

Treatment and Referral Guidelines for Acetaminophen Ingestions

Referral Criteria

Always refer to a health care facility (HCF) if:

1. Intentional ingestion.
2. Symptomatic (abdominal pain, vomiting, or jaundice).
3. The amount ingested is unknown and could exceed the send-in amount (see below).
4. There was a second toxic co-ingestant.

Pediatric Considerations

Calculate the maximum potential amount of acetaminophen ingested per kilogram of the child's body weight. Include all APAP dosing for previous 24 hours.

Refer to HCF

1. Acute exposures-
 - a. Greater than 200 mg/kg in any 24 hour period
2. Chronic exposures-
 - a. 150 mg/kg each day for the preceding 2 days **OR**
 - b. 100 mg/kg each day for the preceding 3 days

Home Management

If APAP less than 200 mg/kg in any 24 hour period or chronic exposures less than above: Observe at Home. Have parent avoid using acetaminophen for the next 24 hours. Have parent call the poison center back if symptoms occur.

Adult Considerations

Refer to HCF

1. Intentional self-harm ingestions
2. Adult with > 6.0 grams of a single ingestion **OR** >10 grams in a 24 period.
3. Symptomatic patients
4. Chronic Exposures:
 - a. Adult who has taken >6.0 grams APAP in any 24-hour period for 2 or more days.
 - b. Adult who has taken >4.0 grams APAP in any 24-hour period **AND** has chronic use of alcohol, or isoniazid, **OR** chronic illness.

HCF Recommendations

Initial Labs / Documentation

1. [APAP]:

Obtain APAP concentration 4 hours after ingestion or as soon as possible thereafter. (Exposures to APAP products combined with opiates or anticholinergics are not managed any differently).

- If APAP concentration had been obtained between **1 and 4 hrs after ingestion** and is:

- < 10 mcg/mL - no additional concentration is needed. Be aware some hospitals have a negative APAP concentration other than < 10 mcg/mL, e.g. < 5 mcg/mL. Clarify the hospital's negative value each time. In this guideline, we will use < 10 mcg/mL as the negative value.
- > 300 mcg/mL – Start IV NAC protocol and a 4-hour concentration is not necessary.
 - o Patients with 1-4h [apap] > 300mcg/mL have a 97% chance of having a 4h [apap] over the treatment line. Clin Toxicol 2017; 55(2): 102-108

Always document time of [APAP]

2. AST/ALT:

- Obtain a baseline AST/ALT concentration on all patients except pediatric cases with accidental unknown/questionable amounts (they are very unlikely to have abnormal AST or ALT)
- Always document time of AST and ALT draw

3. Other tests:

- If patient has altered mental status or hypotension or AST or ALT over 1000 IU/L, then request these labs:
 - o VBG, lactate, glucose, BUN, creatinine and metabolic panel.
- Order INR if AST or ALT are elevated, > 50 IU/L.
- If suspected rhabdomyolysis (e.g. prolonged down time), check CPK.
- If patient develops an altered level of consciousness (not attributable to any other co-ingestion), consider a head CT to determine if cerebral edema has occurred.

HCF Assessment Criteria for NAC Treatment

1. ALT/AST normal (< 50 IU/L) **and** 4 hour APAP concentration <10 mcg/mL or below nomogram treatment line (**Or** if AST/ALT < 50 IU **and** APAP concentration from 1 hr – 4 hr less than 10 mcg/mL).

- a. Discharge with instructions to return if signs of hepatic injury occur
- b. Advise of safe APAP dosing

2. Initiate NAC treatment if:

- a. APAP above treatment line on nomogram OR
- b. If time of ingestion is unknown and
 - Initial APAP > 10 up/ml **OR**
 - AST or ALT > 50 IU/L (Note, if ALT or AST > 50 IU/L, start NAC EVEN if APAP is Negative)
- c. If APAP is taken chronically, and if the last dose taken is known:
 - If concentration is > 30mcg/ml at 90 minutes post last dose, start NAC.
 - If concentration is > 10mcg/ml at 4 hours post last dose, start NAC.

