



Episode 180

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3 clinical presentation scenarios of acetaminophen poisoning

It is useful to think of the clinical presentation as one of the 3 scenarios to help guide management:

1. Single recent acetaminophen overdose with purposeful intent
2. Supra-therapeutic acetaminophen overdose over prolonged period over time or staggered, intended or unintended
3. Massive acetaminophen overdose

Most acetaminophen poisoning deaths are a result of either a delayed presentation after deliberate overdose, or from supra-therapeutic dosing for fever or pain over several days.

Pitfall #1 is failing to recognize the seriousness of an acetaminophen overdose when it is delayed or in patients who have been taking supra-therapeutic doses over several days
Acetaminophen poisoning is sometimes missed because often patients do not know that many medications include acetaminophen such as Percocet, NyQuil/DayQuil, Excedrin, Alka-Seltzer Plus, Mucinex, Robitussin, Goody's.

Pitfall #2 is neglecting to ask patients about all the medications they take including over-the-counter ones and exactly how much they take of each; supra-therapeutic dosing of over-the-counter medications may be the first clue to a life-threatening acetaminophen overdose

Patient factors that may augment toxicity in the setting of an acetaminophen overdose include:

- Additional hepatotoxic medications/medications that are known to potentiate liver toxicity of acetaminophen (e.g. Phenytoin, Trimethoprim/sulfamethoxazole)
- co-ingestions which may require additional treatment
- chronic alcohol use
- malnutrition
- chronic liver disease

Pitfall #3 is failure to recognize patient factors that may potentiate or augment acetaminophen toxicity including other medications, co-ingestions, chronic alcohol use and malnutrition.

Other factors on presentation that are associated with poor outcomes or death include:

- Hypoglycemia
- Coagulopathy
- Lactic acidosis
- Altered LOA
- Bradycardia
- AKI/Rhabdomyolysis
- Hypothermia/Hypothermia

The stages of acetaminophen poisoning occur after a single recent overdose

Stage	Clinical manifestations
Stage I (0.5-24hrs)	<p>In the first 24hrs after OD, patients often manifest with nausea, vomiting, diaphoresis, pallor, lethargy and malaise. Some patients may remain asymptomatic. Lab studies are typically normal.</p> <p>After massive acetaminophen overdose, CNS depression and elevated AG metabolic acidosis may be seen but rarely. Such symptoms in acetaminophen-poisoned patients are usually due to co-ingestants such as diphenhydramine, opioids, or ASA.</p> <p>Serum aminotransferase concentrations are often normal but may rise as early as 8-12hrs after ingestion in severely poisoned patients</p>
Stage II (24-72hrs)	<p>Lab evidence of hepatotoxicity and occasionally nephrotoxicity become evident. Initially, stage I symptoms resolve, patients appear to improve clinically while worsening subclinical elevations of hepatic enzymes (AST and ALT) develop. Of patients who develop hepatic injury, over half will demonstrate aminotransferase elevation within 24hrs and all have elevations by 36hrs.</p> <p>As stage II progresses, patients develop RUQ pain w/ liver enlargement and tenderness. Elevations of PT and total bilirubin, oliguria and renal function abnormalities may become evident.</p>
Stage III (72-96hrs)	<p>Liver function abnormalities peak during this stage. Systemic signs of stage I reappear in conjunction w/ jaundice, confusion, hepatic encephalopathy, marked elevation in hepatic enzymes, hyperammonemia, and a bleeding diathesis.</p> <p>Signs of severe hepatic toxicity include:</p> <ul style="list-style-type: none"> • ALT and AST levels >10,000IU/L • Prolongation of the PT/INR • Hypoglycemia • Lactic acidosis • Total bili above 4.0mg/dL or 68umol/L (primarily indirect) <p>Acute renal failure occurs in 10-25% of patients w/ significant hepatotoxicity and in more than 50% of those with frank hepatic failure.</p> <p>Death most commonly occurs in this stage, usually from multiorgan system failure</p>
Stage IV (four days to two weeks)	<p>Patients who survive stage III enter a recovery phase that usually begins by day four and is complete by 7 days after OD. Recovery can be slower for severely ill patients, symptoms and lab values may not normalize for several weeks.</p> <p>When recovery occurs, it is often complete. Chronic hepatic dysfunction is not a sequelae of acetaminophen poisoning.</p>

Laboratory investigations and risk stratification in acetaminophen poisoning

Have a low threshold for obtaining serum acetaminophen levels in patients with any overdose self-harm attempt, unexplained altered level of awareness with metabolic acidosis, elevated liver enzymes or INR, unexplained elevated liver enzymes. The typical **threshold for toxicity is 200 mg/kg acetaminophen for the acute one time dose**. All patients with poor outcomes after acetaminophen overdose will have elevated liver enzymes by the 24 hr mark. However, the first 12hrs hours after acute ingestion, liver enzymes are expected to be normal.

