Acetaminophen-related Hepatotoxicity

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INTRODUCTION

Acetaminophen (APAP or paracetamol or N-acetyl-p-aminophenol), a safe and effective antipyretic and analgesic, has been extensively used around the world since 1955. It is available as various formulations, as a single-ingredient medication (eg, immediate-release and extended-release tablets/capsules, suspensions, rectal suppositories, and for intravenous [IV] use) and also as a component of numerous...

KEY POINTS

- Acetaminophen (APAP), a widely available antipyretic and analgesic, is the leading worldwide cause of drug overdose and acute liver failure (ALF).
- Single overdose ingestion and therapeutic misadventure may cause hepatotoxicity.
- Several factors, such as concomitant alcohol use or abuse, concurrent medications, genetic factors, and nutritional status, can influence the susceptibility and severity of APAP hepatotoxicity.
- Early manifestations of APAP hepatotoxicity are nonspecific, but require prompt recognition by physicians.
- Patients with repeated overdose tend to present late, and in such hepatotoxicity may have already evolved.
- The prognosis of patients with APAP-induced ALF is better than other causes of ALF; therefore, liver transplantation should be offered to those who are unlikely to survive and such assessment and decision to proceed with liver transplantation may be made based on the King’s College criteria.
combination over-the-counter and prescription products used for pain and as an anti-
pyretic. In the United States, more than 28 billion doses of APAP were distributed in
2003, and hydrocodone-APAP was the most commonly dispensed medication among
89 million out-patient prescriptions in 2005.1,2

Although APAP is generally considered to be safe at the usual therapeutic doses as
recommended by the manufacturer (1–4 g/day), concerns have emerged over the past
decade as APAP has been increasingly recognized as a major cause of acute liver fail-
ure (ALF) in adults in the United States and many other countries worldwide.3–7 Single
overdose ingestion usually follows attempted self-poisoning and exceeding 15 to 25 g
may cause severe liver injury that is fatal in up to a quarter of the cases.3,8,9 However,
30% to 50% of cases of APAP hepatotoxicity admitted to hospital nowadays result
from a “therapeutic misadventure” wherein the daily dose may not have greatly
exceeded the recommended safe limits but where specific risk factors are present.3,8,9

EPIDEMIOLOGY

APAP has been a major cause of overdose and overdose-related ALF (~50% of
cases) and death in the United States and in many other countries.3–6 In the United
States, APAP overdose is the leading reason for calls to the Poison Control Centers
(>100,000 per year) and accounts annually for more than 56,000 emergency room
visits, 2600 hospitalizations, and an approximate 450 deaths caused by ALF.3 In the
US ALF Multicenter Prospective Study, APAP accounted for 42% (275 of 662) of
ALF cases; the annual percentage of APAP-related ALF rose during the study from
28% in 1998 to 51% in 2003.8 Unintentional overdoses accounted for 48%; intentional
(suicide attempts) 44%; and 8% were of unknown intent.8 Most unintentional patients
reported taking APAP for acute or chronic pain syndromes; 38% took two or more
APAP preparations simultaneously, and 63% used narcotic-containing compounds.8

PHARMACOLOGY AND HEPATOTOXICITY

The therapeutic dose of APAP is 325 to 1000 mg/dose (10–15 mg/kg/dose in children),
given every 4 to 6 hours, with a maximum recommended daily dose of 4 g (80 mg/kg in
children). Although the US Food and Drug Administration (FDA) Advisory Committee
proposed a decrease in the maximum daily dose from 4000 to 3250 mg, this recom-
mandation has not been implemented.10 After oral ingestion, APAP is rapidly absorbed
from the gastrointestinal tract with peak concentrations being achieved within 90 mi-
utes.1,11 Therapeutic serum concentrations range from 10 to 20 μg/mL. The presence
of food in the stomach may delay the time to peak concentration, but not the extent of
absorption.1,11 With overdose ingestion, peak serum concentrations generally are
achieved within 4 hours, but may be delayed beyond 4 hours after overdose of
extended-release preparations or when drugs that delay gastric emptying time (eg, an-
ticholinergics, opiates) are coingested.12,13 Protein binding is minimal at therapeutic
doses with a volume of distribution of approximately 0.9 L/kg.11 The serum half-life
of APAP is 2 to 2.5 hours; however, it is prolonged to more than 4 hours in patients
with hepatic injury and chronic liver disease, and in those who ingested extended-
release preparations.1,11,14

At therapeutic doses, approximately 85% to 90% of APAP undergoes phase II
conjugation to sulfated and glucoronidated metabolites (about two-thirds through glu-
curonidation and one-third through sulfation in adults, whereas sulfation is predomi-
nant in children up to 12 years), which are then excreted in the urine.1,11,15 About
2% of APAP is excreted in the urine unchanged. The remaining APAP (up to 10%) un-
dergoes phase I oxidation by the hepatic cytochrome P-450 (CYP) pathway (primarily
responsible by CYP2E1) to a toxic, highly reactive intermediate, N-acetyl-para-benzo-quinoneimine (NAPQI). Small amount of NAPQI produced from normal doses of APAP is rapidly conjugated by hepatic glutathione (GSH), forming nontoxic mercaptate and cysteine compounds that are then excreted in the urine. Small proportions of APAP are also oxidized by myeloperoxidase and cyclooxygenase-1, but the clinical significance of this pathway is unclear (Fig. 1).

