Guidelines for the Management of Acetaminophen Overdose
Guidelines for the Management of Acetaminophen Overdose

This brochure outlines basic steps in the management of acetaminophen overdose and reviews the application of these management principles to special populations. It is a revision of previous publications and should be used in place of earlier versions. Included herein are flowcharts for managing both acute and chronic acetaminophen overdose, and a nomogram, which uses acetaminophen serum concentrations at various time intervals following a single, acute overdose to determine whether the antidote should be administered.

In January 1985, the United States (US) Food and Drug Administration (FDA) approved the oral administration of acetylcysteine (N-acetylcysteine, NAC) as an antidote for the treatment of acetaminophen overdose. Approval of acetylcysteine for this purpose was based on a nationwide research program conducted by the Rocky Mountain Poison and Drug Center under the sponsorship of McNeil Consumer Healthcare. This research clearly demonstrated the efficacy of acetylcysteine, when used early in the course of treatment, in reducing morbidity and virtually eliminating mortality associated with acetaminophen overdose. In 2004, the FDA approved the intravenous formulation of acetylcysteine (Acetadote®, Cumberland Pharmaceuticals, Nashville, TN). 

This monograph is intended to assist practitioners in managing acetaminophen overdoses and is not meant as a standard of care. For further information concerning complex or difficult cases, please contact your local poison center (1-800-222-1222) or a clinical toxicologist. McNeil Consumer Healthcare sponsors a toll free telephone number (1-800-525-6115), available 24 hours a day, at the Rocky Mountain Poison and Drug Center. Please do not hesitate to use these resources if you need individualized consultation on managing a patient with an acetaminophen overdose.

If you would like additional information about TYLENOL® (acetaminophen), or additional copies of this management protocol, please contact us at the address below.

McNeil Consumer Healthcare
7050 Camp Hill Road
Fort Washington, PA 19034

Prepared by the consultant panel:
G Randall Bond, MD
E. Martin Caravati, MD, MPH
Richard C. Dart, MD, PhD
Kennon Heard, MD
Robert S. Hoffman, MD
Barry H. Rumack, MD
Wayne R. Snodgrass, MD, PhD

With support from McNeil Consumer Healthcare Division of McNEIL-PPC, Inc.
# Table of Contents

**Guidelines for the Management of Acetaminophen Overdose** 38

**Table of Contents** 39

**Introduction** 40

**Definitions** 41

**Management of Acute Overdose** 42

1. Initial Assessment 42
2. Gastric Decontamination/Prevention of Absorption 42
3. Determining the Need for Acetylcysteine 43
   - Acetaminophen Assay 43
4. Administration of Acetylcysteine 43
   - a. Choose a route of administration 43
   - b. Transitioning from oral to intravenous acetylcysteine treatment 44
   - c. Continuation of acetylcysteine treatment 44
5. Other Laboratory Tests 44
6. Supportive Treatment 44
7. Special Considerations 45
   - a. Extended release acetaminophen 45
   - b. Ingestion of acetaminophen combination products 45
   - c. Massive acetaminophen ingestion 45
   - d. Intravenous acetaminophen 45
8. Special Populations 46
   - a. Young children (<6 years of age) 46
   - b. Pregnant women 46
   - c. Patients presenting 24 hours or more postingestion 46
   - d. Chronic alcohol users 46
   - e. Obese patients 46
   - f. Other diseases 46

**Management of Repeated Chronic Supratherapeutic Ingestion** 47

**Clinical Characteristics of Acute Acetaminophen Overdose** 48

- Phase I 48
- Phase II 48
- Phase III 48

**Summary** 49

**Acetaminophen Overdose: Suggested Readings** 54

**List of Figures, Flowcharts, and Charts**

- **Flowchart 1.** Stepwise Management of Acute Acetaminophen Overdose 50
- **Flowchart 2.** Stepwise Management of Repeated Supratherapeutic Ingestion 51
- **Chart 1.** Rumack-Matthew Nomogram 52
- **Chart 2.** Common Adverse Events Associated with the Oral and Intravenous Formulations of n-acetylcysteine 53
An overdose of acetaminophen may result in severe liver injury. Acetylcysteine is an effective antidote to prevent or limit liver injury in patients with potentially toxic acetaminophen levels or evidence of liver injury.
Definitions

