Acetaminophen Poisoning
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Acetaminophen (N-acetyl-para-aminophenol) is one of the most prevalent medications on the market today, available for purchase in multiple different formulations: as an individual product (eg, Tylenol* [Johnson & Johnson Consumer Inc, Fort Washington, PA]), as a component in over-the-counter cold remedies (eg, DayQuil™/Nyquil™ [Procter & Gamble, Cincinnati, OH], Alka-Seltzer Plus® [Bayer Corp, Whippany, NJ], and Dimetapp® Cold & Flu [Pfizer Inc, New York, NY]), and in combination with an opiate (eg, acetaminophen-codeine and Percocet® [Endo Pharmaceuticals Inc, Malvern, PA]). Being so widely available both over the counter and by prescription, it is a common cause of both accidental and intentional ingestions. As a class, analgesics (including acetaminophen) are the most commonly ingested medication, and in 2015, products containing acetaminophen were the reason for approximately 45,000 calls to poison control centers throughout the United States related to children.

Acetaminophen toxicity occurs via its metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which ultimately leads to oxidative hepatic injury. In therapeutic doses, acetaminophen produces only minimal amounts of NAPQI because it is metabolized in hepatocytes via UDP-glucuronosyl transferase (UGT) and sulfotransferase (SULT) mainly to compounds that are readily excreted in the urine. In addition, any NAPQI that is produced is conjugated by glutathione into a nontoxic compound in the liver. However, with an overdose, the UGT and SULT metabolic pathways are saturated and glutathione stores become exhausted, resulting in free NAPQI and its oxidative injury to the liver.

Clinical signs and symptoms of acetaminophen toxicity can be thought of as occurring in 4 distinct stages: the first 24 hours (stage I); 24 to 72 hours (stage II); 72 to 96 hours (stage III); and 96 hours to 2 weeks (stage IV). During stage I, patients may be asymptomatic or may display gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, and/or nonspecific systemic symptoms, such as pallor, diaphoresis, and malaise. Laboratory test results are typically normal at this time, although liver enzyme levels may rise as early as 12 hours after a massive ingestion. When the overdose is from acetaminophen alone, mental status typically is normal at first, although a massive overdose may result in a decreased level of consciousness or coma. In stage II, the initial symptoms typically resolve and evidence of hepatic injury, such as right upper quadrant pain and tenderness, develops. Elevation of liver enzyme levels occurs within 24 to 36 hours; other tests indicative of liver function, such as bilirubin and prothrombin time/international normalized ratio (INR), may begin to show evidence of abnormality. If the patient progresses to stage III, evidence of hepatotoxicity and liver failure ensues: there are massive elevations in transaminase levels, increased bilirubin levels, metabolic acidosis with an increased anion gap, and prolongation of the prothrombin time/INR: jaundice, hepatic encephalopathy, acute kidney injury (potentially hepatorenal syndrome or acute renal failure), and

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multi-organ failure can occur. Most deaths from acetaminophen toxicity occur during stage III. Stage IV is the recovery stage, where clinical symptoms resolve and laboratory abnormalities return to normal.

The diagnosis of acetaminophen toxicity is confirmed by obtaining a serum acetaminophen concentration. Toxicity may result from either an acute overdose or from repeated supratherapeutic ingestions of acetaminophen or acetaminophen-containing products. A single dose greater than 150 mg/kg in children and greater than 7.5 g in adults or supratherapeutic repeated doses amounting to greater than 200 mg/kg over 1 day or 150 mg/kg per day over 2 days is concerning for potential toxicity. Because acetaminophen is a common co-ingestant, a serum level should be obtained on all patients who present with any known or possible substance ingestion, even if acetaminophen is not explicitly mentioned. If possible, the level should be obtained 4 hours after an acute ingestion to best determine the risk of toxicity and assist with management. A level performed earlier may indicate acetaminophen ingestion but cannot accurately assess the risk of toxicity. When the time of ingestion is unknown, the earliest possible time that acetaminophen could have been taken should be used. For a long-term ingestion, a level should be drawn at the time of presentation. Liver and renal function tests should be drawn 8 to 10 hours after ingestion, although abnormalities often become evident only after 24 hours.