APAP is known to be a dose-related hepatotoxic agent. At toxic doses of APAP, sulfation and glucoronidation pathways become saturated and more APAP is metabolized through CYP2E1 to NAPQI. An increased production of NAPQI eventually results in depletion of GSH, and when GSH stores are depleted by about 70% to 80%, NAPQI binds to hepatocytes causing cellular injury. In the absence of GSH, NAPQI covalently binds to cysteine groups on hepatocyte molecules forming NAPQI-protein adducts (so-called APAP-protein adducts). This process is an irreversible step that leads to oxidative injury and hepatocellular necrosis. Although unclear, mitochondrial damage, nuclear DNA fragmentation, and lipid peroxidation are likely to play an important role in APAP-induced hepatocellular damage. GSH depletion further contributes to oxidative stress, activation of stress proteins and gene transcription mediators, and alterations in the liver’s innate immune system. There is a growing body of evidence suggesting a critical role of innate immunity and sterile inflammation in the progression and repair of APAP hepatotoxicity. The early cell necrosis causes the release of various mediators, such as high-mobility group box 1 protein, DNA fragments, and heat shock proteins, and which enhance proinflammatory cytokine and chemokine formation from macrophages. Although proinflammatory mediators recruit inflammatory cells (eg, neutrophils, monocytes, and natural killer cells) into the liver, neither the infiltrating cells nor the activated resident macrophages cause significant direct cytotoxicity. However, these proinflammatory mediators directly promote intracellular injury mechanisms by inducing nitric oxide synthase or inhibit cell death mechanisms by the expression of acute-phase proteins, which then promote hepatocyte proliferation. Furthermore, the newly recruited macrophages, and possibly neutrophils, are involved in tissue repair through the removal of necrotic cell debris leading to resolution of the inflammation.

Fig. 1. Metabolism of acetaminophen and potential factors influencing its toxicity.
Zone 3 hepatocytes, which are most abundant in CYP2E1, are most vulnerable to injury, and this leads to the characteristic centrilobular pattern of hepatocellular necrosis observed in APAP hepatotoxicity.\(^1\) Passive congestion and scattered infiltration of lymphocytes and neutrophils may also be observed.\(^{15}\)

**FACTORS INFLUENCING APAP-RELATED HEPATOTOXICITY**

The ingested dose of APAP seems to be the most important factor determining the development and severity of APAP hepatotoxicity. In addition, the pattern of use and various factors (eg, age, concurrent use of alcohol and certain medications, genetic factors, pre-existing liver disease, and nutritional status) can also influence the susceptibility to APAP hepatotoxicity through several mechanisms including decreased capacity for glucuronidation or sulfation, excessive CYP activity, and depletion of GSH stores (see Table 1).

**Dose and Pattern of Use**

Although the FDA-labeled doses are clear, some users may ignore the directions and consume APAP amounts exceeding recommended doses, either by intention or by accident (therapeutic misadventure). A single acute ingestion of greater than or equal to 7.5 to 10 g in adults or 150 to 200 mg/kg in children older than 6 years (all APAP consumed within 8 hours) is likely to cause hepatotoxicity and requires prompt evaluation and therapeutic intervention.\(^1\) Repeated overdoses of greater than or equal to 10 g in a 24-hour period or greater than or equal to 6 g per 24-hour period for greater than or equal to 48 hours may be associated with subsequent hepatotoxicity and the patient should undergo evaluation in a health care facility.\(^{22}\) A lower threshold (4–10 g) for evaluation may be considered in a high-risk population (discussed later). Although most studies have reported safety of short-term and long-term use of APAP at the maximum recommended dose of 4 g,\(^{23,24}\) a well-designed, randomized

<table>
<thead>
<tr>
<th>Factors</th>
<th>Potential Clinical Consequences</th>
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<tbody>
<tr>
<td>Chronic alcohol ingestion</td>
<td>↑ APAP hepatotoxicity, particularly with repeated overdoses</td>
</tr>
<tr>
<td>Medications and herbs that induce CYP2E1</td>
<td>Possibly ↑ APAP hepatotoxicity</td>
</tr>
<tr>
<td>(eg, INH, rifampicin, phenobarbital, and St. John's wort)</td>
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<tr>
<td>Medications that compete with hepatic glucuronidation</td>
<td>Possibly ↑ APAP hepatotoxicity</td>
</tr>
<tr>
<td>(eg, zidovudine and trimethoprim-sulfamethoxazole)</td>
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<tr>
<td>Gilbert syndrome</td>
<td>Possibly ↑ APAP hepatotoxicity</td>
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<tr>
<td>Malnutrition</td>
<td>↑ APAP hepatotoxicity, in alcoholics</td>
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<tr>
<td>Fasting state</td>
<td>↑ APAP hepatotoxicity, in alcoholics</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>↑ APAP hepatotoxicity, particularly in alcoholics</td>
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<tr>
<td>Advanced age</td>
<td>Possibly ↑ APAP hepatotoxicity</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Potential for APAP hepatotoxicity in the fetus</td>
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</table>

Abbreviations: APAP, acetaminophen; CYP, cytochrome P-450; INH, isoniazid.
placebo-controlled study of 145 healthy volunteers reported that the daily intake of APAP of 4 g for 14 days was associated with asymptomatic elevations of alanine aminotransferase (ALT) (>3 times the upper limits of normal) in up to 40% of subjects. These elevations of ALT occurred despite APAP concentrations being within therapeutic limits, and resolved after APAP discontinuation, and without any clinical consequences.