3. If high CPK could account for elevated LFTs, then **CHECK with MBU** - (may not need NAC if no recent history of APAP use).

4. If APAP concentration is > 600 mcg/mL, **contact MBU** for discussion of possible:

- a. Fomepizole 15mg/kg IV x 1 dose OR
- b. Hemodialysis if pH < 7.2 or lactate > 5 mmol/L.

Massive acetaminophen ingestions:

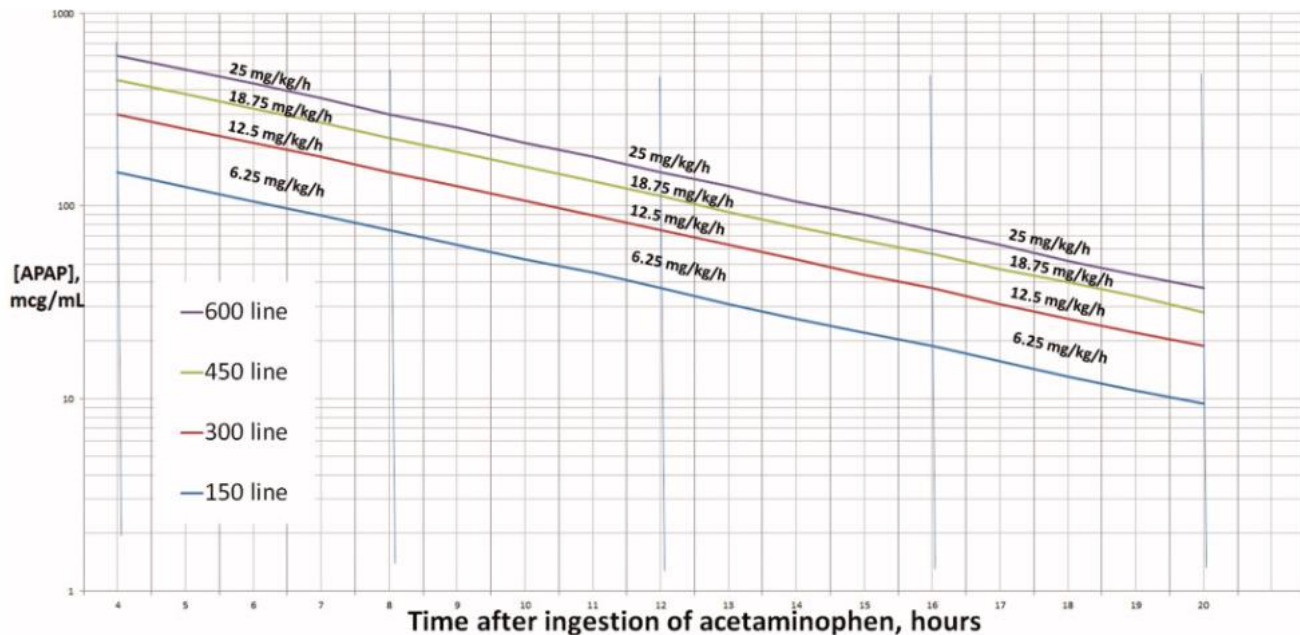
Massive acetaminophen ingestions are defined as an ingestion that is > 30 grams or an acetaminophen concentration that is above the “300-line”, that is a line starting at 4 hours and 300 mcg/mL and parallel to the “150-line” (or treatment line), so ending at < 10 mcg/mL at 24 hours.

