ACETAMINOPHEN POISONING:
A COMPREHENSIVE REVIEW
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ABSTRACT
Acetaminophen toxicity is the most common cause of acute liver failure in the United States, Europe, and Australia. Decisions made to treat acetaminophen toxicity are often determined by the age and at-risk presentation of the patient. The Rumack-Matthew nomogram is a proven highly sensitive tool to determine patients at risk and requiring treatment. Treatment may include the administration of acetylcysteine; and, the route of administration includes considerations of its efficacy, safety and cost. Poor outcomes can include liver failure and death. If treated promptly, patient recovery and survival from acetaminophen toxic overdose is almost assured.
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Statement of Need
In toxic overdosing, acetaminophen can cause liver damage and failure, and can lead to costly medical treatment and transplantation. Health teams need to understand the basis for diagnosis and treatment of acetaminophen overdose, which includes clinical manifestations of toxicity and use of the Rumack-Matthew nomogram to interpret acetaminophen plasma concentrations.
**Course Purpose**
This course will help nurses identify patients at risk of liver damage and failure due to acetaminophen toxic overdose and to know the appropriate treatment to support full recovery and survival.

**Learning Objectives**
1. Identify the toxic dose of acetaminophen.
2. Identify how acetaminophen damages the liver.
3. Identify the four criteria used to assess a patient who has taken an acetaminophen overdose of acetaminophen.
4. Identify the proper use of the Rumack-Matthew nomogram.
5. Identify the antidote used to treat acetaminophen poisoning.

**Target Audience:** Advanced Practice Registered Nurses, Registered Nurses, Licensed Practical Nurses, and Associates

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*Please take time to complete the self-assessment Knowledge Questions before reading the article. Opportunity to complete a self-assessment of knowledge learned will be provided at the end of the course.*
1) **Most acetaminophen is changed to harmless metabolites by:**
   a. conjugation  
   b. metabolism by cytochrome P-450 enzymes  
   c. elimination in the urine  
   d. elimination in the stool

2) **Acetaminophen is converted to a toxic metabolite by:**
   a. conjugation  
   b. metabolism by cytochrome P-450 enzymes  
   c. elimination in the urine  
   d. elimination in the stool

3) **The toxic dose of acetaminophen is:**
   a. ≥ 10 grams or 200 mg/kg  
   b. ≥ 7.5 grams or 150 mg/kg  
   c. ≥ 15 grams or 150 mg/kg  
   d. ≥ 20 grams 04 300 mg/kg

4) **The basis of acetaminophen poisoning is:**
   a. rate/amount of NAPQI formation greater than glutathione availability  
   b. rate/formation of conjugation is greater than glutathione availability  
   c. decrease in glutathione effectiveness  
   d. increased sensitivity of the liver to the drug
5) One organ other than the liver that is affected by an overdose of acetaminophen is:
   a. the lungs
   b. the small bowel
   c. the kidneys
   d. the thyroid

6) A massive overdose of acetaminophen can cause a rapid onset of:
   a. metabolic acidosis and coma
   b. arrhythmias and ARDS
   c. pancreatitis and congestive heart failure
   d. coma and myocardial infarction

7. The serum acetaminophen level must be measured _____ after an ingestion.
   a. 8 hours or more
   b. 4 hours or more
   c. 2 hours or more
   d. 10 hours or more

8. Organ damage other than hepatic or renal is common after acetaminophen overdose.
   a. True
   b. False
9. Laboratory tests used to evaluate cases of acetaminophen poisoning are:
   a. LFTs, BUN, creatinine, INR
   b. AST, CBC, and creatinine
   c. ALT, INR, and TSH
   d. AST, CK, and creatinine

10. The antidotal therapy for acetaminophen poisoning is:
    a. glucagon
    b. methylene blue
    c. sodium thiosulfate
    d. N-acetylcysteine (NAC)
INTRODUCTION

The American Association of Poison Control Centers (AAPCC) publishes annual reports documenting the number and nature of drug overdoses. The AAPCC data from 2012 (the latest available data) was similar to the data from almost every previous year. Acetaminophen was the most common drug taken in an overdose with intent to cause self-harm, and therapeutic errors with acetaminophen that caused liver damage are also quite common.\textsuperscript{1} Acetaminophen (the drug is called paracetamol in Europe) overdose is now the most common cause of acute liver failure in the United States, Europe, and Australia.\textsuperscript{2}

The majority of patients who have taken an overdose of acetaminophen and who are treated correctly and promptly will survive with no permanent damage; in more than 90\% of these cases, the patients will recover completely.\textsuperscript{3} However, there are hundreds of deaths every year in the United States caused by acetaminophen poisoning, and the mortality rates for patients with acute liver failure caused by acetaminophen overdose can be as high as 28\%.\textsuperscript{4}

ACETAMINOPHEN: PHARMACOLOGY

Acetaminophen is an over-the-counter analgesic used for mild to moderate pain and as antipyretic; it appears to have minimal anti-inflammatory action. Although it is not completely understood how acetaminophen works, it is thought to

\begin{quote}
The name acetaminophen, and the brand name Tylenol\textsuperscript{®}, are both derived from combinations of the letters of the chemical term for acetaminophen, N-acetyl-p-aminophenol.
\end{quote}
produce its analgesic/antipyretic effects by these mechanisms of action: ⁵,⁶

- It inhibits synthesis of prostaglandins in the central nervous system;
- It blocks pain impulse generation peripherally;
- It acts as an antipyretic by inhibiting the heat-regulating center of the hypothalamus.

**Learning Break:** Prostaglandins are hormone-like substances that are involved in sensitizing some neurons to pain and mediating many physiological functions, i.e., the inflammatory response.

In therapeutic doses, the drug is rapidly and completely absorbed from the gastrointestinal tract. The serum concentration of an oral dose peaks within 10 to 60 minutes, the onset of action is within one hour, and the therapeutic concentration is 10 to 20 μg/ml. ⁵,⁶ First pass metabolism removes approximately 25% of a therapeutic dose.