**Alcohol**

The interaction between ethanol, a competitive substrate of CYP2E1, and APAP is complex. Acute alcohol ingestion is not a risk factor for APAP hepatotoxicity and may actually be protective by competing with APAP for CYP2E1. In a prospective observational study of 362 patients presenting within 24 hours after acute APAP overdose, concurrent acute alcohol intake was reported by 49% of patients. The prevalence of hepatotoxicity was 5.1% (95% confidence interval, 2.6%–9.5%) in those who ingested ethanol, compared with 15.2% (95% confidence interval, 10.7%–21.2%) in those who did not (P = .0027). Particularly, acute ethanol intake conferred a lower risk of hepatotoxicity in patients who had APAP concentrations above or below the “200-line” on the nomogram and was independent of the interval between ingestion and assessment. In contrast, chronic alcohol ingestion may potentiate APAP hepatotoxicity by upregulating CYP2E1 and decreasing GSH synthesis. Chronic alcohol ingestion enhances CYP2E1 activity about twofold by enzyme stabilization (half-life increases from 7 to 37 hours) and increased synthesis. This effect lasts for up to 10 days and, interestingly, is maximal around 6 to 8 hours of abstinence suggesting that the risk of APAP hepatotoxicity is particularly increased in those recently abstinent from alcohol. In addition, alcoholics are often malnourished, a state associated with depleted hepatic GSH stores thus further predisposing them to hepatotoxicity. Most available data have concluded that chronic alcohol consumption is associated with an increased risk of APAP hepatotoxicity in patients with repeated overdoses (therapeutic misadventure). However, alcoholics do not seem to be at an increased risk of APAP liver injury at a therapeutic dose or in a single overdose setting, particularly if they are treated within 8 hours. A review of more than 2000 cases in the literature indicates that the only reports linking alcohol and enhanced toxicity were retrospective reviews and case reports with no such link found in prospective reports.

**Medications and Herbs**

Concomitant use of medications that induce the CYP system, such as anticonvulsants (eg, phenobarbital, phenytoin, and carbamazepine) and antituberculosis agents (eg, isoniazid and rifampicin), may predispose to APAP hepatotoxicity by increased production of NAPQI by way of the oxidative pathway. Severe APAP hepatotoxicity associated with the concurrent use of these medications has been anecdotally reported, although there are no compelling data that this occurs at a therapeutic dose. Phenytoin is primarily metabolized by CYP3A4 and not CYP2E1 and as such there is an insignificant amount of APAP metabolite being produced. Thus, concomitant phenytoin use should not be considered a predisposing factor for APAP hepatotoxicity, but may in fact be protective in APAP overdose by way of enhanced glucuronidation. Phenobarbital also does not significantly induce CYP2E1 but is rather a pleiotropic inducer of phase I and phase II reactions. Some herbs and dietary supplements are inducers of CYP (eg, St. John’s wort, garlic, grapefruit juice, and germander), and theoretically may potentiate APAP hepatotoxicity. Zidovudine and trimethoprim-sulfamethoxazole may augment APAP hepatotoxicity.
by competitive use of the glucuronidation pathway and with subsequent increased metabolism toward CYP.39

**Genetic Factors**

Genetic polymorphisms in the CYP isoenzymes can be associated with an excessive or diminished oxidative metabolism of APAP, but the clinical relevance to toxicity is unknown.15,40,41 Impaired glucuronidation in patients with Gilbert syndrome seems to augment APAP toxicity.42

**Age**

The metabolism of APAP is age-dependent, by which older patients are more susceptible to develop hepatotoxicity compared with young children after an acute overdose.43,44

**Nutritional Status**

In the setting of chronic alcohol consumption, malnutrition and fasting state may potentiate APAP hepatotoxicity by reduced capacity for hepatic glucuronidation and because of depleted GSH stores.15,45,46 Without chronic alcohol consumption, the effect of malnutrition and fasting on APAP hepatotoxicity is unclear. Although hepatic GSH stores are reduced by about 30% in patients with true protein-calorie malnutrition, such as anorexia nervosa, CYP2E1 and metabolic rates of drug metabolism are also decreased, possibly resulting in no change in the risk for APAP toxicity.35,47

**Chronic Liver Disease**

Patients with cirrhosis have a higher area under the curve and lower clearance of APAP compared with healthy subjects.48 In patients with cirrhosis, CYP activity is low or unchanged and does not seem to be inducible, whereas GSH stores may be depleted, but usually not to critical levels.15,49 Although controversy exists, patients with chronic liver disease who do not regularly consume alcohol are not at significantly increased risk for developing APAP hepatotoxicity.15,49 According to available data, less than 4 g/day of APAP seems safe for short-term dosing in patients with cirrhosis. Nevertheless, some experts have recommended less than 2 g/day, particularly for patients with decompensated disease or those who continue ingesting alcohol, given the small margin for error in a high-risk population.49–51

