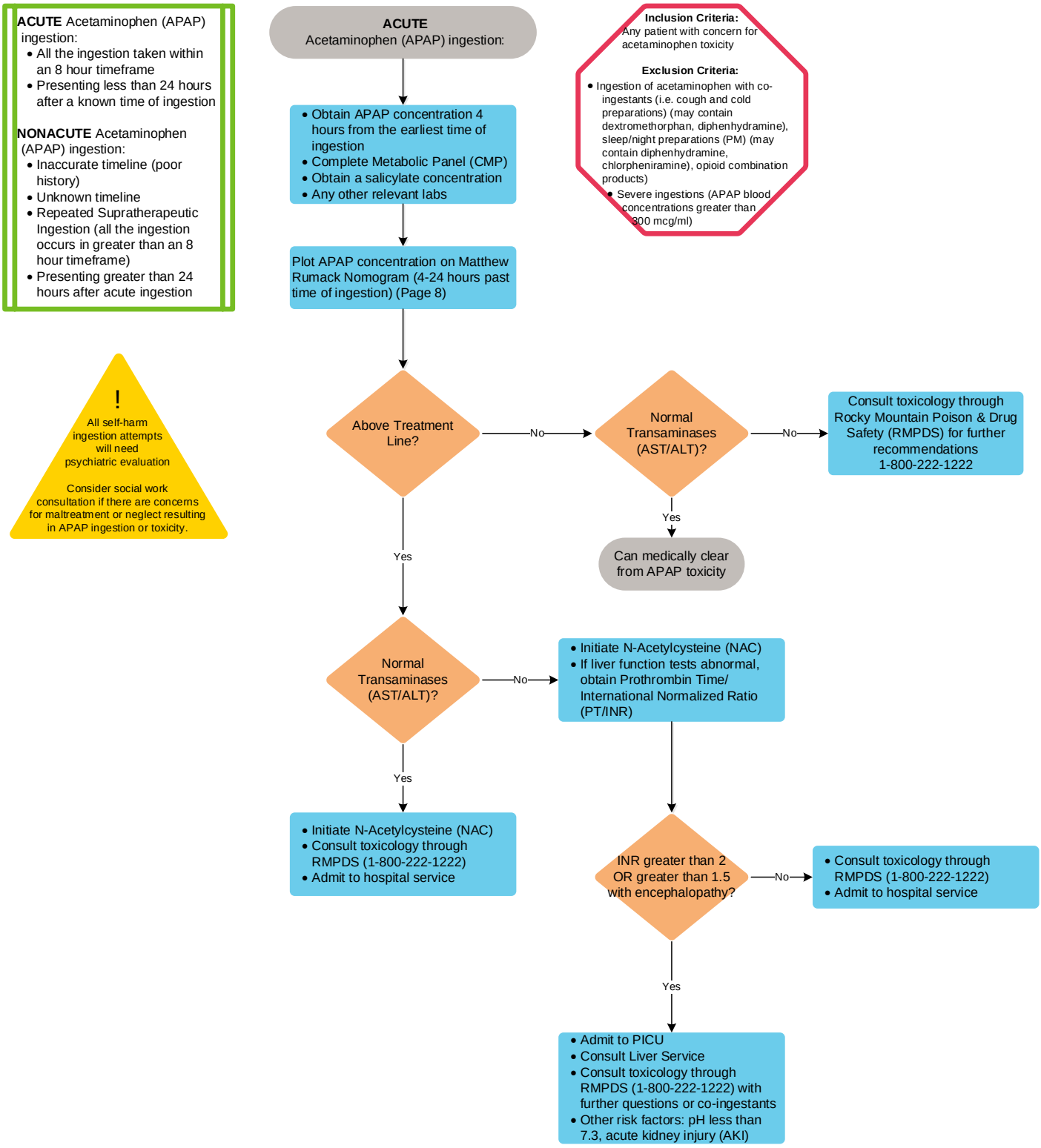
ACETAMINOPHEN (APAP) TOXICITY

ALGORITHM 1. ACUTE Acetaminophen (APAP) Toxicity

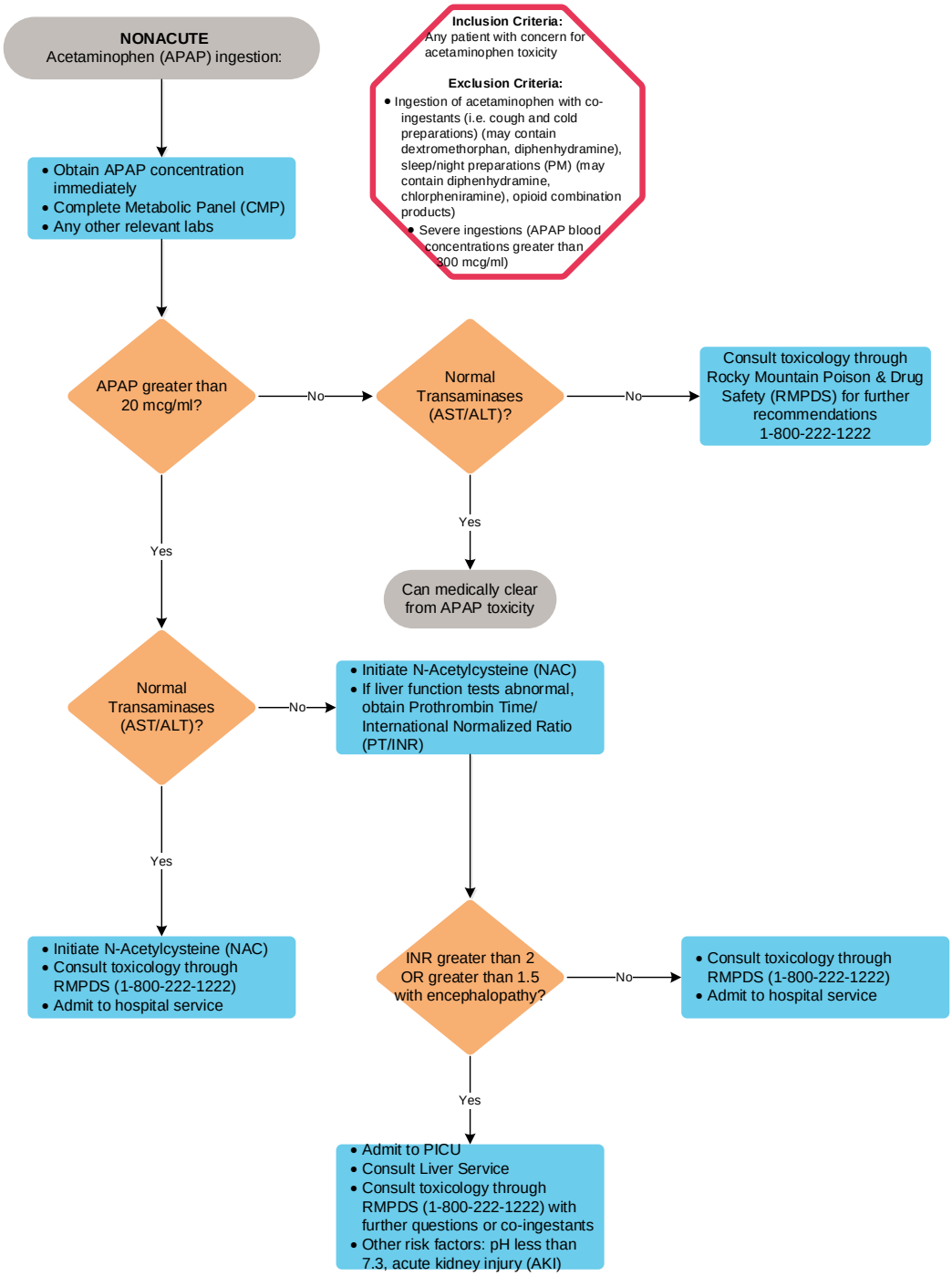


Matthew Rumack Nomogram

ALGORITHM 2. NONACUTE Acetaminophen (APAP) Toxicity

NONACUTE Acetaminophen (APAP) ingestion:
- Inaccurate timeline (poor history)
- Unknown timeline
- Repeated Supratherapeutic Ingestion (all the ingestion occurs in greater than an 8 hour timeframe)
- Presenting greater than 24 hours after acute ingestion

ACUTE Acetaminophen (APAP) ingestion:
- All the ingestion taken within an 8 hour timeframe
- Presenting less than 24 hours after a known time of ingestion



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TARGET POPULATION

Inclusion Criteria

Any patient with concern for acetaminophen toxicity.

