Acetaminophen and Salicylates

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LEARNING OBJECTIVES

1. Evaluate the potential for acetaminophen-induced hepatotoxicity using different methods of risk assessment.
2. Justify the use of alternative acetylcysteine dosing strategies in the treatment of acetaminophen poisoning.
3. Distinguish between the different types of acidosis caused by acetaminophen.
4. Assess the severity of salicylate poisoning in patients presenting without an elevated anion gap.
5. Develop a therapeutic plan for sodium acetate as a salicylate antidote in the absence of sodium bicarbonate.
6. Design a clinical approach to patients with severe salicylate toxicity requiring intubation and mechanical ventilation.

ABBREVIATIONS IN THIS CHAPTER

AT	Aminotransferase
NAPQI	*N*-acetyl-*p*-benzoquinoneimine

Table of other common abbreviations.

INTRODUCTION

Because of their availability OTC and in combination with various products, acetaminophen and salicylates remain some of the most widely used medications worldwide and are among those most common in overdose and toxicity, despite FDA efforts to limit exposures through improved product labeling, modified dosage content available in combination products, and continued educational campaigns. Even with decades of research directed at the presentation and management of acetaminophen and salicylate toxicities, many areas of continued investigation remain.

ACETAMINOPHEN

Review of Acetaminophen Toxicity and Management

Epidemiology

Acetaminophen is used therapeutically for its analgesic and antipyretic activity. Although acetaminophen is considered safe when used appropriately, acetaminophen toxicity is common after both intentional self-poisoning and therapeutic misadventures. The FDA has made several attempts to mitigate the risk of toxicity; however, acetaminophen remains the most common cause of acute liver failure in U.S. patients 15 years and older (Ostapowicz 2002).

Pharmacology/Toxicology

Acetaminophen acts as an indirect inhibitor of cyclooxygenase activity, resulting in central analgesia and fever reduction with minimal effects on peripheral inflammatory cells. Therapeutic doses include 10–15 mg/kg every 4–6 hours up to 75 mg/kg/day (up to 4000 mg daily) in children and 650–1000 mg every 4–6 hours to 4000 mg daily in adults. Serum concentrations are typically 10–20 mcg/mL with therapeutic doses. Acute toxicity may occur after single ingestions of

150 mg/kg in most patients or 200 mg/kg in children younger than 6 years. Chronic toxicity is less well defined but should be evaluated in patients taking more than 200 mg/kg/day (or 10 g/day) in 24 hours or more than 150 mg/kg/day (or 6 g/day) in 48 hours (Dart 2006). The elimination half-life is typically 2–2.5 hours but may be prolonged in overdose situations. A half-life greater than 4 hours has been associated with hepatotoxicity (Wong 2017a; Prescott 1971).

Mechanism of Toxicity

After normal doses, about 5% of acetaminophen is excreted unchanged in the urine, whereas most acetaminophen is metabolized through various pathways in the liver before excretion. The bulk of biotransformation, up to 90%, occurs through glucuronidation and sulfation. Sulfation, which depends on the availability of glutathione as a sulfur donor, may become saturated. The remainder of acetaminophen is converted to a toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), produced by oxidation through CYP2E1. *N*-acetyl-*p*-benzoquinoneimine is then rapidly conjugated with glutathione to nontoxic metabolites. In an acetaminophen overdose, glutathione stores become depleted, resulting in decreased sulfation, increased CYP2E1 conversion to NAPQI, and decreased conjugation of NAPQI to nontoxic metabolites.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter a presumed to be familiar with the following:

- General knowledge of the pathophysiology that leads to toxicity in acetaminophen and salicylate toxicity
- Drug knowledge of antidotal treatment with acetylcysteine for acetaminophen
- Consequences of poorly managed acetaminophen and salicylate toxicity

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Association of Poison Control Centers (1-800-222-1222)
- Dart RC, Erdman AR, Olson KR, et al. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2006;44:1-18.
- Chyka PA, Erdman AR, Christianson G, et al. Salicylate poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007;45:95-131.

In the absence of available glutathione, NAPQI rapidly and irreversibly binds to proteins throughout the cell, inducing a cascade of events that culminate in cell death. Because of the prevalence of CYP2E1 in hepatocytes, particularly in hepatic zone III or the centrilobular areas, cellular pathology typically reflects damage to this region of the liver.

Phases of Toxicity

Acetaminophen toxicity is typically described in four phases. During phase I (first 12–24 hours after exposure), patients are relatively asymptomatic, and hepatic injury has not yet developed. If symptoms are present, they are usually mild and nonspecific and include nausea, vomiting, and malaise. Massive overdose will be discussed further in this chapter but may present rarely with severe metabolic acidosis and depressed mental status. Phase II, or onset of hepatotoxicity, usually occurs within 24 hours of exposure but has been reported as early as 12 hours and is universal by 36 hours. Elevated AST is most notable during this phase, and acetaminophen-induced hepatotoxicity is typically defined as a transaminase concentration greater than 1000 IU/L. Maximal hepatotoxicity occurs during phase III (72–96 hours post-ingestion) and is characterized by fulminant hepatic failure. Noted complications include hepatic encephalopathy, coma, and possibly hemorrhage. Significant elevations in hepatic transaminases (greater than 10,000 IU/L) are common, together with prolonged PT, lactic acidosis, hypoglycemia, acute renal failure, and other signs of hepatic failure. Death during this phase typically results from multisystem organ failure, including respiratory failure, cerebral edema, and hemorrhage. For those surviving toxicity, phase IV is characterized by complete hepatic recovery, with most laboratory values normalizing within 7 days. Transaminases, especially ALT, and SCr may remain elevated for several weeks.

General Management

Management of acetaminophen toxicity involves supportive care and initiation of antidotal therapy. Gastrointestinal decontamination with activated charcoal (without sorbitol) can be considered within 1–2 hours after exposure and may decrease the need for antidotal therapy (Buckley 1999); however, because of the availability of a highly effective antidote and the rapid absorption of acetaminophen, activated charcoal use should not be widespread.

Rumack-Matthew Nomogram

Traditionally, U.S. patients for antidotal therapy have been identified through risk assessment using a modified Rumack-Matthew nomogram. Using this nomogram, a serum acetaminophen concentration greater than 150 mcg/mL at 4 hours post-ingestion indicates that hepatotoxicity is possible and antidotal therapy should be initiated. A line is drawn from this point such that with every 4-hour increase in time, half of the previous concentration would be considered toxic (Figure 1). The original nomogram indicated that hepatotoxicity was

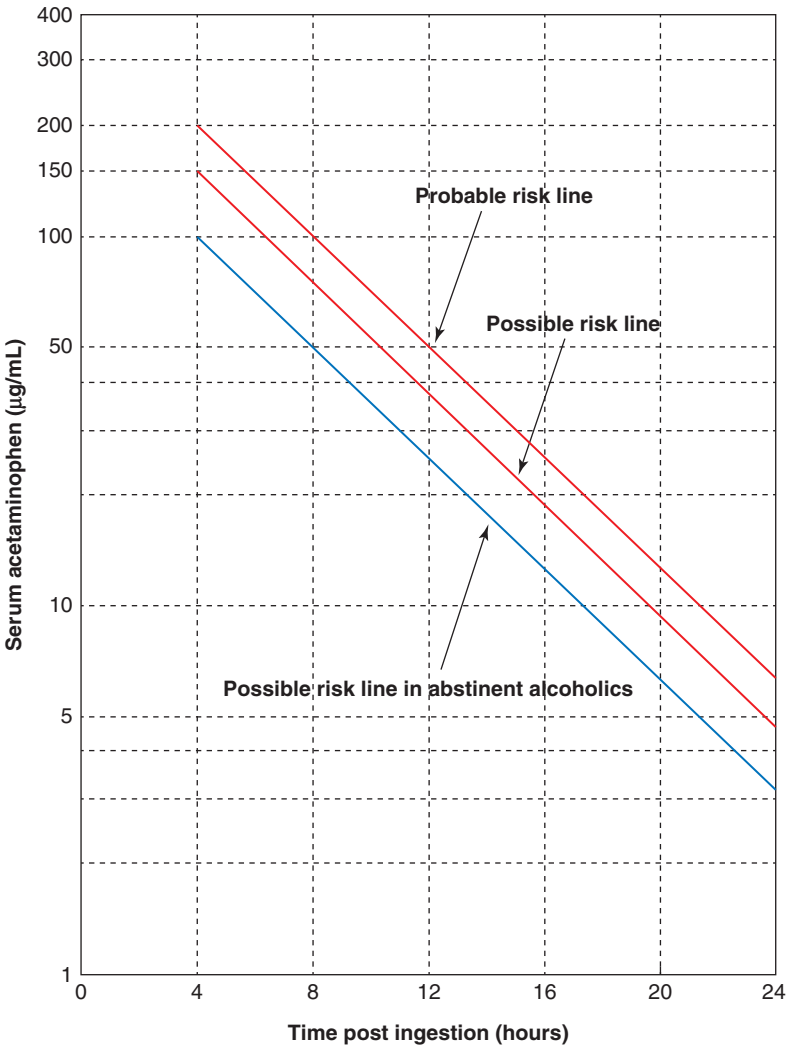

Figure 1. Rumack-Matthew nomogram including a line of 100 mcg/mL at 4 hours line and 25 mcg/mL at 12 hours, for abstinent alcoholic patients after an acute acetaminophen overdose.

Reprinted with permission from: Ali FM, Boyer EW, Bird SB. Estimated risk of hepatotoxicity after an acute acetaminophen overdose in alcoholics. Alcohol 2008;42:213-8.

probable with serum acetaminophen concentrations above 200 mcg/mL at 4 hours; this line is typically still included on nomograms to illustrate this point. A line starting at 100 mcg/mL at 4 hours has also been proposed for certain high-risk groups such as patients with chronic alcohol use disorder without ethanol co-ingestion, those receiving enzyme-inducing medications, and those with malnutrition (Bateman 2014a; Ali 2008). Of importance, this nomogram can only be applied to single, acute exposures to acetaminophen with serum acetaminophen concentrations obtained 4–24 hours postexposure.