Overdosage of acetaminophen can occur following an acute overdose or during repeated overdose. Acute acetaminophen overdose is defined as an ingestion of a toxic amount of acetaminophen occurring within a period of 8 hours or less. In adults and adolescents, hepatotoxicity may occur following ingestion of greater than 7.5 to 10 grams (g) (eg, 24 regular-strength or 15 extra-strength caplets or tablets) over a period of 8 hours or less. Fatalities are infrequent especially when treated with acetylcysteine (0.3% of treated cases).

A chronic overdose is termed repeated supratherapeutic ingestion (RSTI) to differentiate from chronic therapeutic use. Ingestion of a toxic amount over a period greater than 8 hours is considered a repeated supratherapeutic ingestion.

*Acetylcysteine* is the official term designated by USAN (United States Adopted Names) for N-acetylcysteine.
Management of Acute Overdose

To achieve optimal outcome following acetaminophen overdose, a systematic management approach is needed. This section outlines basic steps in managing acute acetaminophen overdose, consistent with FDA approved labeling of acetylcysteine. Flowchart 1 outlines this stepwise approach.

1. Initial Assessment

Adults or adolescents (≥12 years of age) who may have ingested acetaminophen in a purposeful overdose, independent of the amount reported to have been ingested, should be referred for medical evaluation. Their evaluation includes careful estimation of the quantity and dosage form of the acetaminophen ingested as well as assessment of any other substances ingested. The acetaminophen level should be determined at 4 hours post ingestion or as soon as possible thereafter (see also Special Considerations).

Patients who present with a measurable acetaminophen level and no clear time of exposure represent a treatment challenge and there is substantial practice variation. In some cases it is possible to develop a “worst case scenario” for the time of ingestion (e.g. the patient was with their family until 12 hours prior to presentation so ingestion could not have occurred more than 12 hours prior). In these cases, the earliest possible time of ingestion should be used to plot the acetaminophen level on the nomogram (Chart 1). If the time of ingestion is completely unknown, the most conservative approach is to initiate treatment and continue acetylcysteine until the acetaminophen level is undetectable and there is no evidence of progressive hepatic injury (serum transaminases normal or near normal and stable over a 12 hour period).

There is substantial practice variation in the management of patients who have low level transaminase elevations and a questionable history of the time and amount of acetaminophen exposure. In many of these cases the acetaminophen level may be therapeutic or even undetectable. The most conservative approach in these cases is to initiate treatment and continue acetylcysteine until the acetaminophen level is undetectable and there is no evidence of progressive hepatic injury (serum transaminases normal or near normal and stable over a 12 hour period).

2. Gastric Decontamination/Prevention of Absorption

Gastric decontamination should be carried out according to standard treatment guidelines. Activated charcoal reduces the peak serum concentration of acetaminophen. This may reduce the 4 hour acetaminophen level and thereby decrease the number of patients requiring treatment with acetylcysteine. Activated charcoal may be given during the immediate postingestion period, especially in the case of a mixed drug overdose. Data supporting the efficacy of activated charcoal beyond 2 hours after ingestion are limited. Administration of activated charcoal does not require a change in subsequent administration of oral or intravenous acetylcysteine therapy.
3. Determining the Need for Acetylcysteine

Acetaminophen Assay

Rationale

The acetaminophen level provides the basis for determining the need to initiate or continue treatment with acetylcysteine. Either the plasma or serum acetaminophen level may be used; most hospitals determine the serum acetaminophen level. The serum acetaminophen level should be measured at 4 hours following ingestion of an acute overdose or as soon as possible thereafter. It is important to determine the time of ingestion accurately. If the ingestion occurred over a period of time, the time of the initial ingestion is used for plotting on the Rumack-Matthew nomogram (Chart 1). (For example, if the ingestion occurred over the period of 6 PM to 8 PM, the acetaminophen level could be drawn at 10 PM and would be plotted as a 4 hour level on the nomogram.)

