Acetaminophen Toxicity

Practice Essentials

Acetaminophen is one of the most commonly used oral analgesics and antipyretics. It has an excellent safety profile when administered in proper therapeutic doses, but hepatotoxicity can occur after overdose or when misused in at-risk populations. In the United States, acetaminophen toxicity has replaced viral hepatitis as the most common cause of acute hepatic failure and is the second most common cause of liver failure requiring transplantation.

Acetaminophen metabolism occurs primarily in the liver and is illustrated in the image below.

![Acetaminophen metabolism](image)

Signs and symptoms

Most patients who overdose on acetaminophen will initially be asymptomatic, as clinical symptoms of end-organ toxicity do not manifest until 24-48 hours after an acute ingestion. Therefore, to identify a patient who may be at risk of hepatotoxicity, the clinician should determine the time(s) of ingestion, the quantity, and the formulation of acetaminophen ingested.

Minimum toxic doses of acetaminophen for a single ingestion, posing significant risk of severe hepatotoxicity, are as follows:

- Adults: 7.5-10 g
- Children: 150 mg/kg; 200 mg/kg in healthy children aged 1-6 years

The clinical course of acetaminophen toxicity generally is divided into four phases. Physical findings may vary, depending on the degree of hepatotoxicity.

**Phase 1**
- 0.5-24 hours after ingestion
- Patients may be asymptomatic or report anorexia, nausea or vomiting, and malaise
- Physical examination may reveal pallor, diaphoresis, malaise, and fatigue

**Phase 2**
- 18-72 h after ingestion
- Patients develop right upper quadrant abdominal pain, anorexia, nausea, and vomiting
- Right upper quadrant tenderness may be present
- Tachycardia and hypotension may indicate volume losses
- Some patients may report decreased urinary output (oliguria)

**Phase 3: Hepatic phase**
- 72-96 h after ingestion
- Patients have continued nausea and vomiting, abdominal pain, and a tender hepatic edge
- Hepatic necrosis and dysfunction may manifest as jaundice, coagulopathy, hypoglycemia, and hepatic encephalopathy
- Acute renal failure develops in some critically ill patients
- Death from multiorgan failure may occur
Phase 4: Recovery phase

- 4 d to 3 wk after ingestion
- Patients who survive critical illness in phase 3 have complete resolution of symptoms and complete resolution of organ failure

See Clinical Presentation for more detail.

Diagnosis

The serum acetaminophen concentration is the basis for diagnosis and treatment. A diagnostic serum concentration is helpful, even in the absence of clinical symptoms, because clinical symptoms are delayed. The Rumack-Matthew nomogram interprets the acetaminophen concentration (in micrograms per mL), in relation to time (in hours) after ingestion, and is predictive of possible hepatotoxicity after single, acute ingestions of acetaminophen.

Recommended serum studies are follows:

- Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), bilirubin [total and fractionated], alkaline phosphatase)
- Prothrombin time (PT) with international normalized ratio (INR)
- Glucose
- Renal function studies (electrolytes, BUN, creatinine)
- Lipase and amylase (in patients with abdominal pain)
- Serum human chorionic gonadotropin (hCG) (in females of childbearing age)
- Salicylate level (in patients with concern of co-ingestants)
- Arterial blood gas and ammonia (in clinically compromised patients)

Additional recommended studies are as follows:

- Urinalysis (to check for hematuria and proteinuria)
- ECG (to detect additional clues for co-ingestants)

In patients with mental status changes, strongly consider serum ammonia levels and CT scanning of the brain. Laboratory findings in the phases of acetaminophen hepatotoxicity are as follows:

- Phase 1: Approximately 12 hours after an acute ingestion, liver function studies show a subclinical rise in serum transaminase concentrations (ALT, AST)
- Phase 2: Elevated serum ALT and AST, PT, and bilirubin concentration; renal function abnormalities may also be present and indicate nephrotoxicity
- Phase 3: Severe hepatotoxicity is evident on serum studies; hepatic centrilobular necrosis is diagnosed on liver biopsy

Rumack-Matthew nomogram

- Used to interpret plasma acetaminophen values to assess hepatotoxicity risk after a single, acute ingestion
- Nomogram tracking begins 4 hours after ingestion (time when acetaminophen absorption is likely to be complete) and ends 24 hours after ingestion
- About 60% of patients with values above the "probable" line develop hepatotoxicity

See Workup for more detail.

Management

Gastrointestinal decontamination agents can be used in the emergency setting during the immediate postingestion time frame. Administer activated charcoal (AC) if the patient is alert and presents, ideally, within 1 hour post ingestion. This time frame can be extended if the patient has ingested an acetaminophen-based sustained-release medication or if the ingestion includes agents that are known to slow gastric emptying. Patients with acetaminophen concentrations below the "possible" line for hepatotoxicity on the Rumack-Matthew nomogram may be discharged home after they are medically cleared.

Admit patients with acetaminophen concentration above the "possible" line on the Rumack-Matthew nomogram for treatment with N-acetylcysteine (NAC). NAC is nearly 100% hepatoprotective when it is given within 8 hours after an acute acetaminophen ingestion, but can be beneficial in patients who present more than 24 hours after ingestion. NAC is approved for both oral and IV administration.

The FDA-approved regimen for oral administration of NAC (Mucomyst) is as follows:

- Loading dose of 140 mg/kg
- 17 doses of 70 mg/kg given every 4 hours
- Total treatment duration of 72 hours

The IV formulation of NAC (Acetadote) is commonly used in many institutions for the treatment of acetaminophen ingestion. Use of the IV formulation of NAC is preferred in the following situations:

- Altered mental status
Surgical evaluation for possible liver transplantation is indicated for patients who have severe hepatotoxicity and potential to progress to hepatic failure. Criteria for liver transplantation include the following:

- Metabolic acidosis, persistent after fluid resuscitation
- Renal failure
- Coagulopathy
- Encephalopathy

See Treatment and Medication for more detail.
References