Hendrickson RG. What is the most appropriate dose of N-acetylcysteine after massive acetaminophen overdose? *Clin Toxicol* 2019; 57(8): 686-691

Treatment guidelines:

1. MDAC: Treat with 50g activated charcoal every 4 hours for 6 doses, if not contraindicated (e.g. obtunded, unprotected airway)
2. Increased dose NAC: **NAC is only increased in patients who weigh > 40kg (adults)**. NAC dosing should be increased until the acetaminophen concentration is below 40 mcg/mL, then the normal NAC dosing can be continued until the “stop criteria” are met.
 - a. If [apap] is greater than the “300-line”, but less than the “450-line”, infuse NAC at 12.5 mg/kg/h after the loading bolus (see instructions below)
 - b. If [apap] is greater than the “450-line”, but less than the “600-line”, infuse NAC at 18.75 mg/kg/h after the loading bolus (see instructions below)
 - c. If [apap] is greater than the “600-line”, then infuse NAC at 25 mg/kg/h after the loading bolus (see instructions below)
 - d. If [apap] is greater than the 700 mcg/mL, the call MBU to consider hemodialysis.

	4 hour	8 hour	12 hour	16 hour	20 hour
“300 line”	300 mcg/mL	150 mcg/mL	75 mcg/mL	38 mcg/mL	19 mcg/mL
“450 line”	450 mcg/mL	225 mcg/mL	113 mcg/mL	56 mcg/mL	28 mcg/mL
“600 line”	600 mcg/mL	300 mcg/mL	150 mcg/mL	75 mcg/mL	38 mcg/mL



Instructions for increasing the dose of N-acetylcysteine in massive acetaminophen overdoses (> 40kg patient):

1. Mix and administer the loading bolus (first bag) of NAC as normal: 150mg/kg IV over 1 hour
2. To make a 12.5 mg/kg/h infusion:
 - a. Add 200 mg/kg (to a max of 20g) NAC into 1000mL of D5W infused over 16 hours
3. To make an 18.75 mg/kg/h infusion:
 - a. If 40-70kg: Add 300 mg/kg (to a max of 30g) NAC into 1000mL of D5W infused over 16 hours
 - b. If 71kg-100kg: Add 300 mg/kg (to a max of 30g) NAC into 1000mL of sterile water infused over 16 hours (sterile water is used in patients > 70kg because using D5W would be hyperosmolar)
 - c. If > 100kg, use 100kg dosing
4. To make a 25 mg/kg/h infusion:
 - a. Add 400 mg/kg (to a max of 40g) NAC into 1000mL of sterile water infused over 16 hours (sterile water is used because using D5W would be hyperosmolar)
5. When do I stop the high-dose infusion? Once the acetaminophen concentration is below 40 mcg/mL, the N-AC infusion can be converted to the traditional 6.25 mg/kg/h infusion until criteria are met to stop the infusion entirely.

Transfer to a Liver Transplant Center

Cases with any one of the following should also be considered for transfer to a liver transplant center or an ICU, and consultation with the on-call toxicologist is strongly encouraged:

1. Increased INR >2

2. Metabolic acidosis (pH < 7.30) due to liver failure
3. Hypoglycemia (< 60 mg/dl) due to liver failure
4. Hepatic encephalopathy / acute cerebral edema
5. Rapidly rising liver enzymes

OHSU Transfer Center: 503-494-7000 (for cases where patient needs to be transferred, based on our liver transplant criteria.)

NAC Administration

If the serum acetaminophen concentration is above the Treatment Line (i.e. above the “possibly toxic” concentrations below), treat with NAC.

Time since ingestion	Possibly Toxic
4 hours	150 mcg/mL
8 hours	75 mcg/mL
12 hours	38 mcg/mL
16 hours	19 mcg/mL
20 hours	10 mcg/mL
24 hours	5 mcg/mL

IV NAC (Acetadote®)

1. Loading Dose: 150 mg/kg over 1 hour - as a 3 % solution
2. Maintenance Dose: These are 2 sequential infusions -
 - Next: 50 mg/kg diluted in 500 ml D5W to run over 4 hours (12.5 mg/kg/hr) (125 ml/hr);
 - Then:** 100 mg/kg diluted in 1,000 ml D5W to run over 16 hours (6.25 mg/kg/hr) (62.5 ml/hr).

NOTE: Total duration of treatment is 21 hours.