When to obtain

Blood should be drawn immediately for the acetaminophen serum assay if 4 hours or more have elapsed post-ingestion. If less than 4 hours have elapsed post-ingestion, it is important to wait until the 4 hour point to draw blood. If the acetaminophen level is clearly in the toxic range (ie, above the treatment line on the Rumack-Matthew nomogram), dosing with acetylcysteine should be initiated immediately. Use of levels obtained before 4 hours has not been studied and may not be reliable. Such levels should not be plotted on the nomogram (Chart 1).

If an assay for acetaminophen cannot be obtained, it is necessary to assume that the overdose is potentially toxic and acetylcysteine treatment should be initiated. Treatment should continue for the full course of therapy or until an acetaminophen level can be obtained and is clearly below the treatment line on the nomogram (Chart 1).

Interpretation of acetaminophen assays

The Rumack-Matthew nomogram is used to interpret the acetaminophen level (Chart 1). If the initial acetaminophen level plots above the treatment line (starting at 150 mcg/mL at 4 hours), then acetylcysteine treatment is recommended. If the initial acetaminophen level, determined at least 4 hours following an overdose, plots below the treatment line described above, the risk of hepatotoxicity is minimal and acetylcysteine treatment is not necessary. If already initiated, the acetylcysteine treatment can be discontinued. (see also Special Considerations: Ingestion of acetaminophen combination products)

Only the initial acetaminophen level is used in making the decision to initiate or continue acetylcysteine treatment (see also Special Considerations: Extended-Release Acetaminophen and Ingestion of Acetaminophen, Combination Products). A complete course of acetylcysteine should be provided if the initial level is above the treatment line, even if subsequent acetaminophen levels plot below the treatment line.

4. Administration of Acetylcysteine

If a patient presents within 4 hours of an acute overdose, treatment with acetylcysteine should be withheld until acetaminophen assay results are available, provided that initiation of treatment is not delayed beyond 8 hours following the ingestion.

If a patient with a potential acetaminophen overdose presents for care more than 8 hours after ingestion, acetylcysteine should be administered immediately, regardless of the quantity of acetaminophen reported to have been ingested. It is important not to wait for results of the acetaminophen assay before initiating acetylcysteine.

There are multiple treatment protocols for managing acetaminophen overdoses. While there are substantial variations in treatment practices, we are presenting 2 commonly accepted treatment protocols.

The following procedures are recommended:

a. Choose a route of administration

Both intravenous and oral formulations of acetylcysteine are available and approved by the US FDA. The oral formulation has been used for many years in the United States. Intravenous administration has become the most common route of acetylcysteine treatment (www.acetadote.net); however, either the oral or intravenous drugs are acceptable for most patients.

The primary adverse events of concern with the intravenous formulation of acetylcysteine are anaphylactoid reactions such as pruritus and bronchospasm. In rare cases death has occurred. The primary adverse events with the oral formulation are nausea and vomiting which can lead to insufficient absorption of the administered dose. See Chart 2 for a list of common adverse events associated with the intravenous and oral formulations.

i) Intravenous administration

The US FDA approved regimen for the intravenous administration of acetylcysteine (Acetadote®) involves 3 sequential infusions over a total period of 21 hours. For patients with body weight above 40 kg, the loading dose is 150 mg/kg in 200 mL of 5% dextrose (DSW), infused over 60 minutes. The second infusion is 50 mg/kg in 500 mL D5W, infused over 4 hours (12.5 mg/kg/h). The third infusion is 100 mg/kg in 1000 mL D5W infused over 16 hours (6.25 mg/kg/h). In patients weighing less than 40kg, this dosing regimen provides too much free water and can cause hyponatremia and seizures. The package insert should be referenced when treating patients weighing less than 40kg.

ii) Oral administration

The US FDA approved dosage regimen of oral acetylcysteine involves a loading dose of 140 mg/kg followed by 17 doses of 70 mg/kg at 4 hour intervals (total duration of treatment, 72 hours). If the patient vomits the loading dose or any maintenance dose within 1 hour of administration, the patient should be switched to the intravenous formulation (see product prescribing information for complete details). Some toxicologists have adopted shorter courses of oral therapy based on their own specific clinical parameters*.