Acetylcysteine Therapy

After patients have been identified for treatment using available risk assessment techniques or expert consultation, antidotal therapy with acetylcysteine should be initiated. Many mechanisms for acetylcysteine in the treatment of acetaminophen toxicity have been described. Acetylcysteine acts as a sulfur donor to decrease the amount of NAPQI formed while increasing the liver's capacity to detoxify NAPQI. In addition, acetylcysteine provides nonspecific benefits such as antioxidant effects and improved oxygen delivery, which are particularly beneficial after progression to fulminant hepatic failure. Optimal time for treatment initiation is usually thought to be within 6–8 hours of ingestion, by which time glutathione stores are thought to reach a critically low concentration that results in the onset of hepatic injury.

Hepatic Transplantation

Hepatic transplantation is considered in patients not improving with acetylcysteine therapy and supportive care.

Traditionally, patients requiring transplantation have been identified using the King's College Hospital criteria, which were established in patients with fulminant hepatic failure from acetaminophen toxicity (O'Grady 1989). These criteria include a serum pH of less than 7.3 after resuscitation or the composite of SCr greater than 3.3 mg/dL, PT greater than 100 seconds (or INR greater than 6.5), and grade III or IV encephalopathy. Other suggested prognostication tools include the Sequential Organ Failure Assessment score, the Model for End-Stage Liver Disease score, and the Acute Physiology and Chronic Health Evaluation II. Currently, no consensus exists regarding identifying patients requiring hepatic transplantation.

Alternative Methods of Risk Assessment

The Rumack-Matthew nomogram is currently considered the mainstay of risk assessment in acute acetaminophen toxicity cases. There are no consensus recommendations regarding risk assessment and treatment initiation in patients who do not meet the criteria for using the nomogram. This situation may lead to questions of treatment initiation in many clinical scenarios such as repeated supratherapeutic ingestions, unknown times of ingestion, detectable acetaminophen concentrations and mild elevations of transaminases, or evidence of hepatic injury without known acetaminophen exposure. Recent literature has evaluated several alternative methods of risk assessment that aim to better answer questions regarding which patients are likely to develop severe consequences after overdose. Although some of these methods can easily be incorporated into clinical practice, others involve new laboratory tests that are not widely available; these will be introduced as potential diagnostic measures for future use.

Disadvantages of Traditional Risk Assessment

Although the original Rumack-Matthew nomogram has been in use for decades and is currently the standard of care for addressing the risk of hepatotoxicity and need for acetylcysteine, many factors should be considered related to its applicability. The original nomogram, developed on the basis of observational data from 64 patients without antidote use, suggested that hepatotoxicity was likely if a 4-hour serum acetaminophen concentration was greater than 200 mcg/mL (Rumack 1975). These data were based on patients with single, acute ingestions of immediate-release acetaminophen with serum concentrations obtained 4–24 hours post-ingestion. Validation outside these conditions such as with extended-release formulations, combination products, repeated supratherapeutic ingestions, or patients unable to provide exposure timing history has not been reported. There are currently no consensus recommendations for risk assessment in these scenarios. In addition, hepatotoxicity was arbitrarily defined as a transaminase concentration greater than 1000 IU/L. No randomized controlled trials have determined the degree of clinically significant hepatic injury or, similarly, the appropriate timing of antidotal therapy to prevent adverse outcomes. Because this nomogram used population-based data, there is always a risk that certain patients will be at risk of developing complications even with serum concentrations below the threshold recommended for initiating treatment (see Figure 1).

Although acetylcysteine has very high rates of preventing hepatotoxicity when administered within 8 hours of exposure, hepatotoxicity and death may occur despite early intervention (Doyon 2009). Reliability of these reports may vary because ingestion times are typically patient reported. The nomogram was developed before acetylcysteine was available and therefore does not indicate who is at risk of developing morbidity and mortality when acetylcysteine is administered. Questions remain regarding alternative methods of risk assessment that can be used in a wide range of clinical scenarios to identify patients at risk of clinically significant hepatotoxicity and those who may develop toxicity despite standard therapy (Box 1).

Use of Lower Acetaminophen Concentration Nomograms

Treatment of acetaminophen toxicity in most countries typically involves use of the traditional Rumack-Matthew nomogram with a serum concentration of 200 mcg/mL at 4 hours or the modified nomogram with a concentration of 150 mcg/mL at 4 hours (Wong 2017a). Formerly, the UK used the traditional nomogram. The UK also adopted an additional line in the 1990s starting at 100 mcg/mL at 4 hours that was used for specific high-risk patients, including those with chronic alcohol use disorder, those receiving enzyme-inducing medications, and those with malnutrition (see Figure 1). In 2012, treatment recommendations for acetaminophen toxicity were altered after a fatal case of acetaminophen poisoning in a patient who did not meet the criteria for acetylcysteine administration according to the initial serum acetaminophen concentration. Subsequent investigation

Box 1. Current Dilemmas in Risk Assessment of APAP Toxicity

- Identifying patients at risk of hepatotoxicity with serum APAP concentrations below traditional nomogram line concentrations used to define risk
- Choice of risk assessment techniques used in patients for whom nomogram application is unsuitable
- Identifying patients at risk of hepatotoxicity even with NAC administration
- Diagnosing acetaminophen poisoning in acute liver failure of unknown etiology

APAP = acetaminophen; NAC = acetylcysteine.

Information from: Wong A, Graudins A. Risk prediction of hepatotoxicity in paracetamol poisoning. Clin Toxicol (Phila) 2017a;55:879-92.

identified 10 patients over a 20-year period who developed fatal hepatotoxicity after initially not meeting the criteria, according to the traditional nomogram. This prompted several changes to national recommendations on managing acetaminophen toxicity, including treatment of patients with repeated supratherapeutic ingestions or an unknown history and treatment of patients with serum concentrations above a nomogram line using 100 mcg/mL at 4 hours (Bateman 2014a).

Although use of lower acetaminophen concentration nomograms was not formally evaluated before introduction in the UK, many studies published clinical experience after these changes were adopted. The initial publication investigated all patients evaluated for acetaminophen overdose at three hospitals for the year before and the year immediately after the change in treatment recommendations to the 100-mcg/mL line at 4 hours (Bateman 2014a). In the year before the protocol change, there were 1703 presentations with 626 receiving acetylcysteine (36.8%), and in the year after the protocol change, there were 1854 presentations with 926 receiving acetylcysteine (50%). An 8.9% increase in presentation was identified after the protocol change, likely related to more patients being referred for evaluation of chronic acetaminophen use. In addition, there was a 13.2% increase in patients requiring admission for acetylcysteine therapy after this practice change. Moreover, the number of patients with adverse reactions to acetylcysteine significantly increased from 87 to 145 after treatment changes; however, the percentage of these reactions was not significantly different (26.9% vs. 28.2%, p=0.682). Similarly, anaphylactoid reactions occurred in more patients, but the incidence was not significantly different (29 [9%] vs. 55 [10.7%], p=0.426). Overall, the authors projected that the treatment changes would save one life every 2.1 years; however, this resulted in an increase of over $10.7 million in costs annually.

A subsequent publication by the same group evaluated a subset of patients with only single, acute ingestions at the same three UK hospitals (Bateman 2014b). In the year before the protocol change, there were 1246 presentations, with 389 receiving acetylcysteine (31%), compared with the year after the protocol change, when there were 1251 presentations with 539 receiving acetylcysteine (43%). The number of patients in this population presenting for evaluation did not differ after the protocol change; however, more patients were treated with acetylcysteine, and more patients were admitted to the hospital after the new treatment recommendations were implemented. Of importance, 76% of additional acetylcysteine treatment courses were in patients within a nomogram group of 100–149 mcg/mL at 4 hours and only 6% within a nomogram group of 150–199 mcg/mL. The authors suggest that lowering the UK nomogram treatment threshold to 150 mcg/mL at 4 hours, which is used by several other countries including the United States, would not substantially increase the number of patients being exposed to acetylcysteine compared with lowering the threshold to 100 mcg/mL.

These two publications investigating the impact of using lower thresholds for acetylcysteine treatment nomograms provided substantial evidence for the risk associated with acetylcysteine therapy (Bateman 2014a, 2014b). Anaphylactoid reactions with acetylcysteine therapy appear to be more common in patients with lower acetaminophen concentrations (see further discussion later) and would therefore be expected to occur more often if lower nomogram thresholds were used. Health care costs continue to be a concern; expanding treatment to all patients with lower acetaminophen concentrations could result in a substantial financial burden when considering both acetylcysteine and hospital admission costs. From decades of published experience treating acetaminophen toxicity, it is apparent that most patients with serum concentrations below the currently used nomogram thresholds (150-mcg/mL line at 4 hours) are at low risk of developing hepatotoxicity without treatment. An alternative path for future research would be to identify risk factors for hepatotoxicity at seemingly low-risk serum acetaminophen concentrations after overdose to avoid unnecessary acetylcysteine administration.

Acetaminophen-Aminotransferase Product

One benefit of the Rumack-Matthew nomogram is the relative ease of application using a commonly available laboratory test. The interest in predicting toxicity in a wide range of clinical scenarios using readily available tests led to the creation of the acetaminophen-aminotransferase (AT) multiplication product (acetaminophen x AT). The initial investigation used the highest AT concentration, but subsequent publications used ALT. Of importance in considering the usefulness of this product is the general trend of serum acetaminophen and AT concentrations after poisoning. If a patient develops hepatotoxicity, acetaminophen concentrations will generally decrease, but AT concentrations are expected to increase quickly, causing the acetaminophen x AT to be persistently elevated. Patients who do not develop hepatotoxicity may have an initially elevated serum acetaminophen concentration that decreases over time with stable AT concentrations, also causing the acetaminophen x AT to decrease over time. For these reasons, use of a single acetaminophen x AT or possibly the trend over time has been suggested as a promising tool for evaluating the risk of hepatotoxicity.

