxicity: can be vague and non-specific and include vomiting, altered mental status, abdominal pain, right upper quadrant (RUQ) abdominal tenderness. In large overdoses, wide anion-gap metabolic acidosis and/or cardiovascular collapse can occur within hours of ingestion.
    - Typical Presentation of APAP overdose includes four clinical stages:
        1. Stage 1 (12-24 hrs after ingestion): anorexia, malaise, nausea/vomiting, diaphoresis. May include transient coma and anion gap acidosis after a high-risk ingestion (see Note 1 for "high risk" definition)
        2. Stage 2 (36-48 hours): may include transaminase elevation, liver enlargement, RUQ pain, oliguria, or may be asymptomatic
        3. Stage 3 (3-5 days): recurrence of anorexia, nausea/vomiting and malaise. Increasing transaminases may be accompanied by hepatic dysfunction including jaundice, coagulopathy, encephalopathy or hypoglycemia. May also develop acute renal injury (e.g. Acute tubular necrosis) or cardiomyopathy.
        4. Stage 4 (> 5 days): Complete recovery or progression to liver failure
- Medical history that might increase hepatotoxicity of APAP: history of liver dysfunction, recent fasting or malnourished patient (diminished glutathione stores), chronic alcohol consumption (depleted glutathione), use of other potentially hepatotoxic drugs (e.g. phenobarbital)

Note 3: Activated charcoal

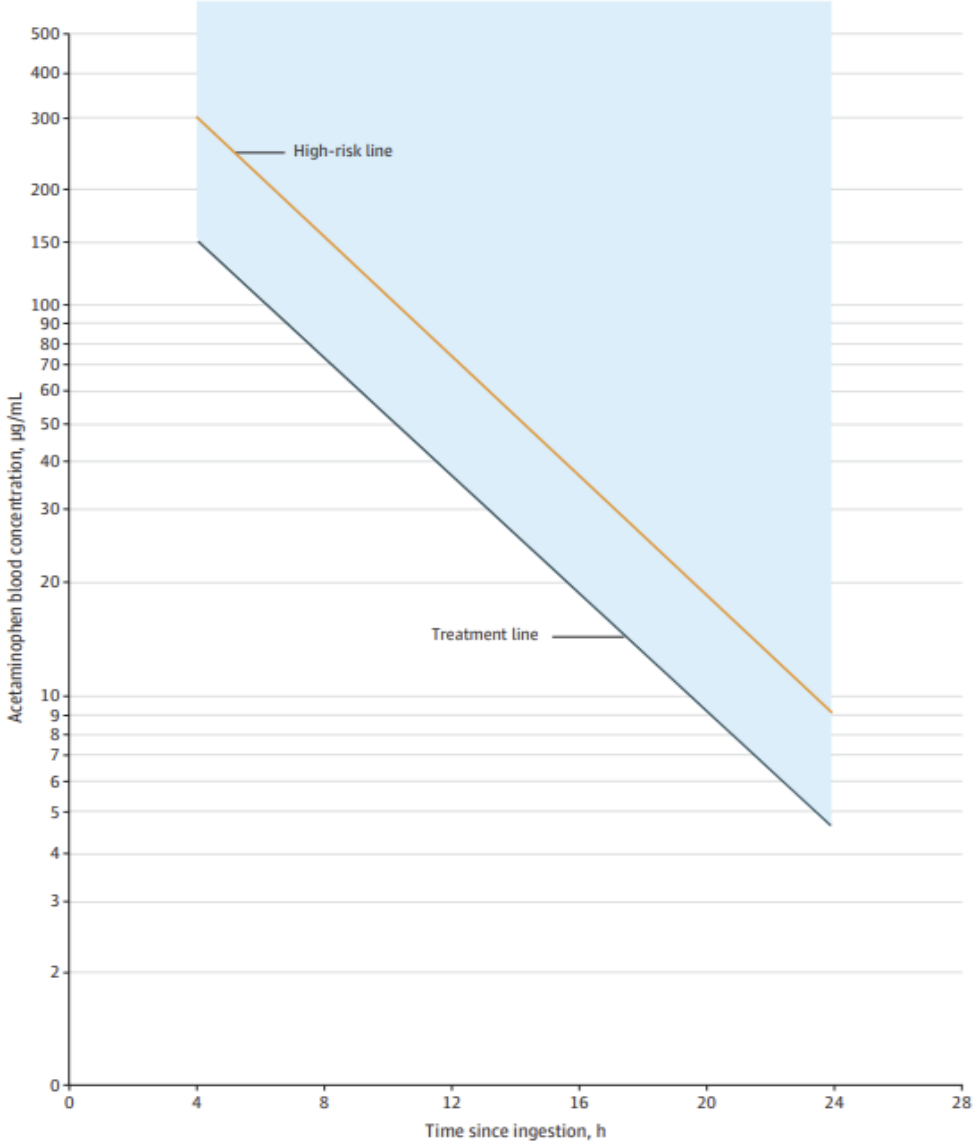
- Contraindications to activated charcoal: patient unable to protect their airway when taking the enteral med, actively vomiting, ileus/absent bowel sounds, or unable/unwilling to tolerate the medication
    - *Co-ingestion is not a contraindication to activated charcoal administration*
- Dosing: 0.5-1 g/kg (max 100 g/dose), can be given orally or via NG
- Situations in which to consider administering activated charcoal after an overdose:
    - Patient presents <4 hours from the time of an APAP ingestion
    - Patient presents > 4 hours from the time of a "high risk" APAP ingestion (see Note 1 for definition of "high risk")
    - Patient presents > 4 hours from an extended-release APAP ingestion
    - Patient presents > 4 hours from ingestion of APAP AND suspected co-ingestion with an opioid or anti-cholinergic

Aim: to standardize the evaluation and management of patients presenting with acetaminophen poisoning

Note 4: Anti-emetics in patients receiving IV NAC
One study identified that patients on IV NAC for APAP toxicity who received ondansetron had increased transaminases compared to those who did not receive ondansetron. Especially for high-risk ingestions, providers can consider alternative anti-emetics such as low-dose IV lorazepam 0.02 mg/kg (Max 0.5 mg/dose) every 6 hours or making ondansetron prn rather than scheduled so it is used sparingly.