*This monograph is intended to assist practitioners in managing acetaminophen overdoses and is not meant as a standard of care. For further information and individualized consultation concerning complex or difficult cases, please contact your local poison center (1-800-222-1222) or a clinical toxicologist. McNeil Consumer Healthcare sponsors a toll-free telephone number (1-800-525-6115), available 24 hours a day, at the Rocky Mountain Poison and Drug Center.
b. Transitioning from oral to intravenous acetylcysteine treatment

If a clinician determines that a patient who has received oral acetylcysteine should be transitioned to intravenous acetylcysteine, we recommend the following approach:

i) If the patient has vomited a loading dose of oral acetylcysteine within 60 minutes, begin with the first infusion of the intravenous protocol.

ii) If the patient has received only a loading dose (140 mg/kg) of oral acetylcysteine and retained it for more than 60 minutes, begin intravenous treatment with the second infusion of the intravenous protocol (12.5 mg/kg/hour for 4 hours).

iii) If the patient has received the oral loading dose (140 mg/kg) and any subsequent oral doses (70 mg/kg), begin with the third infusion of the intravenous protocol (6.25 mg/kg/hour).

c. Continuation of acetylcysteine treatment

Acetylcysteine should be continued beyond the standard time based protocols for all patients with acetaminophen induced acute liver failure. Acute liver failure is defined by a rapid decline in hepatic function characterized by jaundice, coagulopathy (international normalized ratio (INR) >1.5), and hepatic encephalopathy in patients with no evidence of prior liver disease. Treatment may be stopped when the patient’s hepatic encephalopathy has resolved and their clinical condition is improving. The exact duration of treatment may vary.

i) Intravenous administration

In most cases, it is recommended that intravenous acetylcysteine treatment be continued until the patient is clearly improving or transplant is performed. A reasonable endpoint is an alanine transaminase (ALT) of <50% of peak values, an international normalized ratio (INR) <2.0* and an acetaminophen level <10 mcg/mL.

ii) Oral administration

In most cases, prolonged administration of acetylcysteine will utilize the intravenous route of administration. If administration of the oral solution is continued, a common approach is to continue the maintenance dose every 4 hours (eg, 70 mg/kg every 4 hours) until the patient is clearly improving or transplant is performed. A reasonable endpoint is an ALT of <50% of peak values, an INR <2.0* and an acetaminophen level <10 mcg/mL.

5. Other Laboratory Tests

i) In healthy, asymptomatic patients who present early after acute acetaminophen ingestion, only an acetaminophen level is needed.

ii) In a patient with an acetaminophen level above the nomogram treatment line, an ALT and aspartate transaminase (AST) level should be obtained. The ALT or AST should be determined at the end of acetylcysteine infusion (18-20 hours) and repeated every 12 to 24 hours until the patient recovers. If the ALT or AST remains elevated or the acetaminophen level is >10 mcg/mL, the acetylcysteine infusion should be continued until the patient is clearly improving or transplant is performed. A reasonable endpoint is an ALT <50% of peak values an INR <2.0* and an acetaminophen level <10 mcg/mL.

iii) A number of abnormal laboratory tests (prothrombin time (PT) or INR, bilirubin, phosphate, lactate and pH) are associated with a poor prognosis and should be assessed serially in patients with severe liver injury. When such abnormalities are present, consultation may be indicated*.

6. Supportive Treatment

i) It is important to monitor for signs and symptoms of hepatic failure and to provide appropriate supportive care.

ii) In cases in which fulminant hepatic failure develops, appropriate toxicology and/or hepatology consultation should be obtained. In rare cases, referral to a transplant center may be necessary.