The initial study investigation into the use of acetaminophen x AT assessed 94 patients with single, acute acetaminophen ingestions who developed hepatotoxicity (Sivilotti 2010). These findings suggest that patients were at risk of developing hepatotoxicity with an acetaminophen x AT of greater than 1500 mg/L x IU/L and proposed potential usefulness in serial calculations of this product in estimating risk. Many studies have validated this approach and found high sensitivity and specificity for using an acetaminophen x AT of greater than 1500 mg/L x IU/L in single, acute ingestions (Wong 2017a, 2015; Chomchai 2014). Several publications also evaluate the use of acetaminophen x AT in other

acetaminophen overdose scenarios, two of which reported small samples and are currently only available in abstract form (Wong 2017a). To date, the largest study evaluating this tool was a retrospective analysis of 3823 patients with varying acetaminophen overdose scenarios. An acetaminophen x AT of greater than 1500 mg/L x IU/L had 100% sensitivity and 92% specificity in predicting hepatotoxicity for patients with single, acute ingestions (Wong 2015). Developing hepatotoxicity is more likely for an acetaminophen x AT of greater than 10,000 mg/L x IU/L, particularly when taken more than 8 hours after ingestion (Wong 2015; Chomchai 2014). A study evaluating overdose of modified-release preparations found that patients who developed hepatotoxicity had an initial acetaminophen x AT of greater than 10,000 mg/L x IU/L; however, study numbers were small and included 73 total patients, with 5 developing hepatotoxicity (Wong 2017b). Currently, there are no reports of hepatotoxicity developing in patients with an acetaminophen x AT of less than 1500 mg/L x IU/L calculated on presentation (Wong 2017a).

According to current evidence, an acetaminophen x AT greater than 10,000 mg/L x IU/L is associated with a high likelihood of developing hepatotoxicity, particularly in patients who are initiated on acetylcysteine therapy more than 8 hours after ingestion. In addition, an acetaminophen x AT less than 1500 mg/L x IU/L is associated with a low likelihood of developing hepatotoxicity. Although less specific when calculated within 8 hours of exposure, repeat calculations may provide further clarification and appear to have higher specificity than earlier calculations. Currently, this measure has only been evaluated for predicting hepatotoxicity. Future directions for research may include identifying appropriate cutoffs for determining which patients would benefit from acetylcysteine therapy, evaluating alternative acetylcysteine regimens to prevent hepatotoxicity in high-risk patients, and identifying patients at low risk of toxicity who might be suitable for abbreviated courses of acetylcysteine.

Psi Parameter

In an effort to address the pitfalls of the Rumack-Matthew nomogram, a group of researchers in 2005 developed the psi parameter. Similar to the Rumack-Matthew nomogram, the psi parameter mathematical model is applied to patients with single, acute ingestions with known times of ingestion; however, it also considers time to acetylcysteine initiation because this is a known risk factor for developing hepatotoxicity. This parameter estimates the quantity of toxic metabolite produced after overdose, which is expected to be a marker of risk of hepatic damage (Sivilotti 2005a).

The psi parameter was initially evaluated by a retrospective review of 1270 patients from a large multicenter Canadian registry (Sivilotti 2005b). The psi parameter identified all 94 patients who developed hepatotoxicity. In addition, no patients who developed hepatotoxicity were classified as having less than 1% risk, according to the parameter. A sensitivity analysis that used different numbers for several of the assumed contributors to the model found that a 6-hour lag time to NAPQI production provided the best fit. An interesting finding regarding ethanol estimated a median hepatotoxic dose (considering the amount of acetaminophen ingested in addition to the time without acetylcysteine) as ψ = 16.5 mmol/L x hour without ethanol, 27.1 mmol/L x hour with ethanol co-ingestion, and 4.79 mmol/L x hour in patients with alcoholic use disorders without ethanol co-ingestion. These findings support previous hypotheses that patients with alcohol use disorder are at a higher risk of hepatotoxicity with an acetaminophen overdose in the absence of ethanol co-ingestion and that acute ethanol co-ingestion may protect against hepatotoxicity. The authors also developed a nomogram because of their findings that can be used to estimate the risk of hepatotoxicity using patient-specific factors of acetaminophen concentration after overdose and time to acetylcysteine initiation. Of importance, development of this model excluded chronic ethanol users and patients with ethanol co-ingestion; however, the authors provided potential adjustment factors according to their findings for these populations.

Several studies have sought to validate use of the psi parameter in predicting hepatotoxicity. A retrospective analysis of 127 patients in Thailand found a significant relationship between the psi parameter and the development of hepatotoxicity (Chomchai 2011). In contrast to the original study, the authors found that a 4-hour lag time provided the best predictability for hepatotoxicity. This data set was expanded to include 255 patients and used a lag time of 6 hours, as suggested by the original investigation. The authors identified a cutoff value for a psi of 5 mmol/L x hour, above which 62% of patients developed hepatotoxicity. Of interest, in this study, the psi parameter was more sensitive and specific than the acetaminophen x AT product, suggesting that acetaminophen x AT is more useful in patients with unknown ingestion times when neither the Rumack-Matthew nomogram nor the psi parameter can be applied (Chomchai 2014).

Although the psi parameter can only be applied to single, acute ingestions with a known time of ingestion, it has the added benefit of considering time to acetylcysteine treatment and potential risk of hepatotoxicity with later initiation of therapy. The parameter itself may be complex to calculate; however, online tools and the psi nomogram (Figure 2) may prove more user-friendly (Wong 2017a). An additional limitation is that the psi parameter was calculated on the basis of pharmacokinetic models with several assumptions, including the time to critical glutathione depletion causing hepatic damage and the threshold acetaminophen concentration when hepatic damage occurs (Sivilotti 2005a). These assumptions are based on standard calculations of glutathione depletion with acetaminophen toxicity and may not apply to all patients, particularly those at higher risk of

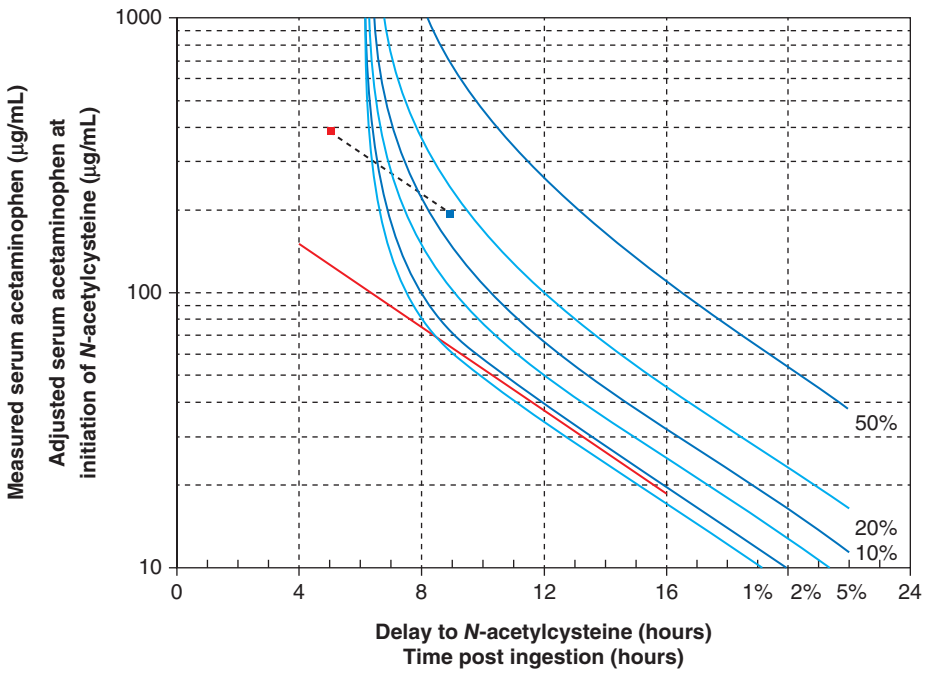

Figure 2. Risk of hepatotoxicity after paracetamol overdose treated with acetylcysteine.

The graph illustrates the probability of developing hepatotoxicity after acute acetaminophen overdose (blue lines). The 150 mcg/mL at 4-hour line of the Rumack-Matthew nomogram is included (red line). To use the graph, plot the [APAP (acetaminophen)] measured at least 4 hr after ingestion; then draw a line parallel to the red Rumack-Matthew nomogram line until reaching the time of acetylcysteine (NAC) initiation. The risk of hepatotoxicity is estimated using the blue lines. For example, a patient with a 5-hr acetaminophen concentration of 380 mcg/mL (red square) is initiated on NAC at 9 hr post-ingestion (blue square) and has a 15% risk of hepatotoxicity.

Reprinted with permission from: Sivilotti MLA, Yarema MC, Juurlink DN, et al. A risk quantification instrument for acute acetaminophen overdose patients treated with *N*-acetylcysteine. Ann Emerg Med 2005;46:263-71.

hepatic damage. According to current studies, it is unclear which lag time input would provide the highest sensitivity/specificity for predicting hepatotoxicity. In addition, one study suggested a psi cutoff of 5 mmol/L x hour as a potential marker of hepatotoxicity, but this was not subsequently evaluated (Chomchai 2014). Another potential application that has been suggested for the psi nomogram includes identifying patients at particularly low risk of hepatotoxicity (less than 1%) with acetylcysteine treatment who may not require laboratory evaluation after treatment completion (Bond 2005). Overall, the psi calculation and nomogram require further validation in larger patient cohorts, particularly for confirming the parameter's ability to identify hepatotoxicity risk in chronic ethanol users or those with ethanol co-ingestion. This ability may provide additional risk characterization in patients with single, acute ingestions and known times of ingestion compared with the traditional Rumack-Matthew nomogram.

Other Biomarkers

Limitations of available risk assessment techniques have led to the investigation of other biomarkers that may provide additional information regarding risk of hepatotoxicity or poor outcomes. Ideally, new biomarkers would be specific to acetaminophen poisoning, have reliable thresholds for risk assessment, and be easily measured in patient samples. Although the following biomarkers are not currently available in clinical practice, their discussion in the text that follows is meant as an introduction for potential future use.

Acetaminophen-Protein Adducts

Acetaminophen metabolism to NAPQI results in the rapid conjugation of NAPQI to hepatic proteins. These protein adducts can be measured in the serum longer than acetaminophen and appear similar kinetically to ALT concentrations (Wong 2017a). Several studies evaluating the use of these adducts after acetaminophen exposure suggest that concentrations greater than 1.1 nmol/mL show acetaminophen toxicity, whereas concentrations less than 0.5 nmol/mL are more consistent with therapeutic doses (Heard 2011). An important

limitation to using adducts for risk assessment in acetaminophen toxicity is the low likelihood of early elevation after overdose because of the delay in NAPQI formation until a critical level of glutathione depletion is achieved. One area in which adduct measurement may provide clinical insight is in the diagnosis of patients with liver failure of unknown etiology (Frey 2015). A rapid immunoassay for detection of adducts has been developed and found to have 100% sensitivity and 86.2% specificity in identifying acute liver failure associated with acetaminophen. Further validation is required before clinical use can be recommended (Roberts 2017).