- Acute supratherapeutic acetaminophen ingestion
- Unknown time of a supratherapeutic acetaminophen ingestion
- Repeated supratherapeutic acetaminophen ingestion

Exclusion Criteria

- Ingestion of acetaminophen with co-ingestants (ie cough and cold preparations (may contain dextromethorphan, diphenhydramine), PM preparations (may contain diphenhydramine, chlorpheniramine), opioid combination products)
- Severe ingestions (APAP blood concentrations greater than 300 mcg/ml)

BACKGROUND | DEFINITIONS

Acetaminophen (APAP) is an over-the-counter analgesic and antipyretic that is commonly used in all ages. Therapeutic mechanism of action is via inhibition of the formation of prostaglandins. In overdose or supratherapeutic settings, it can lead to hepatotoxicity. In extreme circumstances, overdose can lead to liver failure, metabolic acidosis, cerebral edema and death. APAP ingestions are one of the most common reported unintentional and intentional ingestions. In the 2017 National Poison Data System annual review, there were almost 110,000 human exposures to APAP single ingredient and combination products. There were 142 deaths attributed to APAP combination exposures, and 140 acetaminophen alone exposures. In pediatrics, APAP ingestions are one of the most common presenting toxicological complaints in the emergency room and is a leading toxicological diagnosis requiring admission to both the inpatient ward and ICU.

In normal metabolism, APAP is renally eliminated unchanged (5%) or metabolized via hepatic glucuronidation (40-65%) and sulfation (20-45%). In supratherapeutic ingestion, these metabolic pathways become saturated and metabolism occurs via CYP 2E1 to NAPQI, which can lead to cellular toxicity (specifically hepatotoxicity). NAPQI is normally conjugated to glutathione to form nontoxic APAP conjugates which are eliminated in the urine. However, it is overproduced in overdose settings, leading to hepatotoxicity.

DEFINITIONS

- ACUTE ingestion: all of the ingestion of APAP taken within an 8-hour timeframe, and presenting less than 24 hours after initial time of ingestion
- NON- ACUTE ingestion:
  - Inaccurate timeline (poor history)
  - Unknown timeline
  - Repeated Supratherapeutic Ingestion (RSTI): ingestion occurs in greater than an 8 hour timeframe
  - Presenting greater than 24 hours after ingestion

CLINICAL MANAGEMENT

Obtain thorough history and perform physical exam.

History:

- Inquire about past medical history (hospitalizations, recent illness, psychiatric history including past suicidal ideation or attempts)
- Take a medication history. This includes regular medications, or recently taken medications. Potential other medications that the patient could have access to is also important in ruling out other ingestions.
- Obtain details of events including: timeline of events (when ingestion occurred), the maximum amount suspected (tablet strength, size of bottle, estimate of number of tabs remaining), and subsequent timeline of events (any therapies, interventions, symptoms that have developed prior to arrival).

Clinical Symptoms of APAP toxicity:

- Most patients will develop nausea/vomiting after supratherapeutic ingestion of APAP.
- Some patients may be asymptomatic.
- In a large overdose, somnolence or CNS depression may develop.
- APAP is common in combination preparations. Thus, initial symptoms may be due to co-ingestants such as antitussive agents (dextromethorphan), antihistamines (diphenhydramine, chlorpheniramine), and opioids (codeine, oxycodone, hydrocodone). These co-ingestants, specifically antihistamines, can lead to irregular kinetics, erratic absorption, and unpredictable toxicity.

Clinical Progression of APAP toxicity:

- Nausea/vomiting can last 24-36 hours after ingestion. In large overdose, metabolic acidosis and cardiovascular collapse can occur within hours of ingestion.
- Without treatment, liver transaminitis will begin approximately 20-24 hours after time of ingestion (as early as 12 hours in the most severe of ingestions). The aspartate aminotransferase (AST) will be the first to rise, followed by alanine aminotransferase (ALT). Level of transaminitis can range from 2-3 times normal, to greater than 10-20,000 IU/L in severe toxicity. Maximum liver toxicity occurs between 72-96 hours after ingestion. Transaminitis does not universally lead to coagulopathy or liver dysfunction.
- Liver dysfunction (if occurs) can occur approximately 2-3 days after ingestion. Signs will include coagulopathy, and encephalopathy
- Acute kidney injury (if occurs) can occur 2-5 days after ingestion, often peaking at 7 days after ingestion.
- Without treatment, fatalities can occur 3-5 days after acute overdose.