Labs

1. If AST and ALT are normal (< 50 IU/L), repeat APAP concentration and AST/ALT 1 to 2 hours before the expected time to finish the last infusion
2. If LFTs are elevated (> 50 IU/L), repeat AST, ALT and INR every 12 hours. Check APAP concentration every 12 hrs until it is < 10 mcg/mL (or the hospital’s negative value.)

When to stop IV NAC

Special Situation: If we are not sure that the patient took APAP, but we started NAC because the AST/ALT were elevated after an ingestion -

NAC can be stopped if the AST is declining **and** AST <1000 U/L **and** INR is <2.0 **and** APAP negative. (Check with MBU)

Stop IV NAC if an acetaminophen is less than 10 mcg/mL **and** aminotransferases (AST and ALT) are normal (< 50 IU/L). (See below if aminotransferases had been elevated)

Continue IV NAC

Continue IV NAC if the acetaminophen is \geq 10 mcg/mL **OR** aminotransferases are elevated (AST or ALT \geq 50 IU/L). NAC should be continued at 6.25 mg/kg/h **until** all the following are met:

- AST and ALT have peaked and dropped **and**
- AST has fallen below 1,000 IU/L **and**
- INR < 2.0 **and**
- APAP is < 10 mcg/mL (or the hospital’s negative value)

NOTE: If NAC was inadvertently discontinued during an infusion, restart where therapy was interrupted if the interruption was < 2 hours. If > 2 hours, then restart the entire NAC protocol with the bolus. Obtain labs an hour before the end of the 21 hour infusion.

NOTE: If cerebral edema is present contact the Oregon Poison Center, we will likely recommend concentrating the IV NAC mixture to twice the strength in order to half the rate and fluid volume delivered.

Complications of IV NAC

IV NAC can lead to anaphylactoid reactions that usually occur in the first 2-3 hours of the infusion. NAC causes release of histamine from mast cells and patients may develop a histamine reaction that looks like an allergic or anaphylactic reaction, however, this is NOT AN ALLERGY. About 10-20% of patients treated with IV NAC will get nausea and a rash. A smaller percentage will get an urticarial rash and wheezing. Very rarely, patients may develop hypotension.

Anaphylactoid reactions are much more common in patients with low serum acetaminophen concentrations (~25% if acetaminophen is undetectable; <5% if acetaminophen > 150 mcg/mL) because acetaminophen stabilizes the mast cell and prevents histamine release.

Generally, the treatment for all of these reactions is to stop the infusion, wait until the reaction resolves, then restart the infusion at half the rate and slowly increase the rate back up to the infusion rate over an hour or two. If the patient has hypotension or wheezing, they should be treated with IV fluids and IV diphenhydramine. Almost all of these reactions resolve in a few minutes. If the reaction is severe (e.g. wheezing and hypotension) and prolonged, use an IV epinephrine infusion.

Oral NAC Protocol (Mucomyst®)

IV NAC should be considered as the first dose for the patient with nausea or vomiting. Covering the container with plastic wrap to disguise the smell and diluting the NAC with juice or soda to disguise the taste may help. If vomiting occurs less than one hour after a dose of NAC, administer an antiemetic and repeat NAC dose or switch to IV NAC.

