

Acetaminophen Toxicity (Paracetamol Toxicity) in Children — Diagnosis and Treatment

[See online here](#)

Wide usage of Acetaminophen in children is practiced due to its established safety and efficacy. The risk of allergic toxic reactions against acetaminophen is low in children as compared to adults. The unintentional inappropriate doses can induce hepatic toxicity in many pediatric cases. The symptoms represented by paracetamol toxicity in children are non-specific. Hence, delayed diagnosis and management of acetaminophen intoxication can happen in unintentional cases of toxicity due to its overdoses.



Overview of Acetaminophen Toxicity

Acetaminophen (paracetamol) toxicity is defined as the harmful effects of an acute overdose of acetaminophen.

The most common cause of mortality in patients with acetaminophen toxicity is an **acute liver failure**.

Epidemiology of Acetaminophen Toxicity

Acetaminophen toxicity is common in the United States since acetaminophen is one of the most widely used analgesic-antipyretic medication by children. The most common causes of acetaminophen toxicity in children are overdose due to a miscalculation by the caregiver or due to accidental intake by a child.

Acetaminophen toxicity alone was reported in approximately 50,000 cases in 2014 in the United States, which resulted in 65 deaths that year. A clear distinction between the number of cases of acetaminophen toxicity in children and adults is not readily available due to a scarcity of separate epidemiological studies for children.

The prognosis of single dose acute ingestion of acetaminophen has improved after the introduction of the antidote **N-acetylcysteine** (NAC). NAC decreases the mortality and morbidity of acetaminophen toxicity in children and adults.

Classification of Acetaminophen Dosage in Children

An acetaminophen overdose is better appreciated by knowing the recommended doses of acetaminophen in children of different ages.

The maximum acetaminophen dosage in **children > 12 years** of age who weigh 50 kg or more is 4 grams per day, the same as the maximum allowed dosage for adults. This dosage should be divided into 1 gram every 6 hours.

The maximum acetaminophen dosage in **children < 12 years** of age, or those who weigh less than 50 kg, is 80 mg/kg or a cumulative dose of 2.6 g per day. This dose should be divided into three or four times per day.

The **minimum toxic dosage** of acetaminophen is defined as the minimum dose that causes signs and symptoms of toxicity. The minimum toxic dosage is approximately 150 mg/kg for acute acetaminophen overdose.

The **absolute toxic dosage** of acetaminophen is a dose of more than 250 mg/kg for an acute ingestion. Children who ingest these doses are at risk of developing severe acute liver failure.

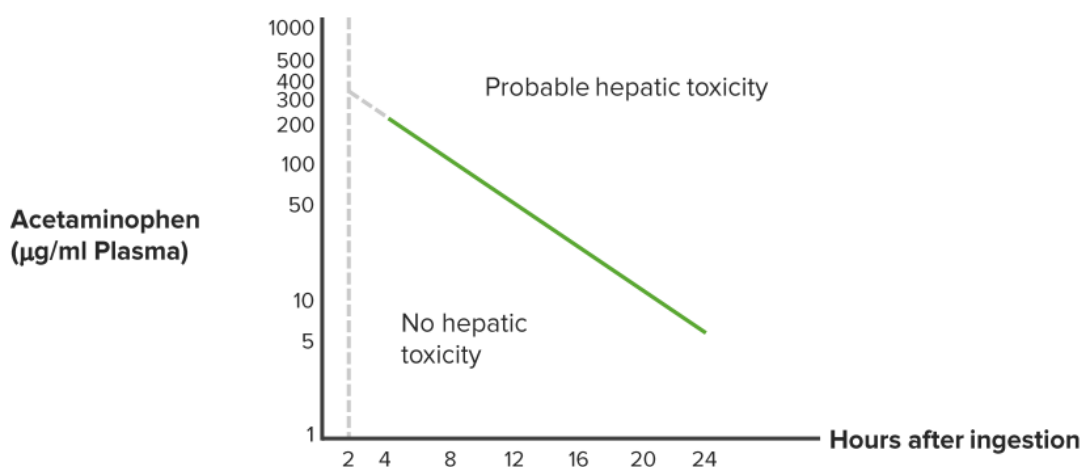
Pathophysiology of Acetaminophen Toxicity

The peak plasma concentration after acute ingestion of an acetaminophen overdose is usually observed after 4 hours. The peak plasma concentration is delayed if acetaminophen is combined with opiates or anticholinergic drugs.

Acetaminophen is primarily metabolized in the **liver**. The intermediate metabolites produced by the hepatic metabolism of acetaminophen are its **sulfate** and **glucuronide conjugates**, which are usually eliminated in the urine.