After absorption, approximately 90% of acetaminophen undergoes hepatic glucuronide and sulfate *conjugation*; the acetaminophen/sulfate and acetaminophen/glucuronic acid complexes are harmless and are eliminated in the urine. A very small amount of the drug is excreted unchanged in the urine, and the remainder (approximately 2% or less) is metabolized by several enzymes of the *cytochrome P450 enzyme system* to N-acetyl-benzoquinoneimine.

*Conjugation* is a process by which the acetaminophen is bound to glucuronic acid and sulfate.
(NAPQI). This metabolite is toxic to the liver and the kidneys. However, if acetaminophen is ingested in therapeutic doses, NAPQI is combined with glutathione and the NAPQI-glutathione complex is converted to non-toxic mercaptine or cysteine, both of which are excreted in the urine and bile. 

**Learning Break:** Glutathione (also known as GSH) is a tripeptide synthesized in the liver and in other organs. It acts an antioxidant and it is a very important part of the body’s defense system against free radicals and oxidative stress.

**Dosing, available forms, contraindications, side effects, and drug-drug interactions**

Currently the adult dose of acetaminophen is 325 mg to 650 mg, every 4 to 6 hours, and the total amount for 24 hours should not exceed 4 grams. The dose for children and adolescents > 12 years of age is the same as the adult dose. Children < 12 years of age, the dose is 10-15 mg/kg, every 4-6 hours, and the 24 hour total should not exceed 2.6 grams.

Acetaminophen is available in oral tablets, caplets, capsules, and geltabs; oral suspensions and solutions; rectal suppositories; and in an intravenous (IV) formulation. Acetaminophen is frequently added to over-the-counter cold and cough and allergy relief products, Triaminic®), over-the-counter medications used for sleep, and over-
the-counter analgesics. Opioid analgesics and acetaminophen are frequently combined, as well.

Acetaminophen is contraindicated if the patient has hypersensitivity to the drug or if the patient has severe hepatic impairment or severe active liver disease. It should be used cautiously if the patient has G6PD deficiency, consumes ≥ three alcoholic drinks a day, or has renal impairment. The oral form of acetaminophen is considered safe to use during pregnancy. Acetaminophen does enter breast milk, and the drug should be used cautiously by nursing mothers.

The side effects of acetaminophen are minimal. Common side effects are mild and temporary gastrointestinal distress and rash; rash is more common in children.

Drug interactions between acetaminophen and commonly used medications include:

- **Aripiprazole:**
  The serum concentration of aripiprazole may be increased.

- **Barbiturates:**
  The metabolism of acetaminophen may be increased, decreasing the effectiveness of acetaminophen and increasing the risk of liver damage.

- **Carbamazepine:**
  The metabolism of acetaminophen may be increased, decreasing the effectiveness of acetaminophen.
• Isoniazid:
  May enhance the toxic effects of acetaminophen.

• Peginterferon Alfa-2b:
  May decrease the serum concentration of CYP2D6 substrates.

• Prilocaine:
  Acetaminophen and prilocaine used together increase the risk of developing methemoglobinemia.

• Probenecid:
  The serum concentration of acetaminophen may be increased.

• Warfarin:
  Acetaminophen may enhance the anticoagulant effect of warfarin if the daily dose of acetaminophen is >1.3 grams for >1 week.

**ACETAMINOPHEN TOXICITY**

**Toxic dose level**

The toxic dose of acetaminophen was for many years considered to be ≥ 150 mg/kg or ≥ 7.5 grams, whichever was lower. These figures are almost certainly very conservative and the toxic dose may be 10 to 12 grams or more for an adult and > 250 mg/kg for children. The American Association of Poison Control Centers (AAPCC), in an evidence-based consensus, decided that the toxic dose of acetaminophen is ≥ 10 grams or 200 mg/kg, for an adult or a child and this appears to be the universally accepted figure.
In recent years concern has been raised that the maximum 24-hour therapeutic amount of acetaminophen and the amount considered to be potentially toxic are both too low. Poison control centers in the United Kingdom (UK) now use ≥75 mg/kg as the toxic dose, and it was decided in the UK that the treatment line on the Rumack-Matthew nomogram (the nomogram will be discussed later) should be lowered from 200 mcg/mL to 100 mcg/mL. The benefits of this approach are at this time uncertain, and, in the United States the dose that is considered to be toxic and the treatment line on the Rumack-Matthews nomogram have not been changed.

**Is the therapeutie dose toxic?**

There has been long-term concern that the 4-gram maximum recommended daily dose of acetaminophen may be too high and potentially harmful. In 2011, the Food and Drug Administration (FDA) asked manufacturers to limit the amount of acetaminophen to 325 mg in prescription combination drugs by January 2014, but no request was made to lower the 4 gram limit. In April 2014, the FDA recommended that a pharmacist who receives a prescription for a combination product with more than acetaminophen 325 mg per dosage unit should contact the prescriber to determine if a product with a lower dose of acetaminophen would be acceptable.

McNeil Pharmaceuticals, the manufacturer of the Tylenol® brand, has decreased the 24 hour maximum recommended dose of its acetaminophen-containing products to 3000 mg of the 500 mg preparations and 3250 mg of the 325 mg preparations. However, other manufacturers of acetaminophen products continue to use 4
grams as the limit and this is the maximum dose that will be found in pharmaceutical references.

There is evidence that 4 grams of acetaminophen can elevate the serum transaminases in both healthy individuals and in people who might be at risk for liver damage.\textsuperscript{14-24} Although these systematic reviews, meta-analyses, and prospective studies have shown that a daily 4 gram dose of acetaminophen can cause abnormally high serum transaminases, these high levels were:

1) not excessively high;
2) returned to normal in almost every case;
3) not associated with death, liver failure, or permanent liver damage;
4) from the literature reviewed of studies that in some cases examined over 30,000 patients, and;
5) of some patients in the case reports that had risk factors which have been associated with an increased susceptibility to damage from acetaminophen.