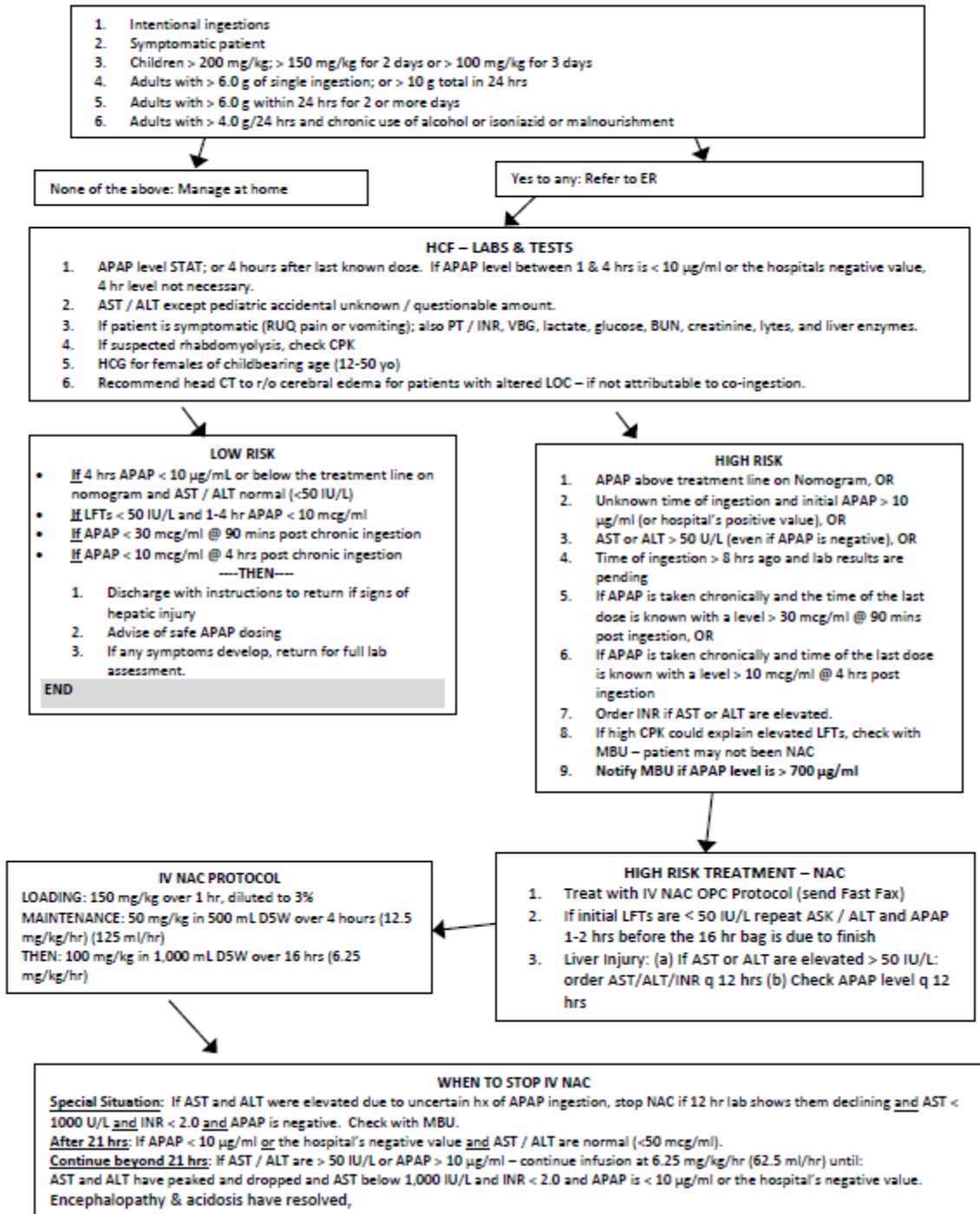
Oral NAC Dosing Regimen

1. Loading Dose: 150 mg/kg, diluted to a 3 to 5% solution
2. Subsequent Dosing: 70 mg/kg, diluted to a 3 to 5% solution, every 4 hours

When to Stop Oral NAC

1. Every 12 hours, measure an acetaminophen concentration **and** liver enzymes (AST and/or ALT).
2. NAC can be discontinued if **both**:
 - Acetaminophen is less than 10 mcg/mL (or other negative value); **and**
 - Liver enzymes (AST and/or ALT) are normal, <50 IU/L.
3. Patients who do not meet these criteria should receive NAC and ongoing evaluation.

Acetaminophen Ingestion: Decision Tree (for INTERNAL USE only)



The following Fast Faxes are associated with this treatment guideline: Acetaminophen - IV NAC, Acetaminophen - Liver Injury, Acetaminophen - IV NAC Massive Acute Ingestions, Acetaminophen - Oral NAC Reconstitution Tables