Management of acetaminophen toxicity begins with evaluation and stabilization of the patient’s airway, breathing, and circulation. Activated charcoal may be useful if administered within 2 hours of ingestion, but it should be avoided in a patient with altered mental status, an unprotected airway, or co-ingestion with a corrosive or proconvulsant substance. The mainstay of treatment for acetaminophen toxicity is N-acetyl cysteine (NAC), which works by providing cysteine as a substrate to replenish hepatic glutathione stores and by shuttling unmetabolized acetaminophen to the SULT pathway, thereby halting production of NAPQI. Also, NAC may directly reduce NAPQI back to acetaminophen, preventing its hepatotoxic effect. The Rumack-Matthew nomogram (Fig) is a useful tool in guiding the management of an acute acetaminophen overdose when the time of ingestion is known and the patient presents within 24 hours. The acetaminophen level is plotted on the nomogram, and the decision whether to treat with NAC is determined accordingly. The treatment line starts at 4 hours after ingestion and decreases linearly over time. Although toxicity is probable at a serum concentration of 200 μg/mL, the treatment line was lowered to start at 150 μg/mL to increase the sensitivity of the nomogram. If the level is above the treatment line, NAC should be initiated. Ideally, treatment with NAC begins within 6 to 8 hours of ingestion, as its protective effect is dramatically higher when given within this period. If treatment will be delayed beyond this time or if the patient is symptomatic, NAC should be administered while the acetaminophen level is pending. The nomogram is not applicable when the time of ingestion is unknown, when the patient presents more than 24 hours after ingestion, and in long-term repeated exposures. In these situations, NAC should be started if the serum acetaminophen level is greater than 10 μg/mL or if transaminase levels are elevated.

Administration of NAC can be oral or intravenous. Both are equally effective in preventing and treating acetaminophen toxicity; however, intravenous NAC should be used preferentially for patients with fulminant hepatic failure, intractable vomiting, or pregnancy. Intravenous NAC is administered over 21 hours and has an associated risk of an anaphylactoid reaction, particularly during the initial loading dose and in patients with asthma. The oral form is given as a course of 18 doses over 72 hours. Aminotransferase levels, INR, and acetaminophen level should be determined before discontinuing NAC therapy. If laboratory abnormalities persist, NAC use should be continued until aminotransferase levels are improving, the INR has normalized, and the acetaminophen level is undetectable. In severely ill patients who progress to fulminant hepatic
failure and do not respond to treatment with NAC, liver transplant may be lifesaving.

Anticipatory guidance at health-care maintenance visits is essential to prevent a toxic acetaminophen overdose. Parents should be advised to keep all products containing acetaminophen in locations inaccessible to children, strictly adhere to weight-based dosing, and avoid adult preparations and co-administration of acetaminophen-containing medications.

**COMMENT:** By far the most common reason for parents to give their children acetaminophen is to combat fever, but in many, if not most, instances this is a fight that is self-defeating. In contrast to the dangers of hyperthermia, fever is regulated by the hypothalamus as a homeostatic response to an inflammatory insult, and of itself almost never poses a threat to the febrile child. In fact, as a physiologic phenomenon fever has survived for millions of years among animals all along the spectrum from invertebrates to mammals, and given that fever comes at a metabolic cost in energy expended, evolution tells us it must have some survival benefit. Experimental evidence documents that fever can impede the growth of many pathogenic bacteria and viruses, although it enhances neutrophil migration, T-cell proliferation, and superoxide and interferon production. Yet our phobic response to fever, both as parents and as physicians, contributes to the more than 25 billion doses of acetaminophen sold in the United States each year, often given for fevers that are not discomforting or are not in fact fevers at all. Granted that most acetaminophen poisonings result from intentional overdosing, the frequency with which parents inadvertently give their children improper doses of medication makes the ubiquity of acetaminophen (and other antipyretics) a real concern.

– Henry M. Adam, MD
Associate Editor, *In Brief*

**In Memoriam**

The staff of Pediatrics in Review notes with sadness the passing of Sydney “Cindy” Sutherland, who for many years served faithfully and skillfully as an Editorial Assistant, working closely with Editors-in-Chief Robert Haggerty and Lawrence Nazarian. She is remembered for her exceptional command of the English language, her understanding of the goals of the journal, her passion for social justice, and her dynamic and delightful personality.