- In recovery phase after ingestion, the AST typically will decline prior to ALT, followed by improvements in liver and kidney function.

Prognosis of APAP toxicity:

- Ingestions that present and receive N-Acetylcysteine (NAC) within 8-10 hours from time of ingestion universally do well and expect a full recovery.
- Even those who present after the 8-10 hour time-frame and receive NAC typically do well
- Patients who present after the setting of a chronic repeated supratherapeutic ingestion (RSTI), late presenting acute ingestion, and/or already with signs of liver dysfunction, have a guarded and potentially poor prognosis
- Lactate greater than 3.0 mmol/l after fluid resuscitation or 3.5 mmol/l at 55 hours after ingestion has been an indicator of increased mortality without transplantation.
- The most commonly used indicator for the need for immediate transplantation in adults with APAP toxicity is the King's College Criteria (KCC). Survival rate of adult patients who meet KCC and do not receive organ transplant is less than 20%. KCC includes
  - pH less than 7.30 after adequate fluid resuscitation

    OR Combination of:
  - Creatinine (Cr) greater than 3.4 mg/ml
  - Prothrombin (PT) greater than 100 s (INR greater than 6.5)
  - Grade III or IV encephalopathy
- Other scores used to assess adult patients for need for transplantation after APAP ingestion include APACHE II score greater than 15, APACHE III score greater than 60, or combination of hypoglycemia, coagulopathy and lactic acidosis.

Differential Diagnosis:

- Although toxicity is quite different, other over-the-counter analgesics are often mistaken for each other, including aspirin, and NSAID's.
- Other etiologies for hepatotoxicity and liver failure, both toxicological and non-toxicological in nature, should be explored.

Monitoring:

- Continuous cardiac/pulse oximetry monitoring is recommended for unstable and critically ill patients.

LABORATORY STUDIES | IMAGING

- For ACUTE ingestions: APAP concentration and complete metabolic panel should be obtained at 4 hours after the earliest known time of ingestion (or upon presentation if after 4 hours). This concentration can be plotted on the Matthew-Rumack Nomogram to determine treatment plan.
- For NON-ACUTE ingestions: APAP concentration and complete metabolic panel should be obtained upon presentation. The Matthew-Rumack Nomogram is not applicable.
- Consider coagulation panel if transaminitis is noted.
- Obtain a venous blood gas for patients with metabolic acidosis noted on their electrolytes, altered mental status, or liver synthetic dysfunction.
- A salicylate concentration should be obtained to rule out erroneous reporting of analgesic ingested.
- Other studies include labs or electrocardiogram to investigate co-ingestants as clinically indicated.

THERAPEUTICS

Routinely Indicated: N-Acetylcysteine (NAC)

- There are no changes in morbidity or mortality between the 2 routes of administration of NAC. IV is more often used due to the ease of use, shorter duration/course of treatment, and difficulties with PO administration with significant nausea/vomiting.
- There may be circumstances in severe overdose when the rate and/or amount of NAC is increased. This should be done in consultation with the Medical Toxicology Service.

Intravenous (IV) N-Acetylcysteine (NAC)

- 2-Bag regimen
- FIRST dose: 200 mg/kg/dose (max: 20 grams) infused over 4 hours
- SECOND dose: 100 mg/kg/dose (max: 10 grams) infused over 16 hours
- IF NEEDED, continuation of treatment beyond the second dose: 100 mg/kg/dose (max: 10 grams) infused over 16 hours. Begin subsequent bags immediately after prior bag finishes.
- IF patient is started on a 3-bag regimen at an outside facility (150mg/kg loading dose over 1 hour followed by 50mg/kg over 4 hours) – may switch patient over to 16 hour 'second' dose on arrival
- Common adverse events:
  - Non-allergic anaphylactic reactions (NAARs) – rash, hives, flushing, throat tightness, angioedema
  - Gastrointestinal – dyspepsia, nausea, vomiting
  - Can administer diphenhydramine, decrease the rate of IV administration, or transition to PO formulation with significant adverse events.
  - Can also cause a slight bump in INR, though should still be less than 2. An INR greater than 2 should not be attributed to IV NAC.