*This monograph is intended to assist practitioners in managing acetaminophen overdoses and is not meant as a standard of care. For further information and individualized consultation concerning complex or difficult cases, please contact your local poison center (1-800-222-1222) or a clinical toxicologist. McNeil Consumer Healthcare sponsors a toll-free telephone number (1-800-525-6115), available 24 hours a day, at the Rocky Mountain Poison and Drug Center.
7. Special Considerations

a. Extended release acetaminophen

There are multiple products available that contain an extended release formulation of acetaminophen. In cases of overdose, the concern is that absorption of extended release acetaminophen is slower than that of immediate release acetaminophen. As a result, the acetaminophen level could plot below the treatment line of the nomogram at 4 hours, but rise above the treatment line with continued absorption.

i) After an acute overdose with an extended release acetaminophen product, the acetaminophen level should be measured at 4 hours after ingestion or as soon as possible thereafter. Because of differences in absorption rates, the significance of delayed rising levels is not clear. Some toxicologists recommend obtaining a second acetaminophen level 4 to 6 hours after the first measurement, whereas others do not. Until there is further evidence, it may be prudent to obtain a second level.

ii) If either of the acetaminophen levels plot above the treatment line of the nomogram, a full course of acetylcysteine treatment should be administered.

iii) If both levels plot below the treatment line, toxicity is unlikely and acetylcysteine treatment is not necessary and, if already initiated, can be discontinued.

b. Ingestion of acetaminophen combination products

The ingestion of acetaminophen-diphenhydramine or acetaminophen-opioid products have been associated with delayed elevations of the acetaminophen level. Patients with rising acetaminophen levels require closer management and may require prolongation of acetylcysteine treatment*. For patients with initial acetaminophen levels that are unexpectedly low, or with exposures involving the above combination products or additional drugs that could affect acetaminophen absorption, a second acetaminophen level at least 4 to 6 hours after the first measurement is recommended.

c. Massive acetaminophen ingestion

While the clinical effects of acetaminophen ingestion are generally delayed for many hours after the ingestion, there are reports of massive acetaminophen ingestion (greater than 50g) producing metabolic acidosis, lethargy, coma and hyperglycemia within 4 hours post ingestion. Clinicians should be aware of this unusual presentation of acetaminophen poisoning. Several of these reports describe successful treatment of these patients using standard acetylcysteine, but it may be prudent to treat longer than the standard 21 hour protocol if the acetaminophen level remains detectable.

d. Intravenous acetaminophen

Intravenous acetaminophen is approved for the short term treatment of mild to moderate pain and fever reduction in both adults and children in numerous countries worldwide and was recently approved in the United States. There have been several reports of young children experiencing a 10-fold dosing error. The timing of risk assessment, indications for acetylcysteine and optimal acetylcysteine dosing has not been established. Consultation with your local toxicologist or poison center is recommended*.
8. Special Populations
a. Young children (<6 years of age)
Serious toxicity and death have been extremely infrequent following an acute acetaminophen overdose in young children, possibly because of differences in acetaminophen metabolism. Oral overdoses in children should be managed in the same manner as adults, with a diagnostic acetaminophen level drawn at 4 hours post ingestion or as soon as possible thereafter. The dose of acetylcysteine is the same on a weight basis. However, in children who weigh less that 40 kg, the administration of acetylcysteine by the intravenous route should be altered because the dilution provides excessive free water and may result in symptomatic hyponatremia. Consult the Acetadote® package insert for information on handling these cases*.

b. Pregnant women
The use of acetylcysteine does not change for pregnant patients. (See Determining the Need for Acetylcysteine and Administration of Acetylcysteine)
c. Patients presenting 24 hours or more postingestion
An acetaminophen level and the serum ALT or AST concentration should be determined in patients presenting 24 hours or more postingestion. No further treatment is needed for patients without liver injury (ALT and AST levels are normal) if the acetaminophen level is also <10 mcg/mL.