In addition, many people who received a 4-gram daily dose or doses of up to 8 to 12 grams a day did \textit{not} develop elevated transaminases.\textsuperscript{14,23}

The studies are not conclusive, and there could certainly be outliers of individuals that could be harmed by ingesting 4 grams of acetaminophen in a 24-hour period. But available evidence suggests that 4 grams of acetaminophen ingested over a 24-hour period will not cause serious or permanent harm to the liver and in most cases will cause no damage at all.
Learning Break: An elevation of serum transaminases that is temporally related to ingestion of acetaminophen is concerning. But serum transaminase levels are influenced by age, body mass index, gender, race, and the time of day at which they are measured. It has also been shown that serum transaminase levels of both healthy individuals and people with stable liver disease can vary by 10-30% from day to day. Someone whose serum transaminase is typically near the top level of normal may have periods in which the level is abnormally high.

THE TOXIC PROCESS OF ACETOMINOPHEN POISONING AND LIVER DAMAGE

When acetaminophen is taken in therapeutic amounts, the pathways of glucuronidation and sulfation effectively metabolize 90% of the dose and there are sufficient stores of glutathione available in the liver to effectively bind and neutralize the NAPQI. But when acetaminophen is taken in toxic amounts, the conjugation pathways become saturated, and a larger proportion of the ingested dose is metabolized to NAPQI.

The rate of formation of NAPQI and the amount of NAPQI produced depletes the liver’s glutathione stores and outstrips the liver’s ability to make more glutathione. When hepatic glutathione stores have been depleted to approximately 70% of pre-exposure levels - a process that takes approximately about 8 hours - NAPQI covalently binds to hepatocytes and liver damage will occur.
The precise mechanisms by which NAPQI damages the hepatocytes are not known.\textsuperscript{3,26} It may cause oxidative stress, it may cause mitochondrial dysfunction, or it may be that high amounts of NAPQI can alter the immune function of the liver, producing an abnormal immune response with inflammation that can irreversibly damage hepatocytes.\textsuperscript{27,28} However, despite the uncertainty as to exactly how an acetaminophen overdose and excess NAPQI can cause liver damage, there is \textit{no doubt} that acetaminophen poisoning and liver damage occur when the rate of formation of NAPQI outstrips the liver’s ability to make glutathione and the amount of NAPQI formed is greater than the amount of available glutathione stores in the liver. \textit{That} is the basis of acetaminophen poisoning.

\textbf{Learning Break:} The primary effect of acetaminophen poisoning is liver damage. But the renal parenchyma can also from NAPQI and kidney injury is a very unusual but well documented effect of acetaminophen poisoning.

\section*{SIGNS AND SYMPTOMS OF ACETAMINOPHEN OVERDOSE}

\textbf{Hepatic damage}

The clinical presentation of acetaminophen poisoning has traditionally been described as having four phases.\textsuperscript{29} There can be some individual variation in the presentation, but in most cases, these four phases are easily identifiable and follow each other quite predictably.
**Phase I:**
This phase occurs from 0 to 24 hours post-ingestion. Nausea, vomiting, abdominal pain, and anorexia are commonly observed but occasionally the patient may be asymptomatic and there are no signs or symptoms that are specific to acetaminophen poisoning. There is usually no laboratory evidence of liver damage, but occasionally the serum transaminases will begin to rise during the first 24 hours after ingestion.

**Phase II:**
This phase occurs from 24 hours to 72 hours post-ingestion. The gastrointestinal signs and symptoms typically diminish or disappear, but some patients develop right upper quadrant pain. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (together, the AST and ALT are commonly called liver function tests or LFTs) may begin to rise above normal levels; levels at or above 10,000 IU/L are not uncommon. The international normalized ratio (INR), and prothrombin time (PT) may also begin to rise above normal levels. Occasionally, serum blood urea nitrogen (BUN) and creatinine will also become elevated.

**Learning Break:** AST and ALT are enzymes contained in hepatocytes. If the AST and ALT are elevated, that indicates liver damage. The INR and the PT are measures of the liver’s ability to produce clotting factors; the INR provides information about the liver’s functional ability.
• **Phase III:**
  This phase develops from 72 hours to 96 hours post-ingestion, and it is characterized by recovery or progression to liver failure. Most patients, even those who do not receive treatment, will have a mild to moderate degree of liver damage but this resolves.

  Other patients develop fulminant hepatic failure and either recover or succumb. Patients with fulminant hepatic failure may develop metabolic acidosis, acute respiratory distress syndrome (ARDS), coagulopathies, coma, hypoglycemia, cerebral edema, and renal failure. These serious cases happen very soon after a massive ingestion of acetaminophen or if the patient presents very late after ingestion.

• **Phase IV:**
  This phase is from 96 hours post-ingestion to approximately two weeks post-ingestion, and is characterized by return of liver function. Patients who have survived Phase III, hepatic damage and function are completely healed.

**Learning Break:** If the patient has ingested a massive amount of acetaminophen, he/she may not present with the normal progression through the phases. These patients will rapidly become comatose and acidotic and may need a liver transplant.
**Renal damage**

Acute renal failure happens in approximately 1% to 2% of all cases of acetaminophen poisoning. The renal parenchyma may form NAPQI, but it is not clear if this explains renal damage in these cases. Renal failure following an acetaminophen overdose can occur without elevates LFTS or evidence of fulminant hepatic failure, but this is even more unusual.

It does not appear that there is a reliable way to predict which patients with acetaminophen overdose will develop renal failure. The onset of renal failure typically begins after evidence of liver damage and liver failure. The peak serum creatinine levels may not be seen until two to seven days after the ingestion.