**Pregnancy**

APAP is the most common drug overdose in pregnancy.52 Although, the metabolism of APAP is altered (increased clearance caused by increased activity of glucuronidation and oxidative pathways) during pregnancy, there is insufficient evidence to suggest pregnancy as a predisposing factor for APAP hepatotoxicity. APAP has been demonstrated to cross the placenta and, at toxic doses, may harm maternal and fetal hepatocytes.52,53 Although several cases of neonatal deaths and prematurity have been reported, most pregnancies with APAP overdose had normal outcomes, and APAP does not seem to increase adverse pregnancy outcome unless severe maternal toxicity develops.52,53 Until available data on risk-stratification of toxicity to the fetus emerge, most physicians would consider pregnant women as a higher-risk group, in whom the strategy for antidote intervention should be more aggressive.
CLINICAL MANIFESTATIONS

Early recognition of APAP overdose is likely to prevent subsequent morbidity and mortality. The early manifestations of APAP overdose are frequent, mild, and nonspecific, and include nausea, vomiting, malaise, and abdominal pain. In general, these symptoms do not reliably predict subsequent hepatotoxicity. However, a study of 291 patients suggested that an increase in episodes of vomiting at first presentation seems to be a risk marker of subsequent hepatotoxicity. The clinical course of APAP hepatotoxicity in patients with single overdose can be classically divided into four sequential stages (see Table 2), but it should be noted that the course is variable and influenced by several factors, such as dose and formulation of APAP, coingested drug, and pre-existing liver disease.

APAP hepatotoxicity is acute and characterized by marked elevation of serum aminotransferase (often >3000 IU/L), which typically starts increasing within 24 to 36 hours, and peaks around 72 hours after overdose. The aspartate aminotransferase (AST) can be greater than 10,000 IU/L, and often more elevated than the ALT. The degree of aminotransferase elevation correlates roughly with the degree of hepatocellular damage. Maximal liver injury typically peaks between 3 and 5 days after ingestion, and may have features of jaundice, coagulopathy, and encephalopathy. Prothrombin time that continues to increase beyond 4 seconds after overdose, and with a peak prothrombin time greater than or equal to 180 seconds are associated with approximately 90% mortality without liver transplantation (LT). Patients may develop progressive central nervous system symptoms of lethargy, confusion, and coma, requiring intubation. Lactic acidosis is a poor prognostic marker in

<table>
<thead>
<tr>
<th>Stage I (first 24 h)</th>
<th>Nausea, vomiting, malaise, lethargy, diaphoresis (some patients remain asymptomatic)</th>
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<tbody>
<tr>
<td></td>
<td>AST/ALT are typically normal (AST/ALT may begin to rise at 8–12 h after massive overdose)</td>
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<tr>
<td>Stage II (24–72 h)</td>
<td>Stage I symptoms usually improve or resolve (so-called latent period)</td>
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<tr>
<td></td>
<td>Subclinical AST/ALT elevation</td>
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<td></td>
<td>In severe cases, RUQ pain, tender hepatomegaly, jaundice, and prolonged PT may be seen</td>
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<td></td>
<td>Nephrotoxicity (elevated creatinine and oliguria) may become evident</td>
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<tr>
<td>Stage III (72–96 h)</td>
<td>Systemic symptoms of stage I reappear</td>
</tr>
<tr>
<td></td>
<td>AST/ALT elevation, typically peak at 72–96 h after ingestion</td>
</tr>
<tr>
<td></td>
<td>(often &gt;3000 IU/L)</td>
</tr>
<tr>
<td></td>
<td>Jaundice, encephalopathy, prolonged PT, and lactic acidosis may develop</td>
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<td></td>
<td>ARF (10%–50%) and acute pancreatitis (0.3%–5%) may develop</td>
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<tr>
<td></td>
<td>Death often in this stage, usually from multiorgan system failure</td>
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<tr>
<td>Stage IV (96 h–2 wk)</td>
<td>Survivors of stage III enter recovery phase, which often lasts 1–2 wk, but may take several weeks in severe cases</td>
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<td>Histologic recovery occurs slower than clinical recovery and may take up to 3 mo</td>
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<td>When recovery occurs, it is complete; chronic hepatitis has not been reported</td>
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</tbody>
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Abbreviations: ALT, alanine aminotransferase; ARF, acute renal failure; AST, aspartate aminotransferase; PT, prothrombin time; RUQ, right upper quadrant.
APAP hepatotoxicity that can manifest as two scenarios: early onset after massive overdose and before the onset of hepatotoxicity in which large amount of NAPQI critically inhibits mitochondrial function; and later in course, usually after Day 2, resulting from tissue hypoxia together with decreased hepatic clearance of lactate in those with ALF.\textsuperscript{57} Notably, central nervous system symptoms and metabolic acidosis early in the course of disease (stage I) are not common features of APAP toxicity, and other possible causes should be excluded, particularly coingestion of other substances.