Mechanistic Biomarkers

Previous evaluations of acetaminophen toxicity in rodent models identified several alternative markers of hepatotoxicity, including microRNA-122, high mobility group box-1, keratin-18, and glutamate dehydrogenase. These biomarkers were subsequently studied in a human population presenting with single, acute acetaminophen ingestions (Antoine 2013). All patients had serum samples taken for biomarker evaluation before acetylcysteine initiation. Biomarker concentrations at presentation significantly correlated with peak transaminase concentrations during admission. In addition, these biomarkers were significantly higher at presentation in patients with initially normal transaminase concentrations who subsequently developed acute hepatic injury and in patients with samples taken within 8 hours of acetaminophen ingestion. All biomarkers studied had improved positive and negative predictive values for developing hepatic injury within 8 hours of ingestion compared with serum acetaminophen concentration at presentation, extrapolated 4-hour serum acetaminophen concentration, and ALT value.

Alternative biomarkers have shown promise for potential use as early predictors of hepatic injury risk after acetaminophen overdose (Table 1). Of importance, many of these biomarkers appear to be increased before transaminase concentrations, which may provide additional risk assessment for patients presenting early after ingestion (McGill 2014). Further investigation in larger patient cohorts is needed to better define the role of alternative biomarkers in early risk assessment for acetaminophen toxicity.

Alternative Acetylcysteine Dose Strategies

Currently, both oral and intravenous dosing regimens are FDA approved for treating acetaminophen toxicity with acetylcysteine. The oral regimen is administered as a 140-mg/kg loading dose, followed by 70 mg/kg every 4 hours for 17 doses (Smilkstein 1988). This regimen was developed on the basis of estimations of glutathione depletion after a 15.9-g acetaminophen ingestion in a 70-kg adult with an acetaminophen half-life of 4 hours; natural glutathione turnover, higher acetaminophen doses, and longer half-lives in overdose were also considered. Given these calculations, the initial dose presented to the FDA suggested a loading dose of 48 mg/kg, followed by 24 mg/kg every 4 hours for 60 hours. However, the FDA encouraged a more conservative dose, which resulted in the currently approved regimen (Rumack 2012).

The intravenous acetylcysteine regimen ("three-bag" regimen) is approved for administration as a 150-mg/kg load over 1 hour, followed by 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours (Prescott 1979). Thus, the total duration of infusion is at least 21 hours. Development of this dose was likely based on similar assumptions and calculations described previously because the dose and duration would be sufficient to treat a 15.9-g ingestion in a 70-kg adult with an acetaminophen half-life of 4 hours (Rumack 2012). Unlike with the oral regimen, no additional dose adjustments were included to account for larger ingestions or longer half-lives. Clinical experience with the intravenous regimen worldwide led to its approval for use in the United States in 2004 as an alternative option because of its ease of administration (Rumack 2012). The traditional intravenous acetylcysteine regimen was previously shown in a retrospective analysis to improve transplant-free survival in patients with acetaminophen -induced fulminant hepatic failure (Harrison 1990). To date, no randomized controlled trials have evaluated the optimal acetylcysteine dose for preventing morbidity and mortality.

Drawbacks of Traditional Dosing

Despite significant differences in treatment durations between the oral and intravenous regimens, alternative end points of therapy have been suggested. The oral regimen can be discontinued before 72 hours of therapy or the intravenous regimen extended beyond 21 hours if certain criteria are met. Criteria to discontinue oral therapy early, according to expert recommendations, include undetectable serum acetaminophen concentrations, normal or improving hepatic function, and a patient who is otherwise clinically well (Dart 2007). A more recent publication evaluated the potential usefulness of the AST/ALT ratio in predicting hepatic recovery for patients with hepatotoxicity as a surrogate for acetylcysteine cessation. The authors found that a ratio of less than 0.4 was highly sensitive for identifying patients with improving transaminitis (McGovern 2015). Of importance, only 37 patients were evaluated, and this has not been validated in a larger cohort. In addition, patients meeting the King's College Hospital criteria or those receiving a hepatic transplant were excluded from the analysis; therefore, this prediction can only be applied to patients without evidence of a poor prognosis. Despite these limitations, the AST/ALT ratio be a useful end point, particularly if the treatment team is requesting a detailed measure of resolving hepatotoxicity.

Many studies have validated the safety of early cessation of the oral regimen in patients meeting such end points before 72 hours of therapy (Betten 2009; Betten 2007; Tsai 2005;

Table 1. Summary of Alternative Acetaminophen (APAP) Poisoning Risk Assessment Techniques[a]

Technique	Description	Clinical Scenario	Findings	Recommendation/Rationale
Lower APAP concentration nomograms	Rumack-Matthew nomogram with 4-hr concentration of 100 mcg/mL indicating need for treatment	Used in the UK. Originally recommended for patients with chronic alcohol use disorder, those receiving enzyme-inducing medications, and those with malnutrition. Since 2012, used in all patients	1-yr pre/post-protocol change: 31% of presentations in the year prior compared with 43% the year after the protocol change received NAC. Of the additional courses, 76% were in patients in a nomogram group of 100–149 mcg/mL at 4 hr. Estimated cost impact for all changes in treatment of APAP toxicity in the UK was $10.7 million	Recommended in certain patients. Appears appropriate in patients with chronic alcoholic use disorder without ethanol co-ingestion. Use in all patients would likely increase adverse effects and cost with minimal benefit
APAP x AT	Multiplication product of the serum APAP and AT concentration on the same laboratory test	Acute ingestions, repeated supratherapeutic ingestions, or unknown ingestions (all receiving IV NAC therapy)	Hepatotoxicity has not developed in any patient with a product < 1500 mcg/mL x IU/L on presentation. A product over this cutoff was more predictive of hepatotoxicity in patients with repeated supratherapeutic or late-presenting patients. A product > 10,000 mcg/mL x IU/L in patients with single, acute ingestions starting NAC > 8 hr post-ingestion indicates high risk of hepatotoxicity	Available for use in all patients. May be particularly useful in patients with unknown times of ingestion or repeated supratherapeutic ingestions and for identifying patients not requiring repeat laboratory tests after therapy completion. Further study as a technique for identifying patients needing NAC therapy or testing alternative NAC regimens is warranted
Psi	Mathematical calculation identifying the "hepatotoxic dose" considering APAP concentration and time to NAC initiation. Also available as a nomogram (see Figure 2)	Single, acute ingestions receiving IV NAC therapy	Initial study validating equation identified a median hepatotoxic dose of 16.5 mmol/L x hour without ethanol, 27.1 mmol/L x hour with ethanol, and 4.79 mmol/L x hour in alcoholic patients without ethanol co-ingestion. Nomogram developed with lines indicating varying percentage risks of hepatotoxicity. No patients with < 1% hepatotoxicity on nomogram have developed hepatotoxicity	Available for use in all patients with single, acute ingestions. Nomogram appears easier to use than actual calculation. May be particularly useful for identifying patients not requiring repeat laboratory tests after therapy completion (< 1% risk per nomogram). Further validation in patients with alcohol use disorder is warranted
APAP-protein adducts[a]	Products of NAPQI conjugation with hepatic proteins	Evaluated in APAP overdose, therapeutic APAP use, acute liver failure of unknown cause	Concentrations > 1.1 nmol/mL suggest APAP toxicity, whereas concentrations < 0.5 nmol/mL are more consistent with therapeutic doses	May be particularly useful in the diagnosis of patients with acute liver failure of unknown etiology
Mechanistic biomarkers[a]	microRNA-122, high-mobility group box-1, keratin-18, glutamate dehydrogenase	Evaluated on the initial laboratory test at hospital presentation in patients with single, acute ingestions	Significant correlation with peak ALT and INR. Significantly better than ALT, INR, and APAP concentration predicting acute liver injury in patients presenting within 8 hr of ingestion with initially normal ALT	May be particularly useful in the early identification of patients at risk of developing hepatotoxicity. May be increased before transaminase concentrations

Table 1. Summary of Alternative APAP Poisoning Risk Assessment Techniques[a] (*continued*)

[a]Currently available for research purposes only.

APAP = acetaminophen; AT = aminotransferase; IV = intravenous(ly); NAC = acetylcysteine; NAPQI = *N*-acetyl-*p*-benzoquinoneimine.

Information from: Antoine DJ, Dear JW, Starkey Lewis P, et al. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. Hepatology 2013;58:777-87; Bateman DN, Carroll R, Pettie J, et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. Br J Clin Pharmacol 2014;78:610-8; Bateman DN, Dear JW, Carroll R, et al. Impact of reducing the threshold for acetylcysteine treatment in acute paracetamol poisoning: the recent United Kingdom experience. Clin Toxicol (Phila) 2014;52:868-72; Bond GR. A new acetaminophen nomogram with a different purpose. Ann Emerg Med 2005;46:272-74; Bond GR. Acetaminophen protein adducts: a review. Clin Toxicol 2009;47:2-7; Chomchai S, Chomchai C. Predicting acute acetaminophen hepatotoxicity with acetaminophen-aminotransferase multiplication product and the Psi parameter. Clin Toxicol 2014;52:506-11; Chomchai S, Chomchai C, Anusornsuwan T. Acetaminophen psi parameter: a useful tool to quantify hepatotoxicity risk in acute acetaminophen overdose. Clin Toxicol (Phila) 2011;49:664-67; Sivilotti MLA, Green TJ, Langmann C, et al. Multiplying the serum aminotransferase by the acetaminophen concentration to predict toxicity following overdose. Clin Toxicol (Phila) 2010;48:793-9; Sivilotti MLA, Yarema MC, Juurlink DN, et al. A risk quantification instrument for acute acetaminophen overdose patients treated with *N*-acetylcysteine. Ann Emerg Med 2005b;46:263-71; Wong A, Graudins A. Risk prediction of hepatotoxicity in paracetamol poisoning. Clin Toxicol (Phila) 2017a;55:879-92; Wong A, Sivilotti MLA, Dargan PI, et al. External validation of the paracetamol-aminotransferase multiplication product to predict hepatotoxicity from paracetamol overdose. Clin Toxicol (Phila) 2015;53:807-14; Wong A, Sivilotti MLA, Graudins A. Accuracy of the paracetamol-aminotransferase multiplication product to predict hepatotoxicity in modified-release paracetamol overdose. Clin Toxicol (Phila) 2017b;55:346-51.

