Acetaminophen toxicity

December 22, 2016 by Josh Farkas

CONTENTS

- Epidemiology & pharmacokinetics
- Clinical evolution
- Patient evaluation
- Decontamination
- Who needs treatment?
- Acetylcysteine
- Massive acetaminophen poisoning
- Management of established hepatic failure
- Management of renal failure
- Algorithm
- Podcast
- Questions & discussion
- Pitfalls

epidemiology & pharmacokinetics

basics

- Acetaminophen doses above ~8 grams may be toxic, but this varies considerably between patients.¹
- Peak absorption of immediate-release tablets usually occurs within 2-4 hours of ingestion.

phenotypes of acetaminophen poisoning

- (1) Suicide attempt (~50%)
(2) Unintentional poisoning (~50%)
  i) Patients with chronic pain who take acetaminophen along with combination analgesics (e.g. acetaminophen-oxycodone).
  ii) Patients with cold/flu symptoms who take acetaminophen along with combination cold medications (e.g. NyQuil and related products that combine acetaminophen with antihistamines).
  iii) “Alcohol-Tylenol syndrome” – ongoing use of several grams of acetaminophen daily along with alcohol.¹

Factors that increase the risk of acetaminophen toxicity

- Decreased hepatic capacity for glucuronidation
  - Gilbert's disease
  - Zidovudine, trimethoprim/sulfamethoxazole
- Inducers of CYP2E1 (increase metabolism of acetaminophen into toxic NAPQI)
  - Isoniazid
  - Rifampicin, phenobarbital
  - Phenytoin, phenobarbital
- Hepatic depletion of glutathione
  - Chronic alcohol ingestion
  - Chronic acetaminophen use
  - Chronic liver disease
  - Malnutrition

Clinical evolution

Toxicity is typically divided into stages, but this may not work perfectly in every patient (especially in patients who ingested several doses of acetaminophen over time).

Stage I (0-24 hours) = Incubation

- Asymptomatic or nonspecific symptoms (anorexia, nausea/vomiting, diaphoresis).
- Other symptoms during this period usually suggest coingestion or massive ingestion.
  - Massive ingestion (>32 grams) may present with mental status alteration and lactic acidosis within 12 hours of ingestion.² These patients should be considered for specific treatment as discussed below (#massive_acetaminophen_poisoning).
- Labs
  - Liver function tests are generally normal (but may begin to rise 8-12 hours after massive ingestion).

Stage II (24-72 hours) = Latent period
Stage I symptoms resolve or improve.
Right upper-quadrant pain can occur.
Labs:
- AST/ALT elevation occurs.
- Nephrotoxicity may occur.

Stage III (72-96 hours) = Peak liver toxicity
- Systemic symptoms re-appear (nausea/vomiting, anorexia, malaise).
- Hepatic failure emerges (encephalopathy, jaundice, coagulopathy, hypoglycemia).
- Greatest risk of death.
- Labs
  - Transaminases peak 3-4 days after ingestion
  - Hepato-renal syndrome can occur
  - INR elevation
  - Lactic acidosis

Stage IV (4 days-2 weeks) = Resolution
- Patients who don't die make a complete recovery.

patient evaluation

historical elements
- Timing & amount of ingestion
- Single ingestion vs. multiple/chronic ingestions
- History of alcoholism or malnutrition?
- History of known liver disease?

pertinent labs
- Electrolytes & glucose level
- Lactate can be elevated:
  - i) Early-onset lactic acidosis following massive ingestion (within 24 hours)
  - ii) Later-onset lactic acidosis due to hepatic failure (>48 hours after ingestion)
- Acetaminophen level
  - Marked hyperbilirubinemia (>10 mg/dL) may cause a false-positive acetaminophen level, usually in the low range (0-30 ug/ml).\(^1\)
    - Bilirubin elevation in this range usually isn't due to acetaminophen, so other causes of liver injury should be considered.
- INR
- Liver function tests (including ammonia)
- (Additional evaluation for concurrent poisoning with other substances, as clinically warranted)

decontamination?

activated charcoal
- Should be considered if patients present shortly following ingestion and are able to protect their airway (<1-3 hours).
- Could provide the greatest benefit to patients with massive acetaminophen poisoning (e.g. >32 grams).\(^3\)

who needs treatment?
**Preamble: why the ICU perspective is different**

- There are roughly two patient populations with acetaminophen toxicity seen in the ICU:
  - (1) Patients with liver failure due to acetaminophen poisoning.
  - (2) Patients with polysubstance intoxication admitted to ICU for supportive care, who also happen to have a positive acetaminophen level.
- In general, the main challenge regarding acetaminophen toxicity is determining which patients need to be admitted and which can be discharged home. This issue is irrelevant in the ICU, because a decision has already been made to admit the patient.
- Among patients admitted to the ICU, this shifts the risk/benefit ratio towards treatment for acetaminophen intoxication:
  - Risk of treating with acetylcysteine in the ICU is negligible.
  - Benefit of treating with acetylcysteine is potentially large (rarely may be life-saving).