Acute renal failure develops in 10% to 25% of patients with significant hepatotoxicity and is encountered in more than 50% of those with ALF.\textsuperscript{58,59} It often becomes evident around 1 to 3 days after ingestion and often manifests as acute tubular necrosis, either alone or in combination with hepatic necrosis.\textsuperscript{58,59} The mechanism of nephrotoxicity is thought to be related to the toxic metabolites of APAP oxidized by CYP in the kidney.\textsuperscript{59} Acute renal failure is typically reversible, although it may worsen over 7 to 10 days and occasionally may require renal replacement therapy before the recovery occurs.\textsuperscript{58,59} An elevated serum amylase is frequently seen in patients with APAP poisoning particularly in patients with ALF, whereas clinical acute pancreatitis occurs rarely (0.3%–5%).\textsuperscript{60,61} Several cases of severe acute pancreatitis associated with APAP, however, have been reported,\textsuperscript{60,61} and therefore the possibility of APAP poisoning should be kept in mind in patients presenting with ALF and pancreatitis.

Clinical presentation of patients with single overdose versus repeated overdoses is somewhat similar. Patients who unintentionally ingest above the therapeutic APAP doses are more likely to present late (when hepatotoxicity is already recognized clinically) and are more likely to have known risk factors for hepatotoxicity, especially chronic alcohol use.\textsuperscript{32,62} In addition, this group of patient tends to have higher rates of morbidity and mortality than those who attempted suicide, even though the latter had taken higher total amount of APAP.\textsuperscript{32,62,63}

**GENERAL APPROACH AND DIAGNOSTIC TOOLS**

General approach promptly begins with careful history taking and physical examination. The precise time and amount of APAP intake, and 4-hour APAP level, or as soon thereafter as feasible, should be obtained. Other tests, such as hepatic biochemical tests, creatinine, and electrolytes, may also be useful, particularly in patients with repeated overdoses and those who present more than 8 hours after ingestion. Investigations for possible coingested substances and other causes of hepatitis may be required especially in those with an uncertain history.

Given the consequences of missed APAP poisoning, a screening for APAP seems reasonable in patients with unknown or possible drug overdose, or in those with indeterminate hepatitis and ALF.\textsuperscript{1,64} Notably, interpretation of serum APAP levels should be done with caution in patients with serum bilirubin greater than 10 mg/dL because bilirubin interference can cause falsely positive or elevated APAP concentration measuring by enzymatic method.\textsuperscript{65} Conversely, serum APAP concentration may already be negative at the time of established hepatotoxicity, thus not eliminating the possibility of APAP etiology for liver injury.

**Evaluations After Acute Single Overdose**

The Rumack-Matthew nomogram is a valuable tool for handling patients with single acute ingestion who present to a health care facility within 24 hours (Fig. 2).\textsuperscript{1,66–70} This nomogram was constructed in the 1970s to estimate the likelihood of hepatotoxicity caused by APAP for patients with a single ingestion at a known time.\textsuperscript{1,66–70} To use the nomogram, patient’s serum APAP concentration is plotted in line with time interval
Patients with an APAP level above a line between 200 mg/mL at 4 hours and 25 mg/mL at 16 hours after ingestion, known as the “200 line” or the “probable toxicity line,” are at risk for developing severe hepatotoxicity (defined as AST >1000 IU/L) in which N-acetylcysteine (NAC) treatment is recommended even in the absence of clinical or laboratory evidence for toxicity at the time. Without NAC treatment, patients with APAP concentrations above the “200 line” have an approximate 60% incidence of severe hepatotoxicity with 5% mortality. Patients with APAP concentrations above the parallel “300 line” or “high toxicity line” have a subsequent 90% incidence of severe hepatotoxicity with 24% mortality. After the generation of these data, the FDA then imposed an arbitrary 25% safety margin on the “200 line,” which resulted in a parallel line staring at 150 mg/mL at 4 hours, known as the “150 line” or the “treatment line,” and that has been most commonly used in the United States, and in Australia and New Zealand. Although controversy remains, this margin of safety was created to allow for possible errors in the estimated time of ingestion and variation in measured APAP concentration. Treatment outcomes using both the original “200” and the lower “150” lines in the US nationwide NAC study of more than 2500 patients demonstrated a very small rate of nomogram failure, especially with the “150 line.” In addition, the 25% safety margin is also likely to protect hepatotoxicity in high-risk populations, and there is no further convincing evidence to support lowering the treatment line. Thus, using a more conservative “100 line” significantly increases the number of patients being overtreated and also the overall associated cost. In general, a single-time APAP concentration plot on the nomogram is adequate to justify NAC treatment. The caveat from this outcome...
nomogram is that a small change in historical timing can make a huge difference in which segment the patient is classified. If there is any question regarding the history, and the patient is anywhere close to the treatment line, NAC is indicated.35

It should be noted that the Rumack-Matthew nomogram was developed for single overdose with precise time of ingestion. Therefore, it cannot accurately assess risk after repeated overdoses, acute overdose of a sustained-release product, or when the time of ingestion is unknown or patients present beyond 24 hours, and these situations represent nearly half of APAP overdoses in the United States.1,8,9,15,76