**Other organ damage**

There have been rare instances of other organ systems being injured by acetaminophen overdose. Cardiac damage and cardiac effects, such as ECG changes and dysrhythmias, has been reported after acetaminophen overdose, and, autopsy reports in some of these cases did find evidence of myocardial damage. However, given that reports of cardiac effects after acetaminophen poisoning are very rare and the confounding factors in these cases, such as concurrent use of medications that can affect cardiac status, incomplete, the clinical information needed to confirm a diagnosis and the presence of other serious clinical effects (i.e., metabolic acidosis), make it seem safe to assume that if acetaminophen is directly toxic to the heart, cardiac damage is highly unusual.
Acute pancreatitis has occasionally been reported after acetaminophen overdose, \(^{37-40}\) and elevated serum amylase is fairly common. One author found that 246 of 814 patients (28%) who had taken an overdose of acetaminophen had elevated serum amylase; 18% of these patients did \textit{not} have laboratory evidence of liver damage; and 75% of the patients who developed fulminate hepatic failure had hyperamylasemia.\(^{40}\) The pathogenesis of this phenomenon is not clear. It may be an idiosyncratic response, a direct toxic effect of acetaminophen, or, in some cases, it may be associated with hepatic or renal damage caused by the overdose.

**RISK FACTORS FOR ACETAMINOPHEN POISONING**

Acetaminophen poisoning essentially represents a balance between the amount of NAPQI formed and the rate at which it is formed, and the amount of glutathione available and the ability of the liver to produce more. The major toxic effect of acetaminophen poisoning is liver damage and damage to the liver’s functional capacity. It seems reasonable then to assume that anything which: 1) increases the amount or rate of NAPQI formation; 2) decreases the amount and rate of glutathione formation, or; 3) increases the liver’s vulnerability to injury, might increase the risks of liver damage when acetaminophen is taken in a toxic amount.

A question to ponder is: \textit{are there risk factors that may make some people more susceptible to damage from acetaminophen when it is taken in overdose?} Some researchers have speculated that there are, and the potential risk factors that have been identified are listed below: \(^3,29\)
- Liver disease, specifically hepatitis C
- Chronic alcohol abuse or acute alcohol intoxication Medications such as antiepileptics or antitubercular drugs that increase the activity of the cytochrome P450 enzyme that produces NAPQI
- Cigarette smoking
- Genetic polymorphisms in drug metabolizing enzymes
- Age
- Poor nutrition status that may cause decreased glutathione stores.

However, at this point there is no definitive evidence that most of these purported risk factors would increase an individual’s susceptibility to liver damage after an acetaminophen overdose. \(^{41,42}\)

The strongest evidence for such an effect is for hepatitis C. \(^{43,44}\) The role of alcohol as a risk factor is not completely understood and is controversial.\(^{3,45}\) Acute ingestion of alcohol may actually have a protective effect; ethanol competes for the cytochrome P450 enzyme that produces NAPQI. Chronic alcohol ingestion decreases glutathione stores and increases the activity of that specific cytochrome P450 enzyme, but people who chronically ingest alcohol do not seem to have an increased risk of liver damage and liver failure after acetaminophen overdose.\(^{16}\) Yet, there is also some evidence that it is the pattern of use that can make alcohol ingestion risky in these situations. People who chronically abuse alcohol may not be more susceptible to liver injury after an acute overdose of acetaminophen, but may be at a higher risk if they are chronically taking larger than therapeutic doses.
At this time, there is no answer, and the status of these risk factors is still being investigated. And in some ways, the question is unimportant. The prescribing information for acetaminophen states that the drug should be used with caution in people who have alcoholic liver disease and that people who consume ≥ three drinks a day and use acetaminophen may be at risk for liver damage. Alcohol use/abuse and the other risk factors that may increase susceptibility to liver damage from acetaminophen are common and widely distributed, yet with prompt and proper treatment survival after an acetaminophen overdose is virtually assured.

**Children and acetaminophen: is there less risk?**

Children appear to be less at risk for acetaminophen-induced liver damage after an overdose. Significant liver damage or death is almost unheard of after a single, unintentional, pediatric overdose or exposure. Some of the reasons why this occurs are obvious. Young children do not try and harm themselves by taking an overdose. They seldom swallow tablets; they chew them and the bitter taste acts as a deterrent. Generally, by the time parents discover that their child has ingested acetaminophen, the child is stopped from taking the medication before too much can be ingested and/or is brought to an emergency department where treatment can be prompt.

There has been speculation that children are inherently resistant to acetaminophen. Speculation was that the amount of acetaminophen metabolized to NAPQI was proportionately less in children, that children had greater glutathione stores, or that they had another way of detoxifying large amounts of acetaminophen not evident in adults. None of these proposed protective mechanisms has been verified,
however, and the reason why children are inherently more resistant to acetaminophen toxicity than adults is simply size. The size of the pediatric liver is proportionately bigger than it is for adults, so children have greater relative glutathione stores and metabolize acetaminophen faster. 46,47

**ACETAMINOPHEN ACUTE OVERDOSE AND PATIENT TREATMENT**

**Deciding at-risk patients**

Unlike many drugs and toxins for which supportive care is the basis of treatment, there is a highly effective antidote that can be used to treat cases of acetaminophen poisoning: N-acetylcysteine (NAC). Although administering NAC many hours or even days after an ingestion of an acetaminophen overdose may be helpful, NAC is most effective if it is given ≤ 8-10 hours after the ingestion. 3,48,49 After 8-10 hours from the time of ingestion has passed, the effectiveness of NAC begins to decline so prompt identification of patients at risk is very important.

In order to make this assessment and decide which patients are at risk and need antidotal treatment, the health team members would need to obtain the following information from the patient and/or family:

1) The dose that was ingested and when it was ingested;
2) The serum acetaminophen level;
3) The results of pertinent laboratory tests, and;
4) The signs and symptoms the patient is having.

*Dose:*
The toxic dose of acetaminophen is considered to be ≥ 10 grams or ≥ 200 mg/kg. When considering the ingested dose, making the decision
as to whether or not treat a patient who has taken an excess of acetaminophen should be easy; if the amount ingested was ≥ 10 grams or ≥ 200 mg/kg, the patient should receive NAC.

Unfortunately, many patients cannot or do not provide accurate information about the amount of drug ingestion or when the ingestion occurred. The health team involved in treating the patient should try to use all of their resources to determine what the ingested dose and time was, but, in many cases, such as when ingestion involves an attempt at self-harm, this can’t be done.