![Rumack-Matthew Nomogram](image)

**Rumack-Matthew Nomogram**

- This predicts the likelihood of hepatic failure based on acetaminophen level following a one-time ingestion.
- Disagreement exists regarding the ideal cutoff used in the nomogram, as shown above. To err on the side of caution, it may be safest to use the United Kingdom treatment line.
- **Nomogram confounders** might cause the nomogram to fail:
  - Incorrect history about timing of intoxication.
  - Multiple ingestions or chronic acetaminophen use.
  - Factors that increase the risk of acetaminophen toxicity:
    - Chronic alcoholism (not acute alcohol intoxication)
    - Malnutrition
    - Drugs that increase acetaminophen toxicity (INH, rifampin, phenobarbital, phenytoin, carbamazepine, trimethoprim-sulfamethoxazole, zidovudine)
  - Altered pharmacokinetics
    - Extended-release acetaminophen preparations
    - Delayed gastric emptying (e.g. opioids, gastroparesis)
  - Ingestion >24 hours before presentation
  - Wrong units (make sure your units match the nomogram!)
Approach to acetaminophen intoxication

1. **Concern for possible acetaminophen intoxication**

   - **Known ingestion of acetaminophen >8 hours ago?**
     - Yes: Start acetylcysteine, evaluate if you can stop it safely.
     - No: Check serum acetaminophen level & ALT.

2. **Acetaminophen >18 ug/ml (>66 uM) AND ALT < 50 U/L**

   - Are ALL of following conditions met?
     - Single ingestion (not chronic use)
     - Ingestion <24 hours ago
     - Reliable history of timing
     - No alcoholism/malnutrition
     - No synergistic drugs
     - No extended-release formulation
     - No delayed gastric emptying (e.g. opiate or gastroparesis)

   - ALT > 50 U/L (regardless of acetaminophen level)
     - No treatment needed
     - Start IV acetylcysteine
     - Continue until acetaminophen <10 ug/ml (66 uM) and ALT <50 U/L

3. **Acetaminophen level above nomogram line?**

   - Yes: No treatment needed
   - No: Start IV acetylcysteine

---

1. Drugs that may amplify hepatic injury: isoniazid, rifampin, phenobarbital, phenytoin, carbamazepine, trimethoprim-sulfamethoxazole, zidovudine.
2. Don’t delay acetylcysteine pending return of labs: start immediately. Evaluate further to see whether acetylcysteine is actually needed or whether it can be discontinued.
3. >24 hours after ingestion, patients may have hepatic injury with negative acetaminophen levels. Such patients may still benefit from NAC until hepatic injury resolves.

---

This is one approach to acetaminophen intoxication. This strategy places a high priority on not missing cases of acetaminophen injury, and a low priority on avoiding treatment with acetylcysteine.

- For best effect, acetylcysteine should be given within 8 hours of ingestion. If known acetaminophen ingestion occurred >8 hours previously, or if there will be a delay in obtaining acetaminophen levels, it may be safest to start acetylcysteine immediately to avoid treatment delay. You can always stop it later on.
- When in doubt, you’re better off erring on the side of treatment (patients are unreliable, acetylcysteine is safe, and liver failure is bad).
**IV acetylcysteine is preferred over oral regimen**

- Two options are available: a 24-hour IV regimen and a 72-hour oral regimen.
- The 72-hour oral regimen is a logistical nightmare:
  - Oral acetylcysteine smells like rotten eggs and makes patients vomit.
  - Patients will often refuse to continue with the regimen at some point.
- The 24-hour IV regimen is generally used:
  - Extremely safe.
  - Faster & logistically easier than the oral regimen.
  - It rarely can cause an anaphylactoid reaction, with histamine release due to direct action of the medication. However, this isn't a major problem (more on this below).