In patients with an increased serum ALT and/or AST, treatment with acetylcysteine should be initiated. Evidence suggests that acetylcysteine treatment may improve survival in patients presenting late and may be appropriate almost any time after overdose ingestion. A controlled study reported that intravenous acetylcysteine improves survival in patients with established fulminant hepatic failure, caused by purposeful overdose of acetaminophen, who presented 36 to 80 hours postingestion*.

d. Chronic alcohol users
Chronic heavy alcohol users may be at an increased risk for hepatic injury and death following excessive acetaminophen use, although reports of this event are rare. In these cases, acetylcysteine treatment is recommended using the same indications for treatment and method of administration as described for other patients. (See Determining the Need for Acetylcysteine and Administration of Acetylcysteine)
e. Obese patients
The standard recommended doses of acetylcysteine are weight based for both the oral and intravenous protocols. There are no controlled data evaluating the safety and necessity of the high doses of acetylcysteine that would be given to obese patients. Although no data exist, the manufacturer of the intravenous acetylcysteine product recommends a maximum dose based on 100 kg (15 gm loading dose followed by 5 g over 4 hours followed by 62.5 mg/hr) for subjects who weigh more than 100 kg.
f. Other diseases
Several drug-disease interactions have been postulated for acetaminophen. These conditions include infectious hepatitis, alcoholism, malnourishment, treatment with medications known to induce cytochrome 2E1 (CYP2E1), acquired immunodeficiency syndrome (AIDS), starvation, and liver injury from another cause in the presence of acetaminophen use. No prospective data have supported concerns about using labeled doses of acetaminophen in these patients or addressed the management of these patients following an acetaminophen overdose. There is no evidence that these patients would benefit from a different risk assessment strategy or management approach, although some toxicologists will treat acetaminophen overdoses that occur in certain populations or in patients taking medication known to induce CYP2E1 (such as isoniazid or rifampin) at a lower threshold. It is recommended that these patient groups be treated in the same manner as other patients with acetaminophen overdose.

*This monograph is intended to assist practitioners in managing acetaminophen overdoses and is not meant as a standard of care. For further information and individualized consultation concerning complex or difficult cases, please contact your local poison center (1-800-222-1222) or a clinical toxicologist. McNeil Consumer Healthcare sponsors a toll-free telephone number (1-800-525-6115), available 24 hours a day, at the Rocky Mountain Poison and Drug Center.
Management of Repeated Chronic Supratherapeutic Ingestion

For patients 6 years or older, RSTI is defined as ingestion of: 1) at least 10g or 200 mg/kg (whichever is less) over a single 24 hour period, or b) at least 6 g or 150 mg/kg (whichever is less) per 24 hour period for the preceding 48 hours or longer. For patients younger than 6 years of age, RSTI is defined as ingestion of a) 200 mg/kg or more over a single 24 hour period, or b) 150 mg/kg or more per 24 hour period for the preceding 48 hours, or c) 100 mg/kg or more per 24 hour period for the preceding 72 hours or longer. The Rumack-Matthew nomogram cannot be used in these cases.

A number of patients have experienced liver injury following repeated supratherapeutic ingestion of acetaminophen. Most of these patients ingested large doses over a period of several days.

Patients who report a history of RSTI should have the acetaminophen level and transaminase activity determined. If the acetaminophen level is <20 mcg/mL AND the ALT or AST is normal, no treatment is indicated however the patient should be instructed on appropriate acetaminophen use. If either the ALT or AST is elevated OR the acetaminophen level is >20 mcg/mL, acetylcysteine is indicated.

The duration of acetylcysteine treatment has not been established for RSTI. A common approach for the treatment of RSTI is to treat the patient with acetylcysteine for 12 hours and then reevaluate. If the patient is clinically well, the ALT and AST are improving, and the acetaminophen level is <10 mcg/mL, acetylcysteine may be discontinued. Chronic users of alcohol are assessed and treated for RSTI in the same manner as other patients. A stepwise guide for managing repeated supratherapeutic acetaminophen overdose is provided in Flowchart 2*.

*This monograph is intended to assist practitioners in managing acetaminophen overdoses and is not meant as a standard of care. For further information and individualized consultation concerning complex or difficult cases, please contact your local poison center (1-800-222-1222) or a clinical toxicologist. McNeil Consumer Healthcare sponsors a toll-free telephone number (1-800-625-6115), available 24 hours a day, at the Rocky Mountain Poison and Drug Center.
Clinical Characteristics of Acute Acetaminophen Overdose

The principal toxic effect of a substantial acetaminophen overdose is hepatic injury. Normally, acetaminophen metabolism involves 3 separate pathways: (1) conjugation with glucuronide (glucuronidation); (2) conjugation with sulfate (sulfation); and (3) metabolism via the cytochrome P450-dependent mixed function oxidative enzyme pathway to form a reactive intermediate metabolite. The reactive intermediate metabolite formed through the P450 pathway conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The acetaminophen glucuronide, acetaminophen sulfate, and glutathione derived metabolites are not toxic. Thus, toxicity does not occur with normal therapeutic use.