Note 5: Revised Rumack-Matthew Nomogram for Acute Ingestion of APAP:

- NAC should be initiated if an APAP blood level drawn 4-24 hrs after ingestion **falls on or above the treatment line** (see Note 6 for dosing)
- If the concentration falls on or above the **high-risk line**, many clinicians would provide "high-risk dosing" NAC (see Note 6 for dosing)
- An APAP sample drawn before 4 hours after ingestion *cannot* be used to risk-stratify patients on this nomogram. However, if APAP concentration at 2-4 hours after ingestion is nondetectable, it typically excludes any significant ingestion.
    - Consultation with Toxicology is recommended prior to discontinuing monitoring.
- If the APAP level is just below the treatment line (i.e. "borderline"), but any of the following circumstances apply, discuss considering NAC treatment with Toxicology:
    - Poor nutritional status
    - Patient taking isoniazid
    - Ambiguous time of ingestion
    - Underlying liver disease
    - APAP ingestion >4 g or >100 mg/kg per day for at least 2 days (repeat supratherapeutic ingestion)



JAMA Network Open. 2023;6(8):e2327739. doi:10.1001/jamanetworkopen.2023.27739

Aim: to standardize the evaluation and management of patients presenting with acetaminophen poisoning

Note 6: Acetylcysteine (NAC or N-acetylcysteine)- while oral form is equivalent in efficacy to IV for those without liver failure, IV is often preferred for reliability of delivery, particularly if the patient is vomiting or has ileus

- **IV Dosing**:
  - **IV standard 2-bag dosing:** Loading dose of 200 mg/kg (max: 20 g) infused over 4 hours --> second dose of 100 mg/kg (max: 10 g) infused over 16 hrs
  - **Ongoing dosing** (i.e. if patient does NOT meet discontinuation criteria after initial 20 hours of NAC): 100 mg/kg (max 10 g) infused over 16 hours, begun immediately after prior bag completed
  - **IV high-risk dosing (for high-risk ingestion (see Note 1) if recommended by Toxicology):** Loading dose of 200 mg/kg (max: 20 g) infused over 4 hours --> second dose of 200 mg/kg (max: 20 g) infused over 16 hours
- **If patient was started on a 3-bag regimen at an outside facility,** complete treatment *without delay* according to that regimen (150mg/kg over 1 hour, 50 mg/kg over 4 hours, 100mg/kg over 16 hours). If patient was started on an *alternative* 2-bag regimen at an outside facility (i.e. not the standard dosing discussed above), consult with the inpatient pharmacist or Toxicology to determine how to proceed.
  - *2-bag system is preferred over the 3-bag protocol* due to similar effectiveness, fewer anaphylactoid reactions, fewer administration errors and fewer interruptions to NAC infusion
- **Enteral dosing (Mucomyst®):**
  - Loading dose of 140 mg/kg (max: 15 g), followed by 70 mg/kg (max: 7.5 g) Q4H x 5 doses, then repeat labs. Continue 70 mg/kg (max: 7.5 g) q4h until patient meets NAC discontinuation criteria.
  - Can be given via NG drip, over 30-60 min per dose, or by mouth. Should be re-dosed if patient has emesis within one hour of administration.
  - To optimize tolerance of oral NAC: dilute NAC to 5% solution in orange juice or soda pop (i.e. 1 part 20% NAC mixed with 3 parts juice) and serve to patient chilled/over ice, covered and sipped through a straw to reduce odor.
- **If the patient has a non-allergic anaphylactoid reaction to NAC (e.g. flushing, itching, bronchospasm, angioedema):**
  - Pause infusion, stabilize patient with supportive therapy (epinephrine, corticosteroids, antihistamines), then restart infusion at a slower rate. Consult Toxicology for specific guidance.
- **If history of NAC adverse effect:** A prior anaphylactoid reaction is not a contraindication for administration of NAC during a subsequent overdose. If the patient meets criteria for NAC and then the patient develops an adverse reaction, the route and/or rate of administration can be adjusted and diphenhydramine used
- **Efficacy of NAC:** If NAC is started within 8-10 hours of ingestion, patients with "standard-risk" typically have a full recovery
  - Even those who present >10 hours post-ingestion and receive NAC, have a favorable prognosis

Acetaminophen Poisoning Notes

Aim: to standardize the evaluation and management of patients presenting with acetaminophen poisoning

Note 7: Consider **admission to PICU** if unstable vitals, INR >2, INR >1.5 WITH encephalopathy, altered mental status with patient unable to protect their airway, severe acidosis

Note 8: **Altered Mental Status**
- Consider further work-up including VBG, ammonia level, EEG, and head imaging
- Consider transfer to a center for hemodialysis, in addition to treatment with NAC, in a patient with acetaminophen level of ≥ 900 mcg/mL with acidosis or altered mental status

Note 9: If transaminases have not normalized within 1 month, refer to outpatient Pediatrics Gastroenterology

Note 10: **INR Elevation**
- IV NAC can spuriously elevate INR up to 2.0, so an INR level of 1.5-2 after NAC initiation does not warrant treatment with IV Vitamin K or other interventions as it is expected to resolve after treatment with NAC is completed.

Aim: to standardize the evaluation and management of patients presenting with acetaminophen poisoning

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