**Dosing regimen**

- Can be calculated [here](http://acetadote.com/dosecalc.php) (although many hospitals will have a computerized protocol for this as well).
  - 1st infusion = 150 mg/kg over 60 minutes
  - 2nd infusion = 50 mg/kg over 4 hours
  - 3rd infusion = 100 mg/kg over 16 hours

- For patients with very high levels of acetaminophen (above the 300-line, shown in red above), consider higher doses of acetylcysteine (more on this below).

**anaphylactoid reactions from IV acetylcysteine**

- Rapid administration of acetylcysteine can cause an anaphylactoid reaction. This involves histamine release due to a direct action of the medication (not an IgE-mediated allergic reaction).
- Anaphylactoid reactions are uncommon (especially if the initial dose is infused more slowly, over 60 minutes). When they do occur, they are usually mild (involving the skin only). They invariably occur within six hours of initiation of acetylcysteine, most often within the first two hours.\(^5\)
- Treatment may be as follows:
  - Only symptom is flushing: continue acetylcysteine, carefully monitor patient.
  - Urticaria: IV diphenhydramine 1 mg/kg, consider steroid, continue acetylcysteine.
  - Angioedema: IV diphenhydramine 1 mg/kg, steroid, hold acetylcysteine for one hour.
  - Respiratory symptoms or hypotension: IV diphenhydramine 1 mg/kg, steroid, hold acetylcysteine for one hour, epinephrine (intramuscular bolus or infusion).

- These reactions are *not* an allergic reaction. Acetylcysteine can be continued or resumed (perhaps at a lower rate initially). Liver failure has been reported when acetylcysteine was inappropriately stopped due to inappropriate fear of an “allergy.”\(^6\) Don't do this.

- When in doubt, poison control can help provide advice on this (in the United States, 1-800-222-1222).

- Fear of an anaphylactoid reaction shouldn't limit the use of IV acetylcysteine. These reactions are uncommon, mild, and treatable. In one study involving 6,455 treatment courses of acetylcysteine, it doesn't seem that there was any serious harm from anaphylactoid reactions (e.g. death).\(^5\)

**when to stop the acetylcysteine**

- Continue acetylcysteine infusion if there is evidence of liver injury (e.g., ALT > 80U/L) or persistent acetaminophen (>10 micrograms/ml).\(^7\)
  - Treatment failures have been reported if acetylcysteine was stopped prematurely.
  - Continue at the same rate, equal to the rate of the *third* IV dose in the protocol (100 mg/kg infused over 16 hours – repeatedly).
- It's controversial whether acetylcysteine should be stopped after 3-5 days (even if transaminases remain elevated). It's probably OK to discontinue the acetylcysteine once the acetaminophen level is undetectable and the liver is making a robust recovery (transaminases are clearly falling and INR is <2).

**pregnancy**

- Acetaminophen poses a risk of hepatic failure to both mother and fetus.
- Acetylcysteine is safe and beneficial in pregnancy.
- IV acetylcysteine may be especially preferable because it achieves higher serum drug levels and avoids vomiting (of course, IV acetylcysteine is generally the treatment of choice regardless of pregnancy status). If IV acetylcysteine is unavailable, then oral acetylcysteine may be used.
In a prospective observational study of pregnant women, delayed treatment with acetylcysteine was associated with increased risk of miscarriage and fetal death.\(^8\)

**massive acetaminophen poisoning**

Patients with massive acetaminophen poisoning (>32 grams) can die despite standard therapeutic regimens with acetylcysteine. These patients may present in a specific clinical fashion and require more aggressive treatment. One definition of massive poisoning is patients with acetaminophen levels above the "300-line" (red line above) or with known ingestion of >32 grams.\(^9\)

**clinical presentation of massive acetaminophen poisoning**

- Patients develop mitochondrial dysfunction very early (usually within <12 hours of ingestion), before any liver damage occurs.
- Clinical features:
  - Lactic acidosis
  - Altered mental status

**hemodialysis**

- Dialysis can remove both acetaminophen and toxic metabolites (NAPQI). This may be beneficial in massive poisoning, where acetylcysteine won't necessarily work.
- Indications for dialysis based on the EXTRIP guidelines are shown below (note that "ECTR" = dialysis).\(^3\) Full text of these guidelines is freely available [here](https://docs.wixstatic.com/ugd/363318_acfc982c55b84f86a85753800ccf3f18.pdf).
- Dialysis is not an alternative to acetylcysteine. In fact, patients who are dialyzed require higher doses of acetylcysteine.
Rationale for using high-dose acetylcysteine:

- (1) Evidence shows that standard doses of acetylcysteine can be inadequate in the context of massive poisoning. From a basic science standpoint, acetylcysteine neutralizes NAPQI in a 1:1 molar ratio, so the dose of acetylcysteine should be scaled up in proportion to the amount of acetaminophen.
- (2) If dialysis is used, this will remove acetylcysteine, thereby aggravating the mismatch between acetylcysteine dose vs. NAPQI levels. Intermittent hemodialysis may remove up to 50% of acetylcysteine.3

Risks of high-dose acetylcysteine

- Case reports describe toxicity (including hemolysis and cerebral edema) following dosing errors resulting in excessive administration of acetylcysteine (e.g. 5-fold increase in the first dose, or 10-fold increase in the maintenance doses).10,11
- Toxicity from acetylcysteine is therefore clearly possible. Case reports describe toxicity in the context of egregious dosing errors. Whether toxicity might occur at somewhat lower doses is unknown.

One approach to acetylcysteine dosing was recently proposed by Hendrickson 2019.9

- The first and second dose of acetylcysteine are kept the same, but the infusion rate of the third dose is increased in proportion to the severity of intoxication.
  - Intoxications over the 600 line (purple line below): third dose of 25 mg/kg/hr (quadruple the standard dose)
  - Intoxications over the 450 line (green line below): third dose of 18.75 mg/kg/hr (triple the standard dose)
  - Intoxications over the 300 line (red line below): third dose of 12.5 mg/kg/hr (double the standard dose)
- For patients on hemodialysis, consider doubling the acetylcysteine dose compared to what you would otherwise use (but don't increase it any higher than 25 mg/kg/hr).
- This algorithm hasn't been prospectively validated, so consider discussing the case with poison control or a local toxicologist.

**Table 8. Executive summary of recommendations.**

<table>
<thead>
<tr>
<th>General Recommendation</th>
<th>ECTR is suggested in severe APAP poisoning (2D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECTR is recommended</td>
<td></td>
</tr>
<tr>
<td>- If the [APAP] more than 1000 mg/L (6620 μmol/L) and NAC is NOT administered (1D).</td>
<td></td>
</tr>
<tr>
<td>- If the patient presents with altered mental status, metabolic acidosis, an elevated lactate, and an [APAP] is more than 700 mg/L (4630 μmol/L) and NAC is NOT administered (1D).</td>
<td></td>
</tr>
<tr>
<td>- If the patient presents with an altered mental status, metabolic acidosis, an elevated lactate, and an [APAP] is more than 900 mg/L (5900 μmol/L) even if NAC is administered (1D).</td>
<td></td>
</tr>
<tr>
<td>ECTR is not recommended</td>
<td></td>
</tr>
<tr>
<td>- On the basis of the reported ingested dose if NAC is administered (1D).</td>
<td></td>
</tr>
<tr>
<td>- On the basis of reported ingested dose even if NAC is NOT administered (2D).</td>
<td></td>
</tr>
<tr>
<td>- Solely on the basis of the [APAP] if NAC is administered (2D).</td>
<td></td>
</tr>
<tr>
<td>- Cessation of ECTR</td>
<td></td>
</tr>
<tr>
<td>- ECTR is recommended until sustained clinical improvement is apparent (1D).</td>
<td></td>
</tr>
<tr>
<td>Choice of ECTR</td>
<td></td>
</tr>
<tr>
<td>- Intermittent hemodialysis is the preferred ECTR in patients with APAP poisoning (1D).</td>
<td></td>
</tr>
<tr>
<td>- The following are acceptable alternatives if HD is not available:</td>
<td></td>
</tr>
<tr>
<td>- Intermittent HD (1D)</td>
<td></td>
</tr>
<tr>
<td>- CRRT (1D)</td>
<td></td>
</tr>
<tr>
<td>- Exchange transfusion in neonates (2D)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>1. NAC therapy should be continued during ECTR at an increased rate (1D).</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** NAC dose adjustment for massive acetaminophen overdoses. Plot the time and concentration of acetaminophen after massive overdose to determine the continuous NAC infusion rate.

https://emcrit.org/ibcc/acetaminophen/
management of hepatic failure

**Acetylcysteine infusion**

- Acetylcysteine still provides benefit, even if delayed until after hepatic failure has occurred.
  - A RCT demonstrated 28% mortality benefit among patients with established hepatic failure.\(^\text{12}\)
- Acetylcysteine infusion should be started and continued until patient dies or recovers. First give the standard 24-hour regimen and then continue the infusion at a rate equal to the third IV dose in the protocol (100 mg/kg infused over 16 hours – repeatedly).
  - Don't allow the acetylcysteine infusion to stop until the liver is clearly improving and the acetaminophen level is zero (see above).