Oral (PO) N-Acetylcysteine (NAC)

- N-Acetylcysteine 20% (200 mg/ml):

  There is no data for use of the OTC supplement tablets for acetaminophen poisoning. Dosing below is based on effervescent tablet (Cetylev) or a solution for oral administration that is prepared from the solution for oral inhalation:

  - 72-hour regimen: Consists of 18 doses; total dose delivered: 1,330 mg/kg
    - Loading dose: 140 mg/kg; maximum dose: 15 g/dose
    - Maintenance dose: 70 mg/kg every 4 hours for 17 doses; maximum dose: 7.5 g/dose
      - Repeat dose if emesis occurs within 1 hour of administration
      - Note: 72 hour regimen may be shortened, but this should be done in consultation with the medical toxicology service.
- Common adverse events (or difficulties with compliance):
  - Similar to IV, although less NAARs and more GI related ADEs
  - Amount of doses and volume may be hard for patient to tolerate
  - Has sulfur (rotten-egg) smell/taste -- may be mixed in juices, soda, or other vehicles to aid in palatability

Recommended in some patients:

Activated Charcoal

- For *acute* ingestions who present less than 2 hours post ingestion with normal mentation, consider dose of activated charcoal (0.5-1 g/kg), ONLY if the patient can voluntarily self-administer.

Intravenous Fluids

- Patients with severe toxicity and illness, nausea/vomiting, or inability to have oral intake should receive IVF resuscitation and maintenance fluids with appropriate dextrose and electrolytes.

Extracorporeal Removal

- In severe overdose, where toxicity has led to CNS symptoms, metabolic acidosis (which is typically APAP blood concentrations greater than 800 mcg/ml), hemodialysis or continuous renal replacement therapy has been used to correct the metabolic derangements in addition to extracting APAP. This modality is used sparingly and should be used in consultation with Medical Toxicology Service.

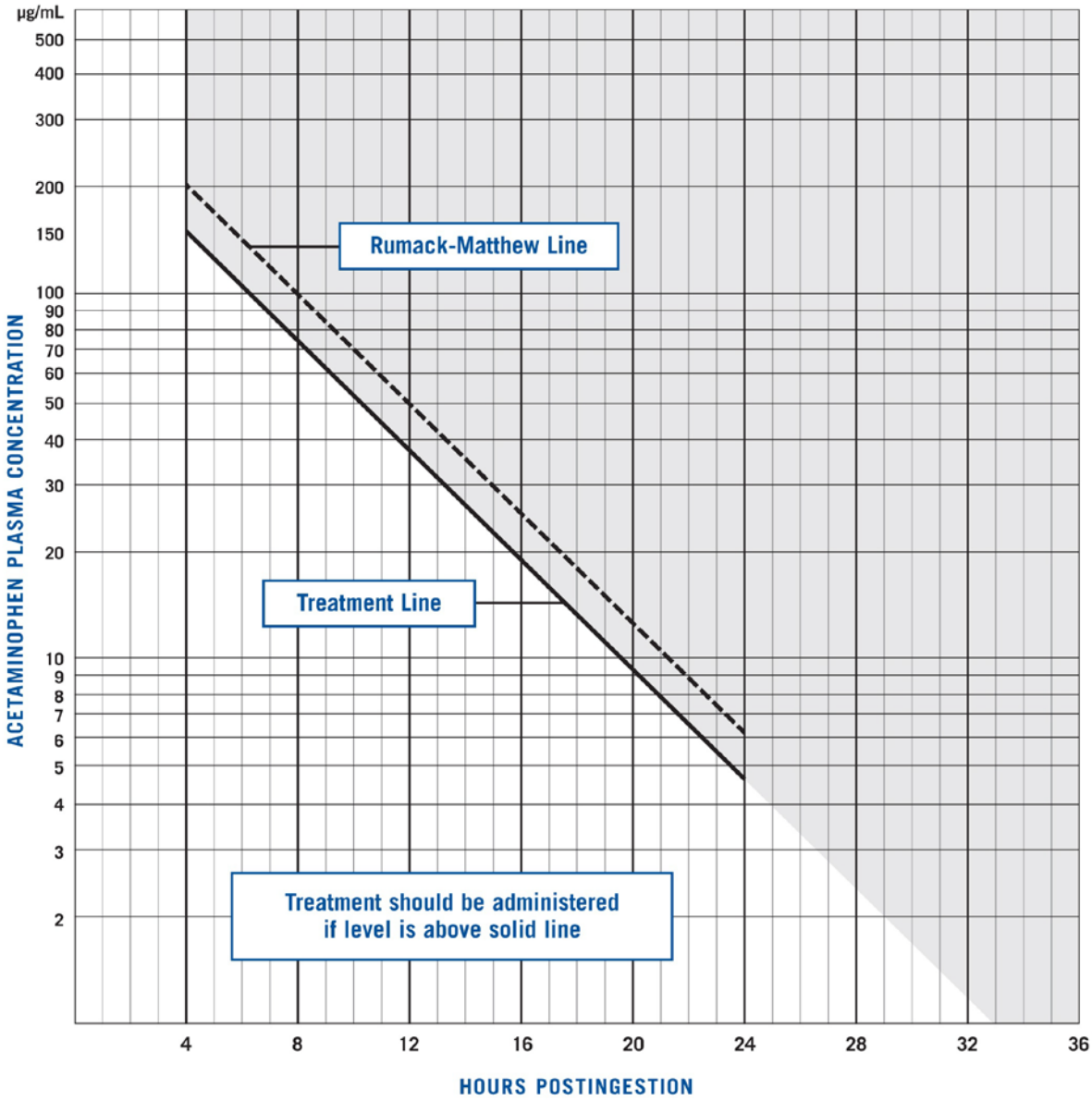
Not Routinely Indicated:

Gastric Lavage, whole bowel irrigation, or cathartics

Disposition

- Acute ingestion: patients with an APAP above the Matthew-Rumack Nomogram Treatment Line will require course of NAC.

Single Acute Acetaminophen Overdose Nomogram



Nomogram: acetaminophen plasma concentration vs time after acetaminophen ingestion (adapted with permission from Rumack and Matthew. *Pediatrics*. 1975;55:871-876). The nomogram has been developed to estimate the probability of whether a plasma acetaminophen concentration in relation to the interval postingestion will result in hepatotoxicity and, therefore, whether acetylcysteine therapy should be administered.

CAUTIONS FOR USE OF THIS CHART:

1. Time coordinates refer to time postingestion.
2. Graph relates only to plasma concentrations following a single, acute overdose ingestion.
3. The Treatment Line is plotted 25% below the Rumack-Matthew Line to allow for potential errors in plasma acetaminophen assays and estimated time from ingestion of an overdose (Rumack et al. *Arch Intern Med.* 1981;141(suppl):380-385).

- Unknown or RSTI: patients with a supratherapeutic concentration (APAP greater than 20 mcg/ml) or elevated transaminitis will require course of NAC

ADMISSION to inpatient/observation

- Consult toxicology via the Rocky Mountain Poison and Drug Safety (RMPDS) at 1-800-222-1222
- Patients without significant liver dysfunction (INR greater than 2) can be observed in the ED or admitted to the inpatient hospitalist service for course of NAC

ADMISSION to ICU

- If INR greater than 2 OR INR greater than 1.5 WITH encephalopathy:
  - Other significant risk factors: pH less than 7.3, acute kidney injury (AKI), metabolic acidosis
- Consult Liver Service who will be primary consultation
- Consult toxicology via the Rocky Mountain Poison and Drug Safety (RMPDS) at 1-800-222-1222 for further questions or if there are co-ingestants
- Patients admitted to ICU with involvement of Liver Service, can be transferred to the Liver Inpatient Service once clinically stable

STOPPING CRITERIA FOR NAC

- For an acute APAP ingestion, repeat LFT's and APAP concentration 1-2hours prior to completing each 16-hour bag or prior to last PO dose.
- For a *nonacute* APAP toxicity, repeat labs q12 hours (LFT's, APAP concentration, and INR, if applicable).
- Duration of NAC may be shortened per toxicology recommendations.
- Recommended stopping criteria for *any* APAP toxicity:
  - APAP less than 20 mcg/ml
  - LFT's (AST/ALT) remain normal (if transaminitis never occurred) OR declining and approximately 50% of peak levels
  - Cr less than 2 mg/dl and declining (if applicable)
  - INR less than 2 and declining (if applicable)
  - Clinically well (without encephalopathy)