Evaluations After Repeated Overdoses

Patients with therapeutic misadventure often present after several days of ingestion with symptoms in which hepatotoxicity may have already begun. They are likely to develop hepatotoxicity if they have significant symptoms and clinical signs (eg, recurrent vomiting, confusion, liver tenderness, and jaundice) or have ingested an amount of APAP above the threshold (discussed previously). Serum APAP concentration should be measured, but the Rumack-Matthew nomogram is not applicable in this setting. Based on limited evidence, patients with supratherapeutic APAP levels of more than 20 μg/mL (or >10 μg/mL in patients with risk factors for toxicity) are at risk for developing subsequent hepatotoxicity, and therapy with NAC is suggested even if their ALT levels are normal.1,15,69 Treatment with NAC seems unnecessary if serum APAP is undetectable or less than 10 μg/mL in asymptomatic patients with normal ALT. Patients with a history of excessive APAP intake and who have elevated ALT levels should receive NAC treatment even with undetectable serum APAP (Box 1).1,15,69

Evaluations After Established Hepatotoxicity and Liver Failure

Cautious monitoring of clinical and laboratory parameters is vital, because greater than 90% of cases with APAP hepatotoxicity can be expected to resolve spontaneously.15,77 However, patients with clinical signs indicating ALF (eg, encephalopathy, coagulopathy, and acidosis) should be transferred to an intensive care unit and a facility where LT is available.78,79 Apart from a specific antidote, the general evaluation and management of ALF from APAP are not much different from ALF from other causes.79–81 Although APAP-induced ALF is associated with more favorable outcomes compared with all other causes of ALF, it still has a high mortality (~30%) without LT.6,8,15,77 LT-free survival rate seems to be similar between intentional and unintentional overdose groups.8 To identify those patients with ALF who are unlikely to survive without LT, several clinical features and laboratory parameters have been evaluated and prognostic models have been developed. One of the most widely used prognostic models was developed at King’s College in London, United Kingdom (Box 2).15,81–83 Based on differences in prognosis, King’s College criteria categorized patients into two groups: non-APAP and APAP-induced ALF. Without LT, patients with APAP-induced ALF who met the criteria had very high mortality (80%–90%)15,82,83 and as such these patients deserve consideration of LT. Although it is the best prognostic model available to date wherein LT-free survival has been evaluated, it still suffers from a variability in its negative predictive value and sensitivity, and thus the challenge in the listing for LT. Several studies evaluating this criteria have shown positive predictive values ranging from 70% to 95% and negative predictive values ranging from 40% to 90%.8,15,78,81–86 Overall, King’s College criteria have proved to have acceptable specificity (<20%–30% of those who met the criteria survived spontaneously) but relatively low sensitivity to determine outcome, in that many patients who would ultimately require LT may be missed.8,15,78,81–86 Nonetheless, it is still the most validated and
Box 1
*N*-acetylcysteine: indications, dosing, and monitoring

**Indications**
- Asymptomatic patients with single overdose: Serum APAP level above the “150 line” on Rumack-Matthew nomogram
- Asymptomatic patients with repeated overdoses: Serum APAP level above therapeutic range (>20 μg/mL) or above >10 μg/mL in patients with significant risk factors, such as chronic alcohol consumption
- Any patient with acute elevations of AST/ALT and a history of ingesting >4 g of APAP per day, irrespective of serum APAP level

**Standard dosing**
- IV regimen: loading 150 mg/kg in 200-mL diluent in 1 hour, then 50 mg/kg in 500-mL diluent over 4 hours, and 100 mg/kg in 1000-mL diluent over 16 hours (IV NAC solution is hyperosmolar and is compatible with D5W, 0.45% NSS, and sterile water)
- Oral regimen: loading 140 mg/kg, then 70 mg/kg orally every 4 hours for 18 doses in total
- Dose adjustment in patients with moderate/severe renal or liver impairment is not required

**Monitoring**
- For patients with especially high risk for developing hepatotoxicity\(^b\), rechecking APAP and ALT levels is recommended before completion of NAC. NAC can be stopped if APAP <10 μg/mL and normal ALT. If APAP ≥10 μg/mL or elevated ALT, NAC should be continued and be reevaluated after 12 hours
- For patients with severe hepatotoxicity or ALF, NAC infusion should be continued (6.25 mg/kg/h) until the patient receives LT or liver dysfunction reverses (ALT or AST have peaked and are improving, encephalopathy resolves, and INR <1.5) with undetectable APAP level.

**Abbreviations:** ALF, acute liver failure; ALT, alanine aminotransferase; APAP, acetaminophen; AST, aspartate aminotransferase; D5W, 5% dextrose in water; INR, international normalized ratio; IV, intravenous; NAC, N-*acetylcysteine; NSS, normal saline solution; PT, prothrombin time.

\(^a\) IV regimen is preferred for patients with ALF and those who have contraindications to oral administration (eg, coma, pancreatitis, bowel ileus or obstruction).

\(^b\) Patients who present 8 hours after ingestion, have an elevated ALT before NAC treatment, or have a very high APAP concentration (>300 μg/mL).