Following a substantial overdose, however, the amount of reactive intermediate metabolite produced may increase markedly. The amount of glutathione available in the liver may become insufficient to conjugate and detoxify the reactive intermediate metabolite. It is estimated that when the amount of available glutathione is reduced to approximately 30% of normal, the reactive intermediate metabolite binds to hepatic cell macromolecules, producing cellular necrosis. The exact mechanism of hepatocellular damage is not known, but is reflected by a rise in serum transaminases. With increasing hepatocellular necrosis, hepatic dysfunction occurs. In severe cases, this may proceed to hepatic failure.

Signs and symptoms of acetaminophen overdose, during the initial management phase, show a typical pattern but are not diagnostic or predictive of risk. The clinical course of acetaminophen overdose generally occurs in a 3-phase sequential pattern:

Phase I
The first phase begins shortly after ingestion of a potentially toxic overdose and lasts for 12 to 24 hours. The patient may manifest signs of gastrointestinal irritability, nausea, vomiting, anorexia, diaphoresis, and pallor. The larger the overdose, the more likely it is that these symptoms are present. Coma or other evidence of central nervous system depression is usually not present unless the patient has taken a massive overdose or has also ingested central nervous system depressants, as may be the case in suicide attempts. Coma accompanied by severe metabolic acidosis has rarely been reported following acetaminophen overdose, but the loss of consciousness was thought to be secondary to the metabolic acidosis rather than the acetaminophen itself. In small children, spontaneous vomiting following a substantial overdose occurs frequently and may play a role in the reduced risk of toxicity in children. However, these symptoms are not unique to acetaminophen, and unless the possibility of acetaminophen overdose is considered during this early phase, it may be overlooked. Many patients with early symptoms never progress beyond the first phase and recover without additional problems.

Phase II
If toxicity continues or is to ensue, there is a latent phase in terms of clinical findings of up to 48 hours. Initial symptoms abate and the patient may feel better. However, hepatic enzymes, bilirubin, lactate, phosphate, and prothrombin time or INR values will progressively rise, with hepatic enzymes often rising to striking levels. Right upper quadrant pain may develop as the liver becomes enlarged and tender. Most patients do not progress beyond this phase, especially if given acetylcysteine treatment. The subsequent clinical course is characterized by a gradual return of liver enzyme tests to normal.

Phase III
A few patients will develop serious hepatic necrosis. Signs and symptoms of this third phase of the clinical course depend on the severity of hepatic damage and usually occur from 3 to 5 days following ingestion. The peak AST and ALT occurs between 72 to 96 hours post ingestion. Symptoms may be limited to anorexia, nausea, general malaise, and abdominal pain in less severe cases or may progress to confusion, stupor, and sequelae of hepatic necrosis including jaundice, coagulation defects, hypoglycemia, and encephalopathy, as well as renal failure and cardiomyopathy. Death, if it occurs, is generally a result of complications associated with fulminant hepatic failure. Mortality rates in patients with toxic acetaminophen levels who do not receive antidotal therapy are in the range of 3% to 4%. In nonfatal cases, serial liver biopsies and liver enzyme tests have shown prompt resolution without significant residual functional or architectural alterations of the liver.
Acetaminophen overdose can be effectively managed by focusing on a few basic principles. As in all cases of poisoning, healthcare providers should obtain a careful history and should have a high index of suspicion. When acetaminophen overdose is a possibility, an acetaminophen level should be obtained and antidotal therapy should be initiated as indicated in these guidelines. When acetylcysteine is administered soon after an overdose occurs, morbidity is significantly reduced and mortality virtually eliminated. The prognosis for patients with acetaminophen overdose is excellent, provided treatment is given expeditiously and appropriately.
Flowchart 1. Stepwise Management of Acute Acetaminophen Overdose