Woo 2000). In contrast, evidence suggests potential harm if the intravenous regimen is discontinued after completing 21 hours but before meeting suggested end points (Doyon 2009; Smith 2008). Questions remain about the necessity of 21 hours of therapy in all patients when shorter courses of therapy may prevent hepatotoxicity and decrease length of stay in certain patients (Bateman 2014c) (Box 2).

Adverse Effects

Oral acetylcysteine is associated with high rates of nausea and vomiting related to the product's strong smell of sulfur. Thus, oral use has declined in recent years (Bronstein 2012; Bebarta 2010). Recently, an alternative oral dosage form became available in the United States as effervescent lemon-mint flavored tablets for oral solution (Cetylev). Despite the goal of providing an alternative treatment experience for patients receiving oral acetylcysteine for acetaminophen toxicity, a small bioequivalence study found no difference in rates of GI adverse effects between the two oral formulations; further research is needed to confirm this finding (Greene 2016).

Parenteral acetylcysteine is also commonly associated with adverse effects. Nausea and vomiting have been described in up to 60% of patients, even without exposure to the product scent during administration (Bateman 2014c). Anaphylactoid reactions are also reported in up to 20% of patients in retrospective studies and over 60% of patients in prospective evaluations (Bateman 2014c; Sandilands 2009). Histamine appears to play an important role in the occurrence of anaphylactoid reactions, given that patients having more severe reactions had higher serum histamine concentrations than did those with milder symptoms (Pakravan 2008). In addition, these reactions appear to be related to higher acetylcysteine concentrations, given that they are more common during the initial hour of therapy and have been reported at a higher frequency in patients receiving inadvertent overdoses of acetylcysteine (Sandilands 2009). In fact, original dose recommendations for the intravenous protocol involved administering the initial bolus over 15 minutes; however, because of concerns regarding anaphylactoid reactions with this approach, the administration time was modified to a 60-minute infusion. These findings call into question whether the current intravenous regimen is ideal or whether providing alternative doses might reduce the occurrence of adverse effects while maintaining the same degree of efficacy.

Anaphylactoid reactions to intravenous acetylcysteine are more common in patients with lower acetaminophen concentrations (Schmidt 2013; Sandilands 2009; Pakravan 2008; Waring 2008). High acetaminophen concentrations have been associated with anti-inflammatory effects

Box 2. Current Dilemmas in NAC Dosing for APAP Toxicity

- Reducing adverse effects
- Reducing medication errors
- Preventing hepatotoxicity in patients with massive overdoses

APAP = acetaminophen; NAC = acetylcysteine.

Information from: Bateman DN, Dear JW, Thomas SHL. New regimens for intravenous acetylcysteine, where are we now? Clin Toxicol (Phila) 2016;52:75-8; and Chiew AL, Isbister GK, Duffull SB, et al. Evidence for the changing regimens of acetylcysteine. Br J Clin Pharmacol 2015;81:471-81.

through cyclooxygenase inhibition and decreased synthesis of prostaglandin and thromboxane. These effects may also reduce anaphylactoid reactions by decreasing the inflammatory response resulting from high acetylcysteine concentrations (Pakravan 2008). This association of anaphylactoid reactions with lower acetaminophen concentrations is of particular concern when considering current practice in many countries that recommend administering acetylcysteine for acetaminophen toxicity even at low serum concentrations (Bateman 2014c; Schmidt 2013). Alternative regimens that reduce peak acetylcysteine concentrations may decrease anaphylactoid reactions and therefore improve overall tolerability. Revised regimens to provide the same overall 300-mg/kg dose as the traditional intravenous regimen, but with modifications to the initial loading dose to reduce peak acetylcysteine concentrations and reduce adverse effects, have been described.

12-Hour Regimen

A randomized, multicenter, double-blind, controlled trial was conducted with four treatment groups including standard and modified intravenous acetylcysteine regimens with and without ondansetron (Bateman 2014c). The modified regimen consisted of 100 mg/kg intravenously over 2 hours, followed by 200 mg/kg intravenously over 10 hours. Nausea and vomiting were significantly reduced with the modified intravenous acetylcysteine regimen compared with the standard regimen and with the use of ondansetron pretreatment compared with placebo. Severe anaphylactoid reactions were reported in 5 of 108 patients (5%) treated with the modified regimens compared with 31 of 109 patients (28%) receiving the standard protocol (adjusted OR 0.23; 97.5% CI, 0.12–0.43). A reported 50% increase in ALT activity was not statistically different between the modified treatment regimen group (12%) and the standard regimen group (8%); however, the study was not powered to measure efficacy. Of interest, a higher frequency of 50% increase in ALT activity occurred in patients receiving ondansetron compared with placebo (adjusted OR 3.3; 97.5% CI, 1.01–10.72). The authors speculate that this was because of altered acetaminophen metabolism, glutathione synthesis, or possibly a direct effect on a stressed liver. Of importance, this did not affect clinical outcomes and requires further investigation for validation.

20-Hour Regimen

A retrospective study reported experience with a "two-bag" intravenous acetylcysteine regimen that combined the first two doses for a modified loading dose and compared this regimen with the standard 21-hour protocol to evaluate the incidence of anaphylactoid reactions and GI effects compared with the traditional regimen (Wong 2016). The study group received an initial dose of 200 mg/kg intravenously over 4 hours at a rate of 50 mg/kg/hour, followed by the traditional third dose of 100 mg/kg over 16 hours. Anaphylactoid reactions were classified as cutaneous reactions or more severe reactions that also included respiratory symptoms and hemodynamic instability. These reactions occurred in 40 of 389 patients (10%) receiving the traditional regimen compared with 9 of 210 patients (4.3%) receiving the modified regimen (OR 2.5; 95% CI, 1.1–5.8). Severe reactions were also decreased in the modified 20-hour dosing regimen group (2.5% vs. 0.5%; p=0.0001). Patients with anaphylactoid reactions had a lower median acetaminophen concentration than those who did not, regardless of the regimen. This finding is consistent with previous studies that have identified higher rates of anaphylactoid reactions with lower serum acetaminophen concentrations. Although the study was not powered for these end points, there were no differences in GI effects and hepatotoxicity.

Variable Duration Regimen

A prospective, observational study evaluated a novel two-phase infusion regimen in patients reporting an ingestion of over 4 g (Isbister 2016). The initial infusion was administered at a dose of 200 mg/kg over 4–9 hours on the basis of time from reported ingestion. After completion of the initial infusion, all patients were given 100 mg/kg intravenously over 16 hours. Acetylcysteine administration was discontinued if the acetaminophen serum concentration was below the nomogram line correlating with a 150-mg/mL concentration at 4 hours or if transaminases were normal at 24 hours post-ingestion for repeated supratherapeutic ingestions. In the 654 patients treated with the regimen, 64% had treatment discontinued early because of a low-risk acetaminophen concentration according to the nomogram. Adverse reactions were reported in 229 of 654 patients (35%), with 173 (26.5%) having GI effects alone; cutaneous hypersensitivity reactions were reported in 50 patients (8%), and severe hypersensitivity reactions with hypotension occurred in three patients (0.5%). Higher rates of adverse effects were identified in patients receiving the full course of acetylcysteine than in those who had the infusion discontinued (111 of 231 [48%] vs. 116 of 420 [28%], p<0.0001). Sixteen patients developed hepatotoxicity, all of whom were initiated on acetylcysteine more than 12 hours post-ingestion. Medication errors were identified four times; three were related to incorrect infusion rate of the first dose and one was acetylcysteine discontinuation in error. The authors concluded that rates of hypersensitivity reactions were lower than those reported in previous prospective studies with similar rates of GI adverse reactions. In addition, the authors concluded that with the rate of adverse reactions identified in low-risk patients, it was likely not beneficial to initiate NAC in all patients when they presented. Although not powered to evaluate efficacy compared with historical controls, the authors advocated giving the initial 200 mg/kg over 4 hours in all patients with toxic acetaminophen concentrations, followed by 100 mg/kg over 16 hours.

Complexity of Traditional Parenteral Regimen

The traditional three-bag regimen consists of three separate intravenous infusions. Each of these infusions are different doses, prepared in different volumes, and administered over different times. A study supporting complexity concerns found that 33% of patients experienced a medication error related to intravenous acetylcysteine administration, including 18.6% of patients with more than a 1-hour interruption in therapy and 13.1% of patients receiving an unnecessary administration (Hayes 2008). It raises additional concern that 13.1% of patients received unnecessary therapy when considering potentially serious adverse reactions with intravenous acetylcysteine administration, particularly in patients with lower serum APAP concentrations. Alternative regimens studied in the United States have aimed to reduce the complexity of the current regimen with the goal of minimizing administration errors and potentially improving efficacy.

Bolus Followed by 14 mg/kg/hr

A single-center published experience with an alternative acetylcysteine regimen in a retrospective study evaluating medication errors, hepatotoxicity resolution, and adverse effects (Johnson 2011). The protocol used a compounded product of 30 g of acetylcysteine in 1000 mL of dextrose 5% in water administered as 150 mg/kg over 60 minutes, followed by 14 mg/kg/hour over 20 hours (total dose 430 mg/kg). Sixty-five patients received the alternative regimen, and five patients received the traditional regimen. Overall, 38% of patients receiving the alternative regimen had a medication error compared with 60% of patients receiving the standard regimen, though the trial was not powered to detect this difference. Therapy interruptions in this 2011 study were identified in 8% of patients, all of whom weighed greater than 69 kg and required more than the 30-g dose initially prepared (Johnson 2011). This rate was lower than in a previously published report, which found a therapy interruption rate of 19% using the traditional intravenous acetylcysteine regimen (Hayes 2008). This previously published report also found that 16 patients experienced hepatotoxicity, with one fatality. In addition, the 2011 study authors identified one adverse reaction attributed to acetylcysteine therapy in a patient developing a severe anaphylactoid reaction with respiratory difficulty and a cutaneous reaction; symptoms resolved with diphenhydramine and decreasing the infusion rate. The authors concluded that this regimen may be acceptable, particularly in institutions with limited experience in using intravenous acetylcysteine as a way to mitigate administration errors (Johnson 2011).