**Consider transfer to liver transplant center**

- Patients with acute hepatic failure can be candidates for transplantation, even if recently suicidal.
- Patients with severe liver injury (e.g. encephalopathy, pH <7.3, severe elevation of INR, renal failure) should be discussed with a regional transplantation center.

management of renal failure

**Renal failure in acetaminophen toxicity**

- Occurs in 10-25% of patients, and >50% of patients with acute hepatic failure.\(^\text{1}\)
- Potential mechanisms?
  - i) Direct effect of toxic metabolites
  - ii) Can occurs as a result of hepa-to-renal syndrome

**Treatment**

- General supportive care (as for any patient with kidney injury).
  - More on this in the chapter on acute kidney injury [here](https://emcrit.org/ibcc/acute-kidney-injury/).
  - Dialysis may be required temporarily (renal recovery generally occurs eventually if the patient survives).
- Treatment for hepatorenal syndrome, if this is present (e.g. with vasopressin and albumin).

Algorithm
Approach to acetaminophen intoxication

1. Concern for possible acetaminophen intoxication
   - Known ingestion of acetaminophen >8 hours ago? Yes, Start acetylcysteine, evaluate if you can stop it safely. No, Check serum acetaminophen level & ALT.
   - Acetaminophen >18 ug/ml (>66 uM) AND ALT < 50 U/L
     - Are ALL of following conditions met?
       - Single ingestion (not chronic use)
       - Ingestion <24 hours ago
       - Reliable history of timing
       - No alcoholism/malnutrition
       - No synergistic drugs
       - No extended-release formulation
       - No delayed gastric emptying (e.g. opiate or gastroparesis)
     - ALT > 50 U/L (regardless of acetaminophen level)
       - Start IV acetylcysteine
         - Continue until acetaminophen <10 ug/ml (66 uM) and ALT <50 U/L
       - Acetaminophen level above nomogram line?
         - No treatment needed

(1) Drugs that may amplify hepatic injury: isoniazid, rifampin, phenobarbital, phenytoin, carbamazepine, trimethoprim-sulfamethoxazole, zidovudine.
(2) Don't delay acetylcysteine pending return of labs: start immediately. Evaluate further to see whether acetylcysteine is actually needed or whether it can be discontinued.
(3) >24 hours after ingestion, patients may have hepatic injury with negative acetaminophen levels. Such patients may still benefit from NAC until hepatic injury resolves.


podcast


The Podcast Episode

Want to Download the Episode?
Right Click Here and Choose Save-As (http://traffic.libsyn.com/ibccpodcast/IBCC_EP_25_Acetaminophen_OD_Final.mp3)

questions & discussion


To keep this page small and fast, questions & discussion about this post can be found on another page here (https://emcrit.org/pulmcrit/acetaminophen/).
The Rumack nomogram may fail for a variety of reasons, so be careful when using it.

IV acetylcysteine has been shown to improve mortality in patients with established liver failure. Even if the patient presents very late, they should still be treated with acetylcysteine.

When using acetylcysteine to treat a patient with established hepatic injury, continue acetylcysteine as an ongoing infusion until the liver recovers (don't stop after 24 hours).

Be aware of the existence of massive acetaminophen poisoning. Patients with extremely high levels may require higher doses of acetylcysteine and even hemodialysis.

Consider acetaminophen toxicity in patients presenting with hepatic injury or failure. About half of cases are inadvertent, so there may be no obvious history of ingestion.

When in doubt regarding the need to treat, it's safest to just give IV acetylcysteine (see tweet below). This allows you to stop agonizing about acetaminophen and focus on other problems the patient may have (e.g., co-ingestants).

---

**Nice 5-minute review:**

- Emily Fridenmaker (@emily_fri)
- Setting—the ICU.
- Med residents: "agonizing over a decision"
- EM resident: Let's just try one of them.
- Med: "agonizing"
- EM: Guys let's just do it.
- Med: "more agonizing"
- EM: Hey let's just see what happens!!
- Med: "agonizing more fervently"
- EM: "agonizes over the agonizing"

1,043 8:09 PM - Feb 26, 2019

173 people are talking about this
Going further:

- **Acetaminophen overdose** (Chris Nickson, LITFL)
- **Acetaminophen toxicity** (Dan Quan, EP Monthly)
- **Acetaminophen toxicity & management** (Maryam Abdrabbo and Cuynthia Santos, emDocs)
- **Acetaminophen toxicity** (WikiEM)

**References**