The time of ingestion and the pattern of ingestion are crucially important. If the ingestion was completed in four hours or less it can be considered acute. The time of ingestion is used to interpret the serum level and this will be discussed in the next section.

**Acetaminophen serum level:**
A serum acetaminophen level should be obtained *four hours or later* after the ingestion. Although, in therapeutic doses the absorption and peak serum level are reached within two hours, in the case of an overdose absorption can be delayed, thus the level should obtained four hours or later after ingestion. The level is then plotted on the Rumack-Matthew nomogram. The nomogram is an assessment tool that has been proven to be very effective.

**Rumack-Matthew nomogram:**
The Rumack-Matthew nomogram was developed through the examination of acetaminophen levels and AST and ALT results. The developers of the nomogram noted a trend that was very consistent.
If the patient had ingested a toxic amount of acetaminophen and the time of ingestion was known with certainty, an acetaminophen level that was obtained at some point four hours or later after that ingestion time could be used to predict which patients would develop liver injury.

Below is a case scenario, which illustrates how the Rumack-Matthew nomogram is used following an overdose of acetaminophen:

A patient reports that he ingested 10 grams of acetaminophen eight hours prior to arrival to the emergency department. A reliable witness confirms the ingestion time. The acetaminophen level is 160 μg/mL. The level is placed on the nomogram and it is clearly above the line labeled probable hepatotoxicity.

The Rumack-Matthew nomogram, proven to be highly sensitive (if not highly specific) always will accurately identify patients at risk when used correctly. Only one level is needed to use the nomogram. Serial levels that are lower than previous ones simply document metabolism of the drug; there is no need to get them and they are of no clinical value. Also, levels that are within the range of normal values should not be considered non-toxic if the time of ingestion is not known or if the level is toxic according to the nomogram. The level is considered toxic or non-toxic depending on when, in relation to the ingestion, the level was obtained; the absolute value in and of itself is of no clinical importance except to confirm that acetaminophen has been ingested. The nomogram assumes that an acetaminophen level measured at four hours post-ingestion represents the peak level. This is almost always true, but exceptions have been noted.
Antihistamines and opioids can slow gut peristalsis, delay absorption and several case reports have documented a delayed peak acetaminophen level caused by a co-ingestion of diphenhydramine or an opioid. 51-55 Delayed peak serum levels have been reported after massive ingestions 56-58 and after ingestion of extended-release products, *i.e.*, Tylenol Arthritis®.59-60

In patients that have ingested an extended release acetaminophen product, an acetaminophen level should be obtained at four hours after the ingestion. Another acetaminophen level should be repeated four to six hours later. If either level is above the treatment line the patient is at risk and should receive antidotal therapy. If neither level is above the treatment line, the patient doesn’t need antidotal therapy. This approach should also be considered if the patient ingested a medication that can slow peristalsis.

**Learning Break:** What if a patient’s serum acetaminophen level measured at three hours post-ingestion is 89 μg/mL? Should another level be measured? It is unlikely that a low serum acetaminophen level measured before the four hour post-ingestion mark will subsequently rise to the toxic level of 150 μg/mL at four hours, but it is not impossible. 61,62 Froberg at al (2013) checked serum acetaminophen levels between one and four hours post-ingestion in 83 patients who had taken an acute acetaminophen overdose. They found a level done during this time that was < 100 μg/mL a yielded false positive rate of 6.5%, so at least five patients with a *non-toxic* level subsequently developed a four-hour level that was toxic.
Laboratory tests:
Elevations of the AST, ALT, and INR certainly can confirm that the patient has taken a toxic dose of acetaminophen. AST and ALT elevations occur first, representing damage to hepatocytes while elevations of INR occur later (representing damage to liver function). The elevation of the AST and ALT typically begin at approximately 24 hours after ingestion, but this can occur as early as eight hours post-ingestion and as late as 36 hours. 63-65

Normal laboratory values may indicate that a toxic ingestion has not occurred, but the goal of treating a patient with an acetaminophen overdose is to prevent harm to the liver. These laboratory studies should be obtained and, if they are abnormal, a patient who has taken an overdose of acetaminophen should be treated. Waiting for evidence of damage is not optimal therapy.

Signs and symptoms:
There are signs and symptoms of liver damage caused by acetaminophen that are commonly observed: abdominal pain, nausea, and vomiting. But these signs and symptoms are to some extent subjective, non-specific, and they may be absent or greatly diminished 24 hours or so after the ingestion.

Although not common, it is possible for the signs and symptoms to be absent and there will be no laboratory evidence of liver damage. The physical exam and the patient’s subjective complaints, signs and symptoms, should be considered; however, these are often unreliable or not highly useful in making a treatment decision.
Of course, there will be many instances in which the information needed to make a treatment decision will be unobtainable, ambiguous, or can’t be interpreted. The case scenario below highlights this:

A patient presents with an undetectable level, however, has symptoms of nausea and vomiting. The patient reports that she ingested 15 grams of acetaminophen but she cannot remember when she did so and the ingestion can’t be confirmed.

Lab serum levels reveal an AST/ALT that are slightly elevated, but there are no medical records available to support the determination of whether these abnormal laboratory values are new or old or caused by a medical problem.

Making the decision as to which patients are at risk and need therapy with NAC can be tricky. The best course of action is to realize that cases in which the data is ambiguous or unavailable are common, consider the situation as a whole, and err on the side of caution. N-acetylcysteine is highly effective and very safe and, if the wrong decision is made, the patient could suffer liver failure and death.

Consider a patient to be at risk and give NAC if:

- The acetaminophen level is above the treatment line on the Rumack-Matthew nomogram;
- If it has been confirmed that the patient has taken a toxic amount of acetaminophen;
- If it is suspected or reported that the patient has taken a toxic amount of acetaminophen and there is a measurable acetaminophen level;
• If there is a measurable acetaminophen level but the time of ingestion is not known;
• If it is suspected or reported that the patient has taken a toxic amount of acetaminophen and there is laboratory evidence of liver damage;
• If the patient has been chronically ingesting toxic or supratherapeutic amounts of acetaminophen and there is a measurable acetaminophen level and/or laboratory evidence of liver damage.