Bolus Followed by 15 mg/kg/hr

A similar retrospective analysis published more recently evaluated an intravenous acetylcysteine dose of 150 mg/kg over 1 hour, followed by a continuous infusion of 15 mg/kg/hour in pediatric patients (2 months to 18 years); this rate was continued until the acetaminophen concentration was less than 10 mcg/mL and until transaminases were normal or trending downward (Pauley 2015). Fifty-nine patients were included in the analysis, with only 3.4% developing hepatotoxicity and 3.4% having an anaphylactoid reaction. These rates were generally lower than in previously published studies of the traditional regimen; however, comparisons are difficult, given the small sample size. No medication errors were identified. In addition, the mean duration of infusion was 30 hours with an average total dose of 600 mg/kg (Pauley 2015), which was longer than the previously reported 25.6 hours in adults using 14 mg/kg/hour (Johnson 2011). The authors concluded that the regimen appeared to be safe and effective compared with the traditional regimen and may be associated with fewer medication errors (Pauley 2015).

Hepatotoxicity Despite Early Treatment Initiation

The intravenous acetylcysteine regimen is considered highly effective for preventing hepatotoxicity after acetaminophen overdose. However, it is still uncertain whether the dose is sufficient in all patients, particularly in those with larger ingestions (Rumack 2012). A retrospective study evaluating efficacy in patients who received intravenous acetylcysteine within 8 hours of acetaminophen ingestion reported that 5.2% had developed hepatotoxicity, leading to one death and one liver transplantation (Doyon 2009). Of importance, the average peak acetaminophen concentration was over 400 mcg/mL in patients requiring intravenous acetylcysteine beyond 21 hours compared with close to 200 mcg/mL in patients not requiring additional therapy. Similarly, a more recent retrospective study evaluated initial serum acetaminophen concentrations on the development of acute liver injury (ALT greater than 150 IU/L and double the admission value) by taking this initial concentration and back-extrapolating to estimate a 4-hour acetaminophen serum concentration using the traditional 4-hour half-life (Cairney 2016). Patients were then separated into groups on the basis of nomogram ranges. Although this method is likely error-prone and does not account for the long half-lives reported in severe toxicity, the findings support a dose-response relationship in acetaminophen concentrations and the development of acute liver injury, even if patients were administered acetylcysteine within 8 hours of ingestion. Rates of acute liver injury were 0% (0–100 mcg/mL), 0.8% (101–150 mcg/mL), 2% (151–200 mcg/mL), 3.6% (201–300 mcg/mL), 12.5% (301–500 mcg/mL), and 33% (greater than 500 mcg/mL).

Acetylcysteine Alternatives for Massive Overdoses

Because the traditional intravenous acetylcysteine regimen was likely based on estimations of glutathione depletion after a 15.9-g ingestion in a 70-kg patient (227.1 mg/kg), calculations could theoretically be used to determine acetylcysteine requirements in patients with larger ingestions (Table 2). Assuming similar conditions of glutathione storage, turnover,

Table 2. Summary of Alternative Acetylcysteine (NAC) Regimens

Regimen	Dose	Clinical Scenario	Findings	Recommendation/Rationale
300 mg/kg IV (12 hr)	100 mg/kg over 2 hr, 200 mg/kg over 10 hr	Randomized controlled trial comparing the standard IV NAC regimen (20.25 hr; n=109) with a modified regimen (12 hr; n=108)	Less vomiting, fewer anaphylactoid reactions, and less need for treatment interruption in patients receiving the modified regimen. 96% had acetaminophen concentration < 20 mcg/mL at the end of the modified regimen (no patients with a normal ALT at this point developed significant liver injury)	Do not recommend regular use. Study was not powered to detect differences in efficacy. Although many patients appear to do well with shorter NAC courses, more evidence is needed to identify appropriate patients for use
300 mg/kg IV (20 hr)	200 mg/kg over 4 hr, 100 mg/kg over 16 hr	Retrospective study comparing the standard IV NAC regimen (21 hr; n=389) with a modified regimen (20 hr; n=210)	Modified regimen was associated with significantly fewer anaphylactoid reactions (10% vs. 4.3%, p=0.02, OR 2.5, 95% CI [1.1–5.8]). No difference in GI complaints were identified (traditional 39% vs. modified 41%, p=0.38; OR 1.17; 95% CI [0.83–1.65])	Consider use in all patients after prospective validation to confirm noninferiority. Provides the same NAC dose over a similar length of time while also associated with significant reduction in anaphylactoid reactions
300 mg/kg IV (variable duration)	200 mg/kg over 4–9 hr, 100 mg/kg over 16 hr	Prospective study of a modified regimen (20–25 hr; n=654). Initial dose started on presentation and given over 4–9 hr based on time from ingestion. Discontinued early if below nomogram line	Adverse reactions occurred in 35% of patients (95% CI, 31%–39%), including 173 with GI issues (26.5%; 95% CI, 23%–30%), 50 with cutaneous reactions (8%; 95% CI, 6%–10%), and three with hypotension (0.5%; 95% CI, 0.1%–1.5%). NAC was discontinued in 64% of patients because of low-risk concentrations. In 200 overdoses < 10 g, one had toxic paracetamol concentrations, but 53 developed reactions	Do not recommend regular use. Adverse effects appear to be mitigated using other strategies that are consistent for every patient and thus more likely to limit confusion and prevent medication errors. Rate of adverse effects in patients not needing NAC was unacceptable
Bolus followed by 14 mg/kg/hr IV	150 mg/kg over 1 hr, 14 mg/kg/hr for 20 hr	Retrospective evaluation of medication errors using a modified regimen (21 hr; n=70) compared with the traditional regimen (21 hr; n=5)	Medication errors occurred in 43% of patients receiving modified regimen compared with 60% of patients receiving traditional regimen (p=0.383; OR 1.53; 95% CI, 0.52–4.57). Average length of therapy was 25.6 hr. Hepatotoxicity developed in 16 patients with one death	Consider use in special circumstances. Providing a single IV product may be favorable at institutions with limited pharmacy availability. Dose is likely higher than necessary for lower-risk ingestions but may play a role in massive overdoses. Larger studies evaluating adverse reactions are warranted
Bolus followed by 15 mg/kg/hr IV	150 mg/kg over 1 hr, 15 mg/kg/hr until criteria met	Retrospective evaluation of a modified regimen in pediatric patients (variable duration; n=59)	Reported no known medication errors. Average length of therapy was 31 hr. Hepatotoxicity occurred in two patients (no deaths). Anaphylactoid reaction occurred in two patients	Do not recommend regular use. Overall length of therapy increased using this regimen, which is likely unnecessary for low-risk ingestions

Table 2. Summary of Alternative NAC Regimens (*continued*)

Regimen	Dose	Clinical Scenario	Findings	Recommendation/Rationale
Doubling the "last IV bag"	150 mg/kg over 1 hr, 50 mg/kg over 4 hr, 200 mg/kg over 16 hr	Retrospective subgroup analysis of patients with massive overdose with APAP ratio ≥ 2 Compared the traditional regimen with an increased dose in the last bag (n=79)	43 patients received increased NAC dose and had a decrease risk of hepatotoxicity compared with the traditional dose (OR 0.27; 95% CI, 0.08–0.94)	Consider use in massive overdoses. May further consider combining 200 mg/kg over 16 hr with a combined initial dose to reduce initial adverse effects while potentially improving efficacy in massive overdoses

APAP = acetaminophen; NAC = acetylcysteine; IV = intravenous(ly).

Information from: Bateman DN, Dear JW, Thanacoody HKR, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. Lancet 2014;383:697-704; Bateman DN, Dear JW, Thomas SHL. New regimens for intravenous acetylcysteine, where are we now? Clin Toxicol (Phila) 2016;52:75-8; Chiew AL, Isbister GK, Duffull SB, et al. Evidence for the changing regimens of acetylcysteine. Br J Clin Pharmacol 2015;81:471-81; Chiew AL, Isbister GK, Kirby KA, et al. Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2). Clin Toxicol (Phila) 2017;23:1-11; Isbister GK, Downes MA, Mcnamara K, et al. A prospective observational study of a novel 2-phase infusion protocol for the administration of acetylcysteine in paracetamol poisoning. Clin Toxicol (Phila) 2016;54:120-6; Johnson MT, McCammon CA, Mullins ME, et al. Evaluation of a simplified *N*-acetylcysteine dosing regimen for the treatment of acetaminophen toxicity. Ann Pharmacother 2011;45:713-20; Pauley KA, Sandritter TL, Lowry JA, et al. Evaluation of an alternative intravenous *N*-acetylcysteine regimen in pediatric patients. J Pediatr Pharmacol Ther 2015;20:178-85; Wong A, Graudins A. Simplification of the standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning results in a lower incidence of adverse drug reactions. Clin Toxicol (Phila) 2016;54:115-9.

and depletion as well as similar acetaminophen kinetics, a 300-mg/kg ingestion would require 8.25 mg/kg/hour of intravenous acetylcysteine, and a 500-mg/kg ingestion would require 13.75 mg/kg/hour. These calculations assume that all intravenous acetylcysteine is delivered directly to the liver and that NAPQI generation is in the expected range. Increased NAPQI generation may be expected with larger overdoses; therefore, even higher acetylcysteine doses may be necessary (Rumack 2012).

The only study published with clinical experience using a higher acetylcysteine dose in patients with massive overdoses was a retrospective analysis, which suggested a possible benefit of increased acetylcysteine doses in this population (Chiew 2017). The authors retrospectively reviewed patients from several databases in Australia and analyzed all patients with acetaminophen ingestions of at least 40 g. A ratio was used to compare concentrations between patients by taking the first acetaminophen serum concentration obtained at 4–16 hours and dividing it by the acetaminophen serum concentration at the same time point of the standard 150-mcg/mL line at 4 hours. Seventy-nine patients were treated within 16 hours of ingestion without initial hepatotoxicity with a calculated ratio of at least 2, which correlates to a serum acetaminophen concentration double that of the standard 150-mcg/mL line at 4 hours. Forty-three patients in this group received higher doses of intravenous acetylcysteine, typically a 200-mg/kg dose over 16 hours for the last infusion. The odds of hepatotoxicity were significantly lower in patients receiving a higher dose of intravenous acetylcysteine than in those receiving the traditional regimen (4 of 43 [9.3%] vs. 10 of 36 [27.8%]; OR 0.27; 95% CI, 0.08–0.94); this remained similar when adjusted for time to acetylcysteine treatment and acetaminophen concentration ratio. Although the study was small and retrospective, it supports previous speculation that the traditional dose of intravenous acetylcysteine is insufficient in patients with massive acetaminophen overdoses.