**Estimate time of ingestion**

- **< 24h since overdose**
  - Administer activated charcoal if < 2h post ingestion
  - Determine acetaminophen level at 4h post ingestion*, or as soon as possible thereafter**
  - PLOT ON NOMOGRAM
  - Consider starting acetylcysteine treatment if acetaminophen level will not be available before 8 hours after ingestion^a

  - Serum level plots BELOW treatment line
    - Stop acetylcysteine
  - Serum level plots ABOVE treatment line^AA
    - Initiate (or continue) acetylcysteine
    - Obtain baseline tests (ALT and AST chemistries) and provide supportive care as indicated

- **> 24h since overdose**
  - Start acetylcysteine and manage in accordance with serum ALT and AST
    - (see Flowchart 2)

---

*Acetaminophen levels obtained before 4 hours after ingestion should not be used for risk stratification

**With extended-release preparations, serum acetaminophen levels drawn less than 8 hours post-ingestion may not represent peak levels. It may be prudent to obtain a second level 4 to 6 hours after the initial level was drawn.

^Acetylcysteine can be withheld until acetaminophen assay results are available as long as initiation of treatment is not delayed beyond 8 hours post-ingestion. If more than 8 hours post-ingestion, acetylcysteine treatment must be started immediately.

^AWith the extended-release preparation, provide acetylcysteine treatment if either level plots above the treatment line.

ALT=alanine transaminase; AST=aspartate transaminase
Flowchart 2. Stepwise Management of Repeated Supratherapeutic Ingestion

- **History of repeated supratherapeutic ingestion**

  - **Draw serum ALT and AST and acetaminophen level**

  - **ALT of AST >50 IU/L**
    - **OR**
    - **Acetaminophen >20 mcg/mL**

    - **Treat with acetylcysteine for 12 hours and reevaluate. Acetylcysteine may be discontinued if patient is clinically well, ALT and AST are improving, and acetaminophen level is <10 mcg/mL.**

  - **ALT and AST <50 IU/L**
    - **AND**
    - **Acetaminophen <20 mcg/mL**

    - **No further treatment needed**

**ALT** = alanine transaminase; **AST** = aspartate transaminase
Chart 1. Rumack-Matthew Nomogram

**Nomogram:** Acetaminophen plasma concentration versus time after acetaminophen ingestion (adapted with permission from Rumack and Matthew, Pediatrics. 1975;55:871-876). The nomogram has been developed to estimate the probability of whether an acetaminophen level in relation to the interval postingestion will result in hepatotoxicity and, therefore, whether acetylcysteine therapy should be administered. Values above the Rumack-Matthew line connecting 200 mcg/mL at 4 hours with 50 mcg/mL at 12 hours are reported to be associated with a potentially increased risk of hepatotoxicity if acetylcysteine is not administered. In order to err on the side of safety, a treatment line has been established that is 25% below the Rumack-Matthew line.

**Cautions For Use Of This Chart:**

1. Time coordinates refer to time postingestion.
2. Graph relates only to plasma (or serum) concentrations following a single, acute overdose ingestion.
3. The Treatment Line is plotted 25% below the Rumack-Matthew Line to allow for potential errors in acetaminophen assays and estimated time from ingestion of an overdose (Rumack et al. Arch Intern Med 1981;141(suppl):380-385).
Chart 2. Common Adverse Events Associated with the Oral and Intravenous Formulations of N-acetylcysteine.

<table>
<thead>
<tr>
<th>Intravenous</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Anaphylactoid</td>
<td>Other</td>
</tr>
<tr>
<td>Nausea</td>
<td>Bronchospasm</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Pruritus</td>
<td>Presyncope/syncope</td>
</tr>
<tr>
<td></td>
<td>Flushing</td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonurticarial rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chest tightness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Anaphylactoid</td>
<td>Other</td>
</tr>
<tr>
<td>Nausea</td>
<td>Bronchospasm</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Pruritus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td></td>
</tr>
</tbody>
</table>
Acetaminophen Overdose: Suggested Readings