**Initial care: stabilization and treatment**

Assess the airway, breathing, and circulation (ABCs). If there are significant derangements in the ABCs, it is possible, but not very likely that these changes are due to an acetaminophen overdose. As mentioned previously, a massive amount of acetaminophen can cause coma and metabolic acidosis shortly after the ingestion, but this rarely happens.\(^66,67\) If the patient with a reported/alleged acetaminophen overdose is acidic, hypotensive, and unresponsive, the health team must act quickly to assess the patient for an acetaminophen overdose. But, remember that presentations such as this are unusual, so considering the possibility of a co-ingestion is prudent.

**Physical exam**

In performing a physical exam its necessary to pay particular attention to the abdominal area. The patient should be asked how much acetaminophen was ingested, what dosage form was ingested (e.g., extra strength, sustained release), when the drug was ingested and over what period of time, and a determination should be made...
whether this was the only ingestion or if the patient had taken any acetaminophen in the hours and days prior to the current ingestion.

Administer a single dose of activated charcoal if the patient presents with any of the following:
1) normal, stable ABCs;
2) mentation is awake and alert;
3) normal gag reflex;
4) no co-ingestant that may lead to a rapid depression in consciousness, and;
5) arrives at the hospital within one hour of the ingestion.

Activated charcoal binds avidly to acetaminophen and if it is given within one hour after ingestion, it may prevent a toxic amount of acetaminophen from being absorbed and converted to NAPQI.\textsuperscript{11}

Another consideration is that activated charcoal will bind to oral NAC. However, it is uncommon to need to administer activated charcoal and NAC at the same time, and, even if it were required to do so, the binding of NAC to charcoal is not considered important and there would be no need to increase the dose of NAC.\textsuperscript{68} Ipecac (a thick oral syrup preparation that induces vomiting) is no longer available; and, gastric lavage (stomach pumping) should not be performed.\textsuperscript{69-71}

\textit{Hemodialysis}

Acetaminophen can be removed by hemodialysis. Using hemodialysis could be considered if the patient’s acetaminophen level is extremely high. However, such a circumstance would be extremely rare, and as
the antidote is safe and easy to administer, extracorporeal removal should not be done.

**Serum acetaminophen level**
Obtaining a serum acetaminophen level should be done four hours or later from the time of ingestion, but, if this time is not known, a serum level should be obtained immediately and then another level in four hours. Also, a serum salicylate level should be obtained. Patients occasionally confuse aspirin and acetaminophen and may use the terms interchangeably.

Additional serum levels that should be obtained include an INR, LFTS, BUN, and creatinine. Once the acetaminophen level is known, it can be plotted on the nomogram and if the time of ingestion is known, the decision to use/not use NAC can be made.

**Antidotal therapy: \( n \)-acetylcysteine (NAC)**

Acetaminophen poisoning results from an imbalance between the rate and the amount of formation of a toxic metabolite and the availability of the body’s glutathione stores and its capability to make more glutathione. At the present time, there are no proven ways to limit the absorption of acetaminophen aside from the timely administration of activated charcoal.

There are no proven ways to increase the conjugation of acetaminophen to glucuronide or sulfate, and there are no proven ways to decrease the metabolism of acetaminophen to NAPQI. The only proven therapy for acetaminophen poisoning is \( n \)-acetylcysteine (NAC). NAC can prevent liver damage and liver failure caused by an
overdose of acetaminophen by increasing the body’s ability to detoxify NAPQI.

There are several ways in which NAC works. Glutathione is synthesized in the liver from the amino acids cysteine, glutamate, and glycine. There is a limited amount of cysteine available in the liver, and NAC provides a source of cysteine so more glutathione can be synthesized. This increased synthesis of glutathione is one of the most important ways that NAC prevents and treats liver damage. NAC may also work by reversing NAPQI back to acetaminophen by: binding directly to NAPQI, increasing the amount of ingested acetaminophen that is conjugated to sulfate, changing and ameliorating the course of liver damage (once NAPQI binds to hepatocytes) by increasing hepatic oxygen delivery, acting as an anti-inflammatory and antioxidant agent, and, increasing hepatic blood flow.

NAC has two important functions: it prevents liver damage and treats liver damage after the damage has begun. It is very effective; and, if given soon after the ingestion, there is almost no risk that a patient will develop hepatic failure. There may be liver damage, but this will resolve and the patient will recover. Less than 1% of patients die who take an overdose of acetaminophen and who are treated promptly with NAC.

When NAC is given from 0 to 10 hours post-ingestion of acetaminophen it is equally effective. There is evidence that NAC given outside of this time period and even several days after an ingestion of acetaminophen may be helpful, and it is recommended that NAC be given in these situations. It can be given orally or IV; the IV form
is Acetadote®. Below are the various NAC administration routes and dosing regimens, as well as the recommended laboratory studies and potential side effects.

- **Oral NAC:**
  The patient is given a loading dose of 140 mg/kg. Seventeen doses of 70 mg/kg are then given, one dose every four hours. If the patient vomits within an hour of administration of dose, repeat the dose. The AST, ALT, INR, BUN, and creatinine should be checked every day.

  Nausea and vomiting are very common side effects. The NAC should be diluted with juice or soda, served cold in a cup with a lid (the odor of NAC is noxious) and sipped slowly. It can also be given through a nasogastric tube.

  Pre-treatment with an anti-emetic may also be helpful: ondansetron or metoclopramide are more effective than traditional anti-emetics such as prochlorperazine. Contradictions to using oral NAC include sensitivity to NAC, the inability to use the gut, or persistent vomiting.

- **IV NAC:**
  The patient (if he/she is > 40 kg in bodyweight) is given a loading dose of 150 mg/kg of Acetadote® in 200 ml of 5% dextrose; and, this is given over 60 minutes. This is followed immediately by a dose of 50 mg/kg in 500 ml of 5% dextrose, and given over four hours. The third dose is given immediately
after the second, and it is 100 mg/kg in 1000 ml of 5% dextrose, which is given over 16 hours.