Special Presentations

Despite extensive clinical experience regarding expected adverse effects during both therapeutic and toxic serum concentrations of acetaminophen, additional toxicities have been described that deserve discussion.

Massive Ingestions

Severe lactic acidosis and altered mental status has been reported early in the presentation of massive acetaminophen overdose (40 g or more). Initially identified in case reports, this phenomenon has occasionally been reported in the literature since the early 1980s, suggesting the rarity (Shah 2010). Animal models have shown that high concentrations of acetaminophen and possibly NAPQI result in mitochondrial inhibition, leading to impaired aerobic cellular respiration (Shah 2010; Zein 2010). These effects occur before cellular injury and are thought to be unrelated to subsequent hepatotoxicity (Shah 2010).

A previously published review of the literature identified 24 cases of lactic acidosis after acetaminophen overdose (Shah 2010). Patients presented at a median time of 5 hours post-ingestion and usually had depressed, altered mental status with a median acetaminophen serum concentration of 844 mcg/mL. Most patients in the series were treated with the standard intravenous acetylcysteine regimen; however, the authors suggested that extended courses are warranted because of prolonged half-lives in overdose, particularly after large ingestions. In addition, extracorporeal elimination such as hemodialysis or hemofiltration was reported in nine patients, and sodium bicarbonate was given to eight patients. Fifty percent of the patients required mechanical ventilation, and 25% developed hepatotoxicity.

Management of a massive acetaminophen overdose centers on providing supportive care, including airway support, if necessary, for patients with altered mental status. A retrospective analysis of 200 patients with reported ingestions of over 40 g identified 33 patients who received activated charcoal within 4 hours of ingestion (Chiew 2017). This study reported a ratio of acetaminophen concentration to the corresponding acetaminophen concentration at the same time on the 150-mcg/mL line of the nomogram. Those who received early charcoal administration had lower reported ratios. This finding suggests the potential for activated charcoal administration to limit acetaminophen exposure after massive ingestions.

Because of the low molecular weight, low volume of distribution, and low protein binding of acetaminophen, extracorporeal elimination provides adequate removal, particularly with serum concentrations after massive overdoses. The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup, an international group of experts including nephrologists and toxicologists, recently published evidence-based consensus recommendations for extracorporeal removal of acetaminophen in overdose (Box 3).

In addition, EXTRIP suggests continuing acetylcysteine during these interventions at increased doses, given that acetylcysteine is also removed by hemodialysis. A previously published three-patient case series reported acetylcysteine extraction ratios of 73%–83% during hemodialysis (Sivilotti 2013). All patients in this series received increased acetylcysteine doses, and none developed significant coagulopathy or evidence of liver failure, despite some elevations in transaminases. The authors suggested a reasonable approach would be to double the acetylcysteine dose in patients receiving hemodialysis. An additional report assessing acetylcysteine removal during hemodialysis in 10 patients (Hernandez 2015) identified a mean extraction ratio of 51%. This suggests that doubling the intravenous acetylcysteine dose or administering oral acetylcysteine should be done in addition to providing intravenous acetylcysteine during hemodialysis. According to current evidence, acetylcysteine is removed during hemodialysis, which is of particular concern given the potential for worse outcomes in patients with significantly elevated acetaminophen concentrations. Increased acetylcysteine doses are likely warranted; however, the strategies suggested require further evaluation to determine the ideal dose to prevent or minimize hepatotoxicity after massive acetaminophen ingestions requiring hemodialysis.

Box 3. EXTRIP Recommendations for APAP Poisoning

- [APAP] > 1000 mcg/mL if NAC is not administered
- [APAP] > 700 mcg/mL with altered mental status, metabolic acidosis, and elevated lactate and NAC is not administered
- [APAP] > 900 mcg/mL with altered mental status, metabolic acidosis, and elevated lactate, even if NAC is administered

APAP = acetaminophen; EXTRIP = Extracorporeal Treatments in Poisoning workgroup; NAC = acetylcysteine.

Information from: Gosselin S, Juurlink DN, Kielstein JT, et al. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. Clin Toxicol 2014;52:856-67.

Pyroglutamic Acid Production

Another acetaminophen toxicity that has been described is the accumulation of pyroglutamic acid, also known as 5-oxoproline, in certain patients after both therapeutic use and overdose. Glutathione is synthesized and degraded through the γ-glutamyl cycle. Under normal circumstances, γ-glutamylcysteine synthetase is inhibited by glutathione concentrations through negative feedback, which prevents further glutathione synthesis. In periods of glutathione deficiency, γ-glutamylcysteine synthetase is no longer under negative feedback and subsequently produces excess γ-glutamylcysteine, which is then converted to pyroglutamic acid (Liss 2013).

Because glutathione is required for negative feedback of the γ-glutamylcysteine synthetase enzyme, clinical scenarios causing glutathione depletion are potential precipitants of pyroglutamic acid accumulation. Several risk factors have been suggested, including malnutrition, underlying infection, renal failure, female sex, and chronic acetaminophen use (Armenian 2012). Enzyme deficiencies may play a role in developing this toxicity, given that no obvious dose-response relationship has been identified in the setting of acetaminophen use (Liss 2013).

Pyroglutamic acid accumulation is typically identified in patients with a high anion gap metabolic acidosis and a negative workup for other potential causes. Although it has been reported after overdose, most reports associated with acetaminophen have been with therapeutic doses. Serum or urine identification of pyroglutamic acid is available, particularly at laboratories that test for pediatric inborn errors of metabolism (Liss 2013).

Management of acetaminophen-associated pyroglutamic acid accumulation involves supportive care for metabolic acidosis. Discontinuation of acetaminophen to prevent

Patient Care Scenario

A 56-year-old man (weight 60 kg) with a history of chronic alcohol use disorder presents to the ED at 6:00 a.m. after a reported ingestion of acetaminophen in a suicide attempt. Initial laboratory tests returning 7:00 a.m. are pertinent for an 8-hour acetaminophen concentration of 70 mcg/mL, AST 132 IU/L, ALT 46 IU/L, and a negative ethanol concentration. You work at a small community hospital, where there will be no pharmacist coverage from 11:00 p.m. to 7:00 a.m. Provide a plan for possible antidote administration and follow-up to manage this patient's acetaminophen overdose.

ANSWER

The first step is to determine whether acetylcysteine therapy is appropriate for this patient. According to the modified Rumack-Matthew nomogram suggested by the FDA, treatment would not be indicated because his concentration is below the treatment line for that period. Chronic alcohol use, particularly in the setting of a negative ethanol concentration, is of concern for the presence of increased CYP2E1 enzyme activity and production of NAPQI. Lower acetaminophen nomogram concentrations have been suggested for patients with certain risk factors such as chronic alcohol use or malnutrition or for those taking other enzyme inducers. The acetaminophen x AT concentration is greater than 1500 mg/L x IU/L, suggesting that the potential risk of developing hepatotoxicity cannot be ruled out.

The next step is to determine a treatment plan with acetylcysteine, given the constraints with hospital pharmacy hours and considering medication safety. If the patient were initiated on the traditional 21-hour protocol at 7:30 a.m., this would end at 4:30 a.m. the following day. If a pharmacist did not arrive until 7:00 a.m. that day, another dose would likely not be ready for administration until at least 7:30 a.m., causing a significant delay. Although several doses could be made the previous evening, this would pose a risk to patient safety if multiple-size infusion bags were at the bedside. Using the psi nomogram, the patient's risk of hepatotoxicity is about 5%, suggesting that his risk is not low enough to discontinue therapy at 21 hours without rechecking laboratory values. In addition, initial investigations using the psi nomogram suggest that the risk of hepatotoxicity is even greater in patients with chronic alcohol use disorder. Considering pharmacy hours, patient safety, and risk of hepatotoxicity with the ingestion, a potential option is to use a previously studied regimen of 30 g of acetylcysteine in 1000 mL of dextrose 5% in water given as an initial 150-mg/kg bolus, followed by 14 mg/kg/hour. The infusion bag would have enough medication for about 25 hours after the initial bolus, providing sufficient time for the team to check laboratory test results the next morning and order more acetylcysteine, if needed.

1. Bateman DN, Carroll R, Pettie J, et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. Br J Clin Pharmacol 2014;78:610-8.
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3. Sivilotti MLA, Yarema MC, Juurlink DN, et al. A risk quantification instrument for acute acetaminophen overdose patients treated with *N*-acetylcysteine. Ann Emerg Med 2005;46:263-71.
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further glutathione depletion is likely warranted if using an alternative antipyretic or analgesic is feasible. Several case reports have suggested that treatment with traditional-dose acetylcysteine aids in glutathione repletion. Of potential concern is that acetylcysteine is also a substrate for γ-glutamylcysteine synthetase, which may increase the production of pyroglutamic acid (Liss 2013).

SALICYLATES

Review of Salicylate Toxicity and Management

Epidemiology

Medicinal use of salicylates has long been described, dating back to ancient civilizations with use for pain relief and fever reduction. These clinical benefits have clearly withstood the test of time because salicylates remain widely used today for analgesic, antipyretic, anti-inflammatory, and antiplatelet activities. Similar to acetaminophen, salicylates are commonly found in the home and remain a common source of exposure in drug overdose and toxicity. Aspirin is the most widely used salicylate and is available in several formulations; other salicylates may be sources of toxicity, especially methyl salicylate or oil of wintergreen.

Pharmacology/Toxicology

Salicylates provide most of their pharmacologic benefit through irreversible inhibition of cyclooxygenase, the enzyme responsible for prostaglandin production, which subsequently prevents prostaglandin-mediated inflammation and fever. Therapeutically, salicylates are reserved for adult patients because of concern for Reye syndrome in children. Doses used vary widely and may be as low as 81 mg daily for cardioprotective effects or as high as 7 g daily in divided doses for inflammatory conditions. Serum concentrations targeted for inflammatory conditions are generally 15–30 mg/dL, with concentrations higher than 30 mg/dL associated with toxicity. Mild toxicity may develop after acute ingestions of 150–200 mg/kg, with severe toxicity

expected at doses exceeding 300–500 mg/kg. Chronic toxicity usually develops after several days of doses exceeding 100 mg/kg/day.