Pitfall #4 is assuming the patient has not taken a life-threatening overdose of acetaminophen if their AST and ALT or normal or only mildly elevated; remember that liver enzymes are usually normal in the first 12 hours after an overdose.

Marked **hyperbilirubinemia (>10 mg/dL) may cause a false-positive acetaminophen level**, usually in the low range (0-30 ug/ml). Bilirubin elevation in this range usually is not due to acetaminophen, so other causes of liver injury should be considered.

Pitfall #5 is assuming that an extreme elevated bilirubin is due to acetaminophen poisoning and not recognizing that extreme elevations in bilirubin may cause a false positive acetaminophen level.

AST levels > 1000 IU/L are more likely to result from acetaminophen poisoning than from chronic hepatitis or alcoholic liver disease and rise earlier than ALT levels in acetaminophen poisoning.

The [APAP x AST multiplication product](#), calculated at the time of presentation and after several hours of antidotal therapy, holds promise for risk stratification after acetaminophen overdose. It requires neither graphical interpretation nor accurate time of ingestion, two limitations to current risk stratification.

Elevated INR may be biphasic – while elevated INR on Day 3 or later is a reliable sign of severe liver toxicity, mild elevations of INR may be seen early after ingestion on Day 1 and do not reflect severe liver toxicity, but rather, are related to the circulating acetaminophen and typically resolves without specific treatment.

[The King's College Criteria for acetaminophen toxicity](#) may help risk stratify patients and remind us of lab tests to order. It includes pH, INR, Cr, encephalopathy, lactate and phosphate.

Hyperphosphatemia has been shown to be a fairly accurate predictor of need for liver transplant after acetaminophen poisoning that may be particularly useful in delayed/late presentations.

The Rumack-Matthew nomogram should be interpreted only the setting of a single recent overdose

The Rumack-Matthew nomogram was intended for patients with a single acute recent (within 24hrs) overdose of regular release acetaminophen. This does not include patients with an unknown time of ingestion, chronic overdoses, staggered overdoses nor repeated supra-therapeutic ingestions.

Only for the patient with a single ingestion within 24hrs should the acetaminophen (APAP) level be obtained at 4 hrs post-ingestion or,

if later than 4hrs, immediately on presentation to the ED, and plotted on the Rumack-Matthew nomogram. Obtaining levels between 2-4 hrs post ingestion may be helpful because if level is undetectable (essentially zero risk of progressing to toxic levels), but anything other than undetectable requires a repeat draw at 4 hrs. A level above the the line on the nomogram has been shown to be associated with an AST >1000 IU/L which has been suggested as an indication for administering N-acetylcysteine (NAC). In North America, the typical cut-off is 1000 mmol/L at 4 hours post-ingestion, but the cutoff varies across countries.

There are “Extended Release” or “Slow Release” acetaminophen preparations. There might be a delay to complete absorption in the patient who takes a massive overdose, in the patient who takes their overdose with an anticholinergic or opioid (combination products). If the initial level is not above the nomogram line at the 4 hour mark, then an 8 hour and 12 hour level should be done (the line crosser) to be sure. If the initial level is above the treatment line, then repeat APAP levels are not necessary.

Opioids and anticholinergic medications may delay the absorption of acetaminophen and make the the interpretation of the nomogram challenging.

***Pitfall #6** is using the Rumack-Matthew nomogram to inform management in patients with delayed presentations and chronic overdoses*

***Pitfall # 7** is misinterpreting the Rumack-Matthew nomogram in the patient who has taken an extended release or slow release preparation, co-ingestion such as opioids or anticholinergics that*

may alter the metabolism of acetaminophen; consider 8 hour and 12 hours levels in these patients.

ED Management of acetaminophen poisoning – activated charcoal, N-acetylcysteine (NAC), fomepizole, dialysis, consult toxicology early

There is a role for activated charcoal in the management of recent acetaminophen overdose

50-100 grams or 1g/kg of activated charcoal should be administered to a cooperative, awake patient if they present within 2 hours of ingestion of a toxic dose of immediate release acetaminophen or within 4 hours of immediate release acetaminophen overdoses > 30g (massive overdose), sustained release formulations or co-ingestion with opioids or anticholinergics.

Indications for N-acetylcysteine (NAC) in acetaminophen overdose

- “Line crosser” on Rumack-Matthew nomogram after single acute ingestion within 24hrs
- Elevated liver transaminases (even in the absence of elevated acetaminophen level) deemed to be caused by acetaminophen overdose

N-acetylcysteine (NAC) needs to be given within 8 hours of a single overdose to be maximally effective

For best effect, N-acetylcysteine should be given within 8 hours of ingestion. There are often significant delays from the time of ordering N-acetylcysteine to the time that the infusion is started. NAC should be a STAT medication. Bring this to the attention of the bedside nurse.