If the patient’s bodyweight is > 100 kg, the maximum dose that should be given is 15 grams, 5 grams, and 10 grams, respectively, regardless of the bodyweight.\textsuperscript{75,76} Adverse reactions to IV NAC are common (56\% in some prospective studies) but easily managed.\textsuperscript{73,77} These reactions usually occur during the loading dose and are anaphylactoid; such as, wheezing, urticaria, rash, pruritus, flushing, nausea, and vomiting.\textsuperscript{73}

Serious reactions such as bronchospasm, dyspnea, and hypotension are uncommon. Diphenhydramine can be given for cutaneous reactions and the IV infusion can be continued, but if the patient develops angioedema, bronchospasm, or hypotension then the infusion should be stopped; and, beta agonists, corticosteroids, diphenhydramine, epinephrine, and IV fluids as needed should be given.\textsuperscript{73}

There should be a waiting period until the reaction subsides, and then the infusion may be cautiously re-started. Two hours prior to the end of the 16-hour infusion, an acetaminophen level, AST, ALT, and INR should be obtained. If there is a measurable

\textbf{Note:} There is a website sponsored by the company that manufactures Acetadote®, \url{www.acetadote.net}, that has a dosing calculator and a lot of useful information about the drug.
acetaminophen level, or abnormal LFTs or INR, it may be advisable to administer more intravenous NAC.

Learning Break: Older references may be found that recommend infusing the loading dose of Acetadote® over 15 minutes. This was the original protocol, but it was soon discovered that the incidence of anaphylactoid reactions was unacceptably high and if the loading dose was infused within 60 minutes, adverse reactions were far less common. This difference is why some articles discussing intravenous NAC will refer to a 20-hour protocol instead of the 21-hour protocol.

No one knows what the optimum treatment is for patients who have received the entire oral or IV course of NAC and have evidence of liver damage or a measurable acetaminophen serum level. The accepted standard is to continue the NAC if, at the end of the course of therapy, there is still measurable acetaminophen and/or abnormal laboratory values indicating liver damage or dysfunction. It has generally been thought that NAC can be discontinued when there is evidence that the liver is recovering, but there is no agreed upon definition of that term.

NAC: Oral versus IV

There have been no randomized, controlled trials that have directly compared the effectiveness of oral versus IV NAC, but the available evidence indicates that when given within 0-10 hours post-ingestion there is no difference. The rate of serious adverse effects is lower
for IV NAC than it is for oral.\textsuperscript{73} Therapeutic overdose with IV NAC has been reported to cause bronchospasm, hypotension, and seizures.\textsuperscript{73}

Clinical evidence suggests that IV NAC may be more effective when it is given to patients who present within 12 hours of an ingestion while the oral form is more effective if a patient presents 18 hours or later after an ingestion.\textsuperscript{81} At this time, the IV form is preferred due to better tolerability and shorter hospital stay, and the issue of which preparation is more effective if patients present early or late has not been resolved.

**CHRONIC INGESTIONS OF EXCESS ACETAMINOPHEN**

Chronic ingestion of an excess amount of acetaminophen is a very common and potentially very serious problem.\textsuperscript{82-85} The U.S. Acute Liver Failure Multicenter Prospective Study found that unintentional overdoses accounted for 48\% of all cases of acetaminophen-related acute liver failure\textsuperscript{85} and doses that were not far above the accepted maximum have caused serious harm.\textsuperscript{84}

Chronic excess ingestion - commonly called *supratherapeutic ingestion* - is also a difficult problem to assess. Patients who have taken large amounts of acetaminophen for several days typically do so because they have dental and musculoskeletal pain, and they often cannot remember their pattern of analgesic use. The Rumack-Matthew nomogram cannot be used to determine if the serum acetaminophen level is toxic or non-toxic. The serum transaminases may not be elevated and the patient may be asymptomatic.
The AAPCC has provided a guideline for assessment and treatment of chronic, supratherapeutic acetaminophen ingestions.\textsuperscript{10}

1. Patients < 6 years of age should be referred to an emergency department if they have ingested:
   a) 200 mg/kg or more over a single 24-hour period;
   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.

2. Patients 6 years of age or older should be referred to an emergency department if they have ingested:
   a) at least 10 g 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.

   If the patient has risk factors that may make them susceptible to acetaminophen toxicity (\textit{i.e.}, history of alcohol abuse, alcoholism, isoniazid use, prolonged fasting), the dose of acetaminophen considered potentially toxic should 4 grams or 100 mg/kg (whichever is less) per day.

Check the acetaminophen level, AST, ALT, INR, BUN, and creatinine. If the patient has signs/symptoms of liver damage, has ingested a toxic amount, has a measurable acetaminophen level, or has abnormal laboratory values, the patient should be considered at risk and treated with NAC. If the patient reportedly ingested a toxic amount of
acetaminophen, but the physical exam is unremarkable, the acetaminophen level is zero, and the laboratory values are normal, the patient would not be considered at risk.

It is not uncommon for patients to present many hours or days after acetaminophen ingestion, and/or after the process of liver damage has already begun. The optimal time for administering NAC is 0-10 hours after ingestion, and NAC is essentially given to prevent liver damage. However, there is evidence that NAC can be effective even if it is given many hours or days after acetaminophen ingestion, and giving NAC in these situations is commonly done.

**LIVER FAILURE AND TRANSPLANTATION**

Acute liver failure can cause sepsis, hypoglycemia, metabolic acidosis, encephalopathy, coagulopathies, and coma. Transplantation can be the only effective therapy in certain cases of acute liver failure. However, some patients will recover and transplantation has many risks, so it is very important to know which patients will and which patients will not, need a transplant.