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Box 2
King’s College criteria for acetaminophen-induced acute liver failure

**Indications**
- Arterial pH <7.3 or blood lactate >3 mg/dL (0.33 mmol/L); after adequate volume resuscitation, irrespective of the grade of encephalopathy
- OR
- Blood lactate >3.5 mg/dL (0.39 mmol/L); after early volume resuscitation
- OR three of the following
- Grade III or IV encephalopathy AND
- Prothrombin time >100 seconds (or INR >6.5) AND
- Serum creatinine >3.4 mg/dL (or >300 μmol/L)
clinically useful prognostic model for APAP-induced ALF and one that has been adopted by most transplant centers and by the American Association for the Study of the Liver.8,15,78,81–86 The Model of End-stage Liver Disease (MELD) is also useful in APAP-induced ALF, but has not proved to be a better discriminator than the King’s College criteria or international normalized ratio (INR) alone.87 The sequential organ failure assessment score, originally designed for grading dysfunction of multiple organ systems, has been shown to be prognostically superior to the King’s College and MELD criteria for APAP-induced ALF caused by single and repeated overdoses.88–90 However, the use of sequential organ failure assessment score to justify LT requires further evaluation. Acute Physiology and Chronic Health Evaluation II score of greater than 15 on admission has been noted to be a sensitive tool to predict progression to ALF and was more sensitive than the King’s College criteria on the day of admission.8,91 A score of greater than 20 was associated with a lower LT-free survival.8

Apart from medical issues, psychiatric problems and family support should also be evaluated before offering LT, especially in patients with intentional APAP overdose, because there remains a concern of the risk of reattempting suicide after LT.

**Roles of APAP-protein Adducts**

APAP-protein adducts are released into blood during hepatocyte lysis and the concentration of adducts in serum of overdose patients has correlated with toxicity.92 The detection of serum APAP–protein adducts by using high-pressure liquid chromatography with electrochemical detection has reliably identified APAP hepatotoxicity and thus may be a useful diagnostic test for ALF of unknown cause or unclear history, and for patients who present more than 1 day after overdose.64,92,93 Interestingly, up to 19% of indeterminate cases in the US-ALF study demonstrated adducts in serum suggesting that unrecognized APAP toxicity caused or contributed to ALF in these patients.64,93 In addition to the application for diagnosis, the role of APAP-protein adducts for determining prognosis and for justifying intervention warrants further study. Unfortunately, the measurement of this adducts is sophisticated and is not yet routinely available in most centers.

**MANAGEMENT OF APAP OVERDOSE**

**Gastrointestinal Decontamination**

Activated charcoal is effective at limiting the absorption of APAP when given within 4 hours after overdose and is recommended in all patients who present early after APAP ingestion, unless there are contraindications (eg, unsecured airway or gastrointestinal tract injury).94–97 Patients who present 4 hours after ingestion are unlikely to benefit from activated charcoal, except in those who ingested extended-release APAP preparations or coingested drugs that delayed gastric emptying time. Gastric lavage and induced emesis are not routinely recommended because they seem to be less effective and have no additional benefit when activated charcoal is given.96,97

**N-Acetylcysteine**

NAC, a GSH precursor, is an established antidote for APAP poisoning and should be administered in all patients with APAP hepatotoxicity or in patients at significant risk for developing hepatotoxicity. The key to effective treatment is to initiate therapy before the onset of ALT elevation. When given early after acute APAP overdose, NAC provides cysteine for the replenishment and maintenance of hepatic GSH stores, thus providing more substrate for the detoxification of the reactive metabolites. Furthermore, it may also enhance sulfation pathway and directly reduce NAPQI
There has been no randomized placebo-controlled trial (such trials were considered unethical) evaluating the efficacy of NAC for APAP overdose. Several case series have observed that severe hepatotoxicity was uncommon (<5%–10%) when NAC was administered within 8 hours after acute APAP overdose, whereas delays beyond 10 hours were associated with an increased risk of hepatotoxicity (20%–30%). Patients with established liver injury may also benefit from NAC because it has been shown to improve LT-free survival among patients with APAP-induced ALF (~20%–30% reduction in mortality). Instead of detoxifying NAPQI, the potential mechanisms of NAC in this state are of improving hepatic perfusion and oxygen delivery, scavenging reactive oxygen and nitrogen species, and refining mitochondrial energy production. Apart from APAP hepatotoxicity, the beneficial effects of NAC have also been observed in patients with early comorbid encephalopathy and with non-APAP ALF.

NAC is available in oral and IV forms and their standard regimens (FDA-approved protocols) are different in the total dose and duration of treatment (see Box 1). The doses of NAC are calculated using patient body weight with a maximum of 110 kg for oral and 100 kg for IV therapy. An observational study of APAP poisoning in patients weighing more than 100 kg found that maximum weight cut-off and actual weight-based NAC dose were safe, but clinicians preferred the latter and hepatotoxicity was similar (up to 33%) with both strategies.