Pitfall #8 is neglecting to administer NAC for late presentations in a timely manner

N-acetylcysteine (NAC) dosing should be discussed with your toxicology on call as dosing is complex and depends on many factors

There are many NAC treatment protocols that vary in timing, dose, and route (IV/PO), with a paucity of head-to-head comparisons of these protocols. Timing/quantity of ingestion, quick vs extended release, co-ingestions, co-morbidities, lab investigations etc all play a role in determining the best dose of NAC for individual patients. It is reasonable to consult toxicology for guidance on dosing for all but the most straight cases. NAC dosing errors leading to cerebral edema seizures have been reported. It is therefore prudent to develop a clear protocol at your hospital for the more straight-forward cases. Anaphylactoid reactions occur in 8% of patients who receive N-acetylcysteine.

Pitfall #9 is using the same dosing protocol of NAC for all acetaminophen toxic patients; our experts recommend consulting

your toxicologist for dosing recommendations for all but the most straight-forward acute overdoses as the dosing has become increasingly complicated.

Massive acetaminophen overdose – early coma and lactic acidosis that may require dialysis and fomepizole

Massive acetaminophen overdose (defined as > 500 mg/kg – approximately 30g in an average sized adult – serum acetaminophen several-fold higher than the treatment threshold) typically presents with a very different toxidrome compared to a non-massive overdose, characterized by early presentation of coma and lactic acidosis as a result of a different pathophysiology. Typically, acetaminophen levels are extremely high and liver transaminases may be normal.

Pitfall #10 is failure to recognize massive acetaminophen overdose in the altered patient with normal liver enzymes; these patients typically present early with coma and lactic acidosis and before liver enzymes begin to rise.

Charcoal is indicated for up to 4 hours after a massive acetaminophen overdose. Consider **securing the airway** prior to administration of charcoal to prevent aspiration in the altered patient.

N-acetylcysteine (NAC) dosing is **higher** for massive overdose compared to non-massive overdose – consult your toxicologist for dosing.

Pitfall #11 is administering the usual protocol-driven dose of N-acetylcysteine (NAC) for the massive overdose patient; the dose for massive overdose is higher than usual – consult your toxicologist.

Typical indications for dialysis: altered mental status, metabolic acidosis, elevated lactate + APAP >900mg/L (5960 umol/L)

General Recommendation
• ECTR is suggested in severe APAP poisoning (2D)
ECTR is recommended:
• If the [APAP] more than 1000 mg/L (6620 μmol/L) and NAC is NOT administered (1D).
• If the patient presents with altered mental status, metabolic acidosis, with an elevated lactate, and an [APAP] is more than 700 mg/L (4630 μmol/L) and NAC is NOT administered (1D).
• If the patient presents with an altered mental status, metabolic acidosis, an elevated lactate, and an [APAP] is more than 900 mg/L (5960 μmol/L) even if NAC is administered (1D).
ECTR is not recommended
• On the basis of the reported ingested dose if NAC is administered (1D).
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• On the basis of reported ingested dose alone even if NAC is NOT administered (2D).
• Solely on the basis of the [APAP] if NAC is administered (2D).
Cessation of ECTR
• ECTR is recommended until sustained clinical improvement is apparent (1D).
Choice of ECTR
• Intermittent hemodialysis is the preferred ECTR in patients with APAP poisoning (1D).
• The following are acceptable alternatives if HD is not available:
■ Intermittent HP (1D)
■ CRRT (3D)
■ Exchange transfusion in neonates (2D)
Miscellaneous
1. NAC therapy should be continued during ECTR at an increased rate (1D).

Source: Gosselin, S. et al. Extracorporeal treatment for acetaminophen poisoning: Recommendations from the EXTRIP workgroup. Clin. Toxicol. 52, 856–867 (2014).

Pitfall #12 is replacing N-acetylcysteine (NAC) with hemodialysis; dialysis should not be considered an alternative to NAC. In fact, patients who are dialyzed require higher doses of NAC (double the dose in patients undergoing intermittent hemodialysis).

Fomepizole in acetaminophen poisoning – an adjunct to NAC to consider in massive overdose

Dose: Fomepizole 15mg/kg IV x1

Mechanism: Early treatment with fomepizole can theoretically prevent liver injury after acetaminophen overdose by halting the formation of NAPQI and inhibits cellular necrosis which NAC does not do.

The **indications for fomepizole** based on current evidence is unclear as there have yet to be robust RCTs published. It is reasonable to consider fomepizole in the massive overdose patient, those requiring hemodialysis and those with evidence of significant hepatic injury.

Summary of the 12 pitfalls in acetaminophen poisoning assessment and management

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Pitfall #2 is neglecting to ask patients about all the medications they take including over-the-counter ones and exactly how much they take of each; supra-therapeutic dosing of over-the-counter medications may be the first clue to a life-threatening acetaminophen overdose.

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