The King’s College Hospital Criteria have traditionally been used to identify patients who need transplantation. These criteria are:

- Serum pH is < 7.30 despite fluid resuscitation.
- The prothrombin time is > 100 seconds.
- The serum creatinine is > 3.3 mg/dL.
- Grade III-IV encephalopathy.
The APACHE II (Acute Physiologic and Chronic Health Evaluation) criteria have also been used, some researchers feel that serum lactate is a better predictor for identifying patients who need transplantation, and other guidelines have been proposed.\textsuperscript{87-89} These approaches all have advantages and limitations and at this time the King’s College Hospital Criteria appear to be the most commonly accepted approach.\textsuperscript{90}

**PREGNANCY AND ACETAMINOPHEN OVERDOSE**

Overdose with acetaminophen by pregnant women has been associated with spontaneous abortion and fetal death. Acetaminophen does cross the placenta and reaches the fetus, and there is evidence that the fetal liver can synthesize a toxic metabolite and the fetal liver can be injured.

The majority of cases of acetaminophen overdose by pregnant women have had good outcomes, but if it is known or suspected that a pregnant woman has taken an overdose of acetaminophen, she should be treated with NAC.\textsuperscript{90} If there are signs of fetal distress and the mother has evidence of severe hepatotoxicity, emergency delivery is indicated.\textsuperscript{91}

**SUMMARY**

Acetaminophen is the drug most commonly taken with intent to cause self-harm. Therapeutic errors with acetaminophen are very common as well, and intentional or accidental acetaminophen overdose is the most common cause of acute liver failure. Acetaminophen overdose can also cause renal damage but this is rare, and damage to other organ
systems has been reported but it is unclear if these case reports are actually describing an effect of acetaminophen. If acetaminophen is ingested in massive amounts a rapid onset of acidosis, coma, and hypotension is possible.

In order to determine if a patient has taken a toxic dose of acetaminophen the health team needs to know:

1) How much acetaminophen has been ingested, and the time taken;
2) The serum acetaminophen level;
3) The LFTs, BUN, creatinine, and coagulation studies, and;
4) The patient’s health history and the physical assessment.

The toxic dose of acetaminophen after an acute ingestion is ≥ 10 grams or ≥ 200 mg/kg. After chronic overdose, the toxic dose of acetaminophen depends on how long the patient has been taking the drug and the presence of risk factors. The serum level must be done at four hours or later after ingestion and it is plotted on the Rumack-Matthew nomogram and will be seen as toxic or non-toxic. If the laboratory studies were abnormally high this would indicate a possible acetaminophen overdose, but laboratory evidence of liver damage typically is not evident for 24 hours after ingestion. Patients may have non-specific gastrointestinal complaints, but these may be absent or resolve 24 hours or so after ingestion.

The same basic assessment should be used for chronic ingestions of acetaminophen. However, the Rumack-Matthew nomogram was designed to evaluate serum acetaminophen levels from acute ingestions and cannot be used to determine if a serum acetaminophen
level is toxic or non-toxic if the ingestion was chronic. An acetaminophen level should be measured in these cases and if acetaminophen is detected then this would be an indication for treatment, but the nomogram cannot be used.

The treatment for acetaminophen overdose is $N$-acetylcysteine. $N$-acetylcysteine is highly effective if it is given within 8-10 hours of the ingestion. The antidote can and should be given if patients present after that time but its efficacy is reduced. $N$-acetylcysteine can be given orally or IV. No direct comparisons between the two forms have been done, but the evidence suggests that they are equally effective. The IV form is preferred because it is a 21-hour dosing protocol and the oral dosing protocol is 72 hours. If patients are treated promptly and correctly, survival is virtually assured and the liver will completely recover.

There are certain conditions that may or may not increase a patient’s susceptibility to liver damage from excess acetaminophen, but even if these potential risk factors are present, the standard treatment protocol should be used. Poor outcomes, liver failure and death, are caused by patients who present late or have taken a massive ingestion. Antidotal therapy should still be used but liver transplantation may be the only hope.

Please take time to help the NURSECE4LESS.COM course planners evaluate nursing knowledge needs met following completion of this course by completing the self-assessment Knowledge Questions after reading the article. Correct Answers, page 43.
1) **Most acetaminophen is changed to harmless metabolites by:**
   a. conjugation
   b. metabolism by cytochrome P-450 enzymes
   c. elimination in the urine
   d. elimination in the stool

2) **Acetaminophen is converted to a toxic metabolite by:**
   a. conjugation
   b. metabolism by cytochrome P-450 enzymes
   c. elimination in the urine
   d. elimination in the stool

3) **The toxic dose of acetaminophen is:**
   a. ≥ 10 grams or 200 mg/kg
   b. ≥ 7.5 grams or 150 mg/kg
   c. ≥ 15 grams or 150 mg/kg
   d. ≥ 20 grams 04 300 mg/kg

4) **The basis of acetaminophen poisoning is:**
   a. rate/amount of NAPQI formation greater than glutathione availability
   b. rate/formation of conjugation is greater than glutathione availability
   c. decrease in glutathione effectiveness
   d. increased sensitivity of the liver to the drug
5) One organ other than the liver that is affected by an overdose of acetaminophen is:
   a. the lungs
   b. the small bowel
   c. the kidneys
   d. the thyroid

6) A massive overdose of acetaminophen can cause a rapid onset of:
   a. metabolic acidosis and coma
   b. arrhythmias and ARDS
   c. pancreatitis and congestive heart failure
   d. coma and myocardial infarction

7. The serum acetaminophen level must be measured ____ after an ingestion.
   a. 8 hours or more
   b. 4 hours or more
   c. 2 hours or more
   d. 10 hours or more

8. Organ damage other than hepatic or renal is common after acetaminophen overdose
   a. True
   b. False
9. Laboratory tests used to evaluate cases of acetaminophen poisoning are:
   a. LFTs, BUN, creatinine, INR
   b. AST, CBC, and creatinine
   c. ALT, INR, and TSH
   d. AST, CK, and creatinine

10. The antidotal therapy for acetaminophen poisoning is:
    a. glucagon
    b. methylene blue
    c. sodium thiosulfate
    d. N-acetylcysteine (NAC)

Correct Answers:

1. A
2. B
3. A
4. A
5. C
6. A
7. B
8. B
9. A
10. D
Footnotes:

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