Approximately 4 % of the ingested dose will be biotransformed into a highly toxic metabolite known as **N-acetyl-p-benzoquinoneimine (NAPQI)**, which is believed to be responsible for hepatotoxicity and hepatic cell damage. When acetaminophen is taken in a therapeutic dose, **glutathione** usually binds to NAPQI rendering it a non-toxic metabolite that can be readily excreted in the urine.

In case of overdose, glutathione stores become depleted and the toxic metabolite NAPQI starts accumulating. This is believed to be the main pathologic mechanism involved in the pathogenesis of hepatotoxicity in these cases.



Acetaminophen Nomogram. Image by Lecturio.

Clinical Presentation of Acetaminophen Toxicity

Adequate history taking is essential to identify what the child ingested, whether it was intentional or accidental and whether acetaminophen was ingested alone or in combination with other drugs. The ingested dose of acetaminophen should also be estimated and the caregivers of the child should be asked to bring the empty tablet boxes with them to confirm the ingested dosage.

During the physical examination of the child, the level of hepatotoxicity should be determined. The level of hepatotoxicity is dependent on the stage of acetaminophen toxicity.

Stage 1: Presentation of hepatotoxicity after acetaminophen overdose (within 24 hours post-ingestion)

At this stage, children usually present with **anorexia**, **nausea**, **vomiting**, and **diaphoresis**. The cardiovascular and central nervous system changes are rare. When the child has an impaired level of consciousness at this stage, the possibility of **co-ingestion of acetaminophen with salicylates or other compounds**, such as opiates, should be excluded.

During this stage, the laboratory investigations, including the liver enzymes (ALT and AST), are within normal limits.

Stage 2: Presentation of hepatotoxicity after acetaminophen overdose (1–3 days post-ingestion)

At this stage, the clinical findings suggestive of the **hepatic involvement**, such as pain and tenderness in the right upper quadrant, are present. The liver enzymes are often elevated. Prothrombin time is increased as the synthetic function of the liver is impaired.

Stage 3: Presentation of hepatotoxicity after acetaminophen overdose (3–5 days post-ingestion)

This stage is characterized by the reappearance of the stage 1 symptoms. Additionally, the affected persons have jaundice, hypoglycemia, encephalopathy, and may develop sepsis. ALT and AST levels remain elevated. Renal failure and heart failure can also occur at this stage. Most fatalities occur during this stage.

Stage 4: Recovery after acetaminophen overdose (5–21 days post-ingestion)

During this stage, **liver enzymes** tend to normalize and **hepatic healing** start to occur. Children can undergo either complete resolution or they might develop fulminant hepatic failure and die during this stage.

Diagnostic Workup of Acetaminophen Toxicity

Serum levels of AST and ALT, bilirubin, and prothrombin time should be assessed in children with acetaminophen overdose.

The diagnosis of acetaminophen toxicity and the risk of hepatotoxicity are usually determined by tracking the blood levels of acetaminophen in the first 24 hours after acute ingestion. These levels are plotted on the **Rumack-Matthew nomogram**, also known as the acetaminophen toxicity nomogram.

For the nomogram to be used, a child must present within the first 24 hours after an acetaminophen overdose. A child who presents late in stage 2 or 3 should only undergo a single acetaminophen concentration test in addition to the assessment of hepatic function. The Rumack-Matthew nomogram should not be used in these patients.

Acetaminophen blood levels within the 4–18 hours' time-window after ingestion are most reliable in the prediction of the risk of hepatotoxicity. Levels above 150 µg/mL or 993 µmol/L at 4 hours post-ingestion predict a high risk of developing hepatotoxicity.

A CT scan of the head should be performed in the children developing an altered level of consciousness to look for cerebral edema and to exclude other causes. Additionally, serum levels of ammonia should be measured, which correlate with the severity of encephalopathy.

Treatment of Acetaminophen Toxicity

N-acetylcysteine (NAC) should be given to any child who presents within the first 24 hours after an acetaminophen overdose having hepatotoxicity, or is at an increased risk of hepatotoxicity. Once NAC is initiated, it should be continued until the normalization of prothrombin time, ALT and AST levels. NAC is usually started at a loading dose of 140 mg/kg, followed by 70 mg/kg every 4 hours.

Gastric lavage and **activated charcoal** should be used within 1 hour of ingestion. They decrease the systemic absorption of acetaminophen and can be life-saving.

Children, who develop **acute liver failure** and consequently metabolic acidosis, renal failure, coagulopathy, and encephalopathy, should be evaluated for possible **liver transplantation**. Without liver transplantation, the prognosis is very poor in these cases.

References

Defendi, G. L., & Tucker, J. R. *Pediatric Acetaminophen Toxicity*. Retrieved March 12, 2018, from <http://img.medscape.com/pi/android/medscapeapp/html/A1008683-business.html>

Legal Note: Unless otherwise stated, all rights reserved by Lecturio GmbH. For further legal regulations see our [legal information page](#).