The choice of oral or IV administration depends on the clinical scenario, and a head-to-head comparison trial has not been performed in adults. Nevertheless, most available data suggest that both treatment strategies are safe and equally effective, and with minimal differences, in most circumstances. Oral NAC has an unpleasant taste and smell and vomiting is common. Nausea and vomiting can be reduced by diluting NAC with soda or juice, holding one’s breath while taking the medication, or administering by a nasogastric tube. Eventually, about 5% of patients may not tolerate oral NAC and require IV therapy. Anaphylactoid reactions (eg, rash, itching, angioedema, bronchospasm, tachycardia, and hypotension) develop in 10% to 20% of patients treated with IV NAC. Patients with flushing alone or mild symptoms do not require intervention and the infusion can be continued with careful monitoring. Patients who develop urticaria, angioedema, hypotension, and bronchospasm should be treated with one or more medications of diphenhydramine, corticosteroids, and bronchodilators. The infusion should be stopped and can be restarted at a slower rate and with close monitoring. In a randomized trial, slowing the initial infusion time from 15 minutes to 60 minutes had not compromised efficacy but also did not lower the incidence of anaphylactoid reactions. IV regimen is preferred for patients with ALF and those who refuse, or have a contraindication to oral administration (eg, coma, pancreatitis, bowel ileus or obstruction).

Given the disparity between a prespecified treatment duration of the two regimens, alternative dosing schedules have been further studied; the 72-hour oral course seems to be too long and the 20-hour IV course may be too short. Shorter courses of oral NAC (20–48 hours) have been evaluated and seem to be effective, particularly if a repeat APAP level is less than 10 μg/mL and there was no increase in serum ALT or INR after a minimum treatment duration of 20 hours. Alternative 48-hour IV regimen (140 mg/kg loading followed by 12 doses of 70 mg/kg every 4 hours) is also effective in APAP overdose patients who present within 24 hours. Some experts have recommended an individualized approach for IV NAC by repeating APAP and ALT levels at the end of a 16-hour infusion period and continuing treatment if the ALT was elevated or if APAP concentration was detectable. This strategy may be particularly important in the patient who presents 8 hours after ingestion; has an
elevated ALT at the time NAC is started; or has a very high APAP concentration (>300 μg/mL). The treatment guideline for single or repeated overdoses with severe hepatotoxicity or ALF is not well defined. However, most experts have advised a standard IV regimen while continuing a final infusion rate of 6.25 mg/kg/h until the patient receives LT or hepatotoxicity reverses (ALT or AST have peaked and are decreasing, encephalopathy resolves, and INR <1.5) with undetectable serum APAP concentration.\(^1,69,103,116\)

**Liver Transplantation**

LT is life-saving in those APAP overdose patients who progress to severe ALF. Several prognostic parameters or criteria have been identified to facilitate the decision-making with regard to the need for LT (discussed previously). A large experience of 1144 ALF cases (54% were APAP-related) from the US Acute Liver Failure Study Group has observed that APAP patients, compared with non-APAP patients, had better 2-year survival in those not transplanted but lower survival in those transplanted, indicating a good discriminatory ability of the physicians in observing versus transplanting those with APAP-ALF.\(^7\) In this analysis, patients were classified into three groups: (1) not listed for LT (N = 697); (2) listed but not transplanted (N = 177); and (3) listed and transplanted (N = 270). The 2-year survival among non-APAP and APAP etiology in Groups 1, 2, and 3 was 34% and 31%, 83% and 59%, 53% and 72%, respectively.\(^7\) Notably, a significant number of patients did not receive LT for a variety of reasons including milder disease and psychosocial disqualifiers.\(^7\) In another experience of 858 patients admitted with APAP-induced hepatotoxicity in the United Kingdom, 60 of 95 patients listed for LT underwent the procedure.\(^6\) Of 60 patients transplanted, 73% survived to discharge and 58% survived at an average of 9 years post-LT. When compared with patients who had LT from other causes of ALF, the incidence of psychiatric disease (principally depression) and 30-day mortality were greatest in the APAP group, but for those who survived beyond 30 days, there was no difference in long-term survival rates between APAP and non-APAP groups.\(^6\) Adherence to follow-up appointments and compliance with immunosuppressive regimens were lower in the APAP overdose group, and was not predicted by any identifiable premorbid psychiatric conditions.\(^6\)

**Other Treatment Modalities**

Other potential treatment options for APAP hepatotoxicity have been evaluated chiefly by three main mechanisms of action: (1) modulation of APAP metabolism, (2) modulation of cytokines and chemokines and the innate immune system, and (3) modulation of oxidative stress-related injury. Cimetidine, an inhibitor of CYP enzymes, theoretically may decrease the formation of NAPQI. In animal models, protection against APAP hepatotoxicity using a combination of cimetidine and NAC was better than that found with either agent alone.\(^117\) However, the use of cimetidine as an adjunct to NAC has shown no benefit in human studies.\(^118,119\) Several biologic agents, such as inducible protein-10, macrophage inducible protein-2, interleukin-6, -11, -22, and anti-interferon-γ, have been demonstrated to decrease susceptibility for APAP toxicity in experimental models.\(^120,121\) Telmisartan\(^122\) and coenzyme Q10\(^123\) can alleviate oxidative stress injury associated with APAP in animal models. However, to our knowledge, none of these agents have come to the clinical phase of study.

**REFERENCES**


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