MEDICAL CLEARANCE

- All self-harm ingestion attempts will need psychiatric evaluation.
- Consider social work consultation if there are concerns for maltreatment or neglect resulting in APAP ingestion or toxicity.
- All discharged patients who have LFT's that have not completely normalized upon medical clearance will need outpatient follow up with repeat LFT's every 1-2 weeks until normalized. If liver tests remain elevated after 1-2 months, they will need follow up with Liver Team as outpatient.

PARENT | CAREGIVER EDUCATION

- Most patients who receive NAC within 8-10 hours within the time of ingestion will fully recover
- Once recovered, long-term liver injury or dysfunction is not expected
- Poison prevention counseling
- Mental health resources

REFERENCES

1. Bernal W, Wendon J, Rela M, Heaton N, Williams R. Use and outcome of liver transplantation in acetaminophen-induced acute liver failure. Hepatology. 1998 Apr;27(4):1050-5.
2. Chiew AL, Gluud C, Brok J, Buckely NA. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database Syst Rev. 2018 Feb 23;2:CD003328. doi: 10.1002/14651858.CD003328.pub3.
3. Craig DG, Ford AC, Hayes PC, Simpson KJ. Systematic review: prognostic tests of paracetamol-induced acute liver failure. Aliment Pharmacol Ther. 2010 May;31(10):1064-76. doi: 10.1111/j.1365-2036.2010.04279.x
4. Dart RC, Rumack BH: Patient-tailored acetylcysteine administration. Ann Emerg Med 2007;50:280–281 [PMID: 17418449].
5. Ghannoum M, Kazim S, Grunbaum AM, Villeneuve E, Gosselin S. Massive acetaminophen overdose: effect of hemodialysis on acetaminophen and acetylcysteine kinetics. Clin Toxicol (Phila). 2016 Jul;54(6):519-22. doi: 10.1080/15563650.2016.1175006.
6. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. Clin Toxicol (Phila). 2018 Dec;56(12):1213-1415. doi: 10.1080/15563650.2018.1533727.
7. Hendrickson, RG, McKeown NJ. Chapter 33: Acetaminophen. Goldfrank's Toxicological Emergencies. 11th edition.
8. Hoyte C, Dart RC: Transition to two-bag intravenous acetylcysteine for acetaminophen overdose: a poison center's experience. Clin Toxicol (Phila). 2019 Jan 28:1-2. doi: 10.1080/15563650.2018.1510127.
9. Levine M, Stellpflug SJ, Pizon AF, Peak DA, Villano J, Wiegand T, Dib C, Thomas SH. Hypoglycemia and lactic acidosis outperform King's College criteria for predicting death or transplant in acetaminophen toxic patients. Clin Toxicol (Phila). 2018 Jul;56(7):622-625. doi: 10.1080/15563650.2017.1420193.
10. Mitchell I, Bihari D, Chang R, Wendon J, Williams R. Earlier identification of patients at risk from acetaminophen-induced acute liver failure. Crit Care Med. 1998 Feb;26(2):279-84.
11. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989 Aug;97(2):439-45.
12. Rumack BH, Bateman DN: Acetaminophen and acetylcysteine dose and duration: past, present and future. Clin Toxicol (Phila) Feb 2012;50(2):91–98. doi: 10.3109/15563650.2012.659252.22320209.
13. Schmidt LE et al: Fewer adverse effects associated with a modified two-bag intravenous acetylcysteine protocol compared to traditional three-bag regimen in paracetamol overdose. Clin Toxicol (Phila). 2018 May 24:1-7. doi: 10.1080/15563650.2018.1475672.
14. Wang GS, Monte A, Bagdure D, Heard K. Hepatic failure despite early acetylcysteine following large acetaminophen-diphenhydramine overdose. Pediatrics. 2011 Apr;127(4):e1077-80. doi: 10.1542/peds.2010-2521.
15. www.kingsalfpredictor.org

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REVIEW | REVISION SCHEDULE

Scheduled for full review on August 1, 2023

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