Mechanism of Toxicity

Aspirin is a weak acid with a pKa of 3.5. In therapeutic doses, it is rapidly absorbed in the stomach, where it is largely nonionized because of the acidic pH; peak concentrations are usually attained within 1 hour of the dose. Salicylates have a small volume of distribution, around 0.2 L/kg, and about 90% is bound to albumin at therapeutic concentrations. Aspirin is rapidly hydrolyzed to salicylate in the serum, which has a half-life of 2–3 hours at low doses and up to 12 hours at higher doses. Metabolism in the liver occurs before renal elimination. In overdose, kinetic changes become important in understanding toxicity. Absorption, particularly of tablet formulations, is slowed because of factors that include the propensity of salicylates to induce pylorospasm and the potential of aspirin tablets to form a bezoar in the stomach. Peak concentrations are often significantly delayed and have been reported as late as 24–36 hours after ingestion. Volume of distribution increases with elevated concentrations or low serum pH, whereas protein binding decreases, both of which result in larger amounts of free drug reaching tissues. Serum half-life is substantially prolonged at toxic concentrations as several pathways of hepatic biotransformation become saturated.

Elevated serum concentrations are associated with well-established toxicities. The primary mechanism is impaired cellular respiration through Krebs cycle inhibition and uncoupling of oxidative phosphorylation. Severe toxicity is expected to cause a metabolic acidosis with a high anion gap because of the formation of lactate and other organic acids. Salicylates also directly stimulate the respiratory center, which manifests as respiratory alkalosis early in the presentation. Because of its chemical properties, salicylate in increased portions exists in the nonionized form during periods of low serum pH, allowing for easier passage across biological membranes. This becomes important in toxicity when serum pH tends to decrease, creating an environment more suitable for the nonionized form, which will readily cross biological membranes (e.g., blood-brain barrier) and have toxic effects. Salicylates impair glucose regulation, which may result in hyperglycemia or hypoglycemia. Of importance, hypoglycemia in the CNS may contribute to several neurologic toxicities such as altered mental status, seizures, and cerebral edema. Other toxicities include GI irritation, tinnitus, acute respiratory distress syndrome, coagulopathy, and rarely hepatic injury.

Acute Toxicity

Acute toxicity typically presents with nausea and vomiting, and many patients will also report tinnitus. Respiratory stimulation may manifest as tachypnea or hyperpnea, and respiratory alkalosis may be shown on blood gas analysis. Progression of toxicity is evidenced by the development of metabolic acidosis and altered mental status. Severe toxicity usually occurs at concentrations exceeding 90–100 mg/dL and is associated with coma, seizures, hypoglycemia, pulmonary edema, and hyperthermia.

Chronic Toxicity

Chronic salicylate toxicity does not follow predictable patterns and is often misdiagnosed because of nonspecific symptoms and a wide differential diagnosis. Acid-base disturbances and salicylate serum concentrations greater than 60 mg/dL with altered mental status may indicate severe toxicity. Complications such as cerebral edema and acute lung injury may also be present.

General Management

Management is centered on supportive care with consideration for antidotal therapy and enhanced elimination techniques. Gastrointestinal decontamination with activated charcoal can be used for acute toxicity, though nausea and vomiting may limit its usefulness. Administration can be considered even in patients presenting more than 1–2 hours after ingestion because of prolonged absorption periods in overdose. Intravenous fluid resuscitation should be initiated, given that many patients will be hypovolemic because of GI losses, hyperventilation, and increased metabolic activity. Supplemental glucose administration may also be warranted and is typically considered, even in cases of normal serum glucose, because of neuroglycopenia expected in toxicity.

Alkalinization Therapy

The mainstay of treatment for salicylate toxicity centers on alkalinization therapy, typically using intravenous sodium bicarbonate. Administration of sodium bicarbonate is beneficial through two processes, which collectively may be called ion trapping. By increasing the serum pH, more drug will be ionized in the serum and thus be less likely to distribute into tissues, such as the CNS. In addition, administration of sodium bicarbonate will alkalinize the urine, thus preventing ionized salicylate from being reabsorbed in the kidneys. Initiation of therapy can be considered in symptomatic patients with elevated serum salicylate concentrations with a goal serum pH of 7.45–7.55 and a goal urine pH of 7.5–8. Typical doses include using sodium bicarbonate 150 mEq in 1000 mL of dextrose 5% in water and infusing at twice the normal maintenance fluid rate. An initial bolus of 1–2 mEq/kg can also be administered, particularly if the urine pH is low. Electrolyte repletion may be necessary during therapy, particularly potassium because hypokalemia prevents the urine from achieving an alkaline pH. No consensus exists regarding specific indications or end points of therapy; alkalinization therapy should be considered in symptomatic patients with

Box 4. EXTRIP Recommendations for Salicylate Poisoning

- [salicylate] > 100 mg/dL
- [salicylate] > 90 mg/dL with impaired renal function OR if supportive therapy fails
- [salicylate] > 80 mg/dL with impaired renal function AND if supportive therapy fails
- Altered mental status of hypoxemia requiring supplemental oxygen

EXTRIP = Extracorporeal Treatments in Poisoning workgroup.

Information from: Juurlink DN, Gosselin S, Kielstein JT, et al. Extracorporeal treatment in salicylate poisoning: systematic review and recommendations from the EXTRIP workgroup. Ann Emerg Med 2015;66:165-81.

elevated salicylate concentrations and likely should be continued until acid-base disturbances have improved and serum salicylate concentrations are obviously trending downward and within the normal range.

Hemodialysis and EXTRIP

Hemodialysis is effective for removing salicylate from the serum and should be considered in cases of severe toxicity. The EXTRIP workgroup recently published evidence-based consensus recommendations regarding the use of hemodialysis in salicylate poisoning (Box 4).

Although the serum concentrations represented in these recommendations are more likely with acute intoxication, chronic toxicity would likely still meet the criteria, given other factors such as acidemia, altered mental status, or hypoxemia. Other resources have generally recommended hemodialysis for patients with chronic intoxication and concentrations greater than 60 mg/dL with evidence of severe toxicity. Hemodialysis should be discontinued when there is obvious clinical improvement with a salicylate concentration less than 19 mg/dL.

Absence of Anion Gap Metabolic Acidosis

Salicylate toxicity, which commonly causes an anion gap metabolic acidosis, is typically considered in the differential diagnosis for patients presenting with an anion gap metabolic acidosis of unknown origin. A clinically relevant salicylate overdose would be expected to cause an anion gap metabolic acidosis because of the accumulation of organic acids associated with impaired cellular respiration. In fact, a previous study suggested that universal screening for salicylates is not needed, given that the patients with salicylate poisoning that was not reported had an anion gap of over 20 mEq/L on laboratory evaluation (Sporer 1996). If this practice were widely accepted, any patient with severe salicylism who did not have an anion gap metabolic acidosis or a history of exposure might potentially be missed unless other symptoms of toxicity were recognized.

Laboratory Interference with Chloride Assay

Because of the common association between salicylate toxicity and an anion gap metabolic acidosis, any interference with this laboratory finding may potentially impede diagnosis. Recently, there have been reports of elevated salicylate concentrations causing falsely elevated chloride concentrations, which consequently cause the anion gap to be erroneously low. This laboratory error appears to occur when chloride is measured by certain ion-selective electrodes, which may falsely read salicylate for chloride. Falsely elevated chloride concentrations may occur when the electrode is near the end of its operational life span. Although manufacturer information for laboratory tests will generally list interferences with assays, not all potential offenders may be cited (Mori 1997).

Currently, no large reviews have evaluated the potential impact of laboratory interference in salicylate toxicity and the impact of pseudo hyperchloremia; however, many case reports provide evidence for this phenomenon in clinical practice. In a two-patient case series, salicylate concentrations appeared to correlate linearly with the chloride concentration; one patient had a peak salicylate concentration of 110 mg/dL, at which time the chloride concentration and anion gap were reported as 123 mmol/L and 3 mmol/L, respectively (Jacob 2011). Another case series involving three patients reported similar findings of hyperchloremia, including one patient with suspected salicylate toxicity who was not identified on initial workup; this patient received sodium bicarbonate and hemodialysis because of metabolic acidosis and later admitted a several-day history of aspirin ingestion before presentation (Bauer 2016).

Although uncommon, laboratory interference with elevated salicylate concentrations causing pseudo-hyperchloremia may falsely lower the serum anion gap. Patients presenting without a history of salicylate toxicity may be particularly vulnerable to this interference, given the common practice of testing for salicylates after identifying an anion gap metabolic acidosis of unknown origin. Elevated chloride concentrations in the presence of other common signs of salicylism should stimulate further investigation, such as discussion with the laboratory regarding the chloride assay. Salicylate concentrations should be obtained without delay if there is any suggestion of toxicity, even in the absence of an elevated anion gap.

Sodium Acetate for Alkalinization

Sodium bicarbonate is widely used and has particular importance in the management of salicylate toxicity. Recent shortages of sodium bicarbonate have prompted an evaluation of alternative alkalinizing agents such as sodium acetate. The mechanism by which sodium acetate increases pH is best understood through Stewart's approach, which suggests that the strong ion difference (concentration of strong cations minus strong anions) causes an increase in pH. Acetate forms acetyl CoA when taken up by cells, which

then enters the Krebs cycle, with CO_2 and water formed as byproducts. These byproducts are in equilibrium with bicarbonate through carbonic anhydrase activity, which increases cations, and the strong ion difference leads to alkalosis. This process is thought to occur mainly in the liver; however, it also occurs in skeletal muscle, which accounts for continued conversion in patients with hepatic dysfunction (Neavyn 2013).

In general, sodium acetate 1 mEq is considered equivalent to sodium bicarbonate 1 mEq and can be prepared and administered in a similar fashion. Although the metabolism of bicarbonate is almost instantaneous through carbonic anhydrase, many pathways contribute to acetate metabolism, which may lead to symptoms of acetate overload if administered too quickly. Symptoms of acetate overload have been described after use of sodium acetate as a buffer for hemodialysis and include myocardial depression and hypopnea. In addition, flushing has been reported when sodium acetate is administered as an intravenous bolus. Because of this concern, bolus doses of sodium acetate should be administered over 15–20 minutes, which would be sufficient to avoid overwhelming standard metabolic pathways (Neavyn 2013).

Despite frequent drug shortages in recent years, including shortages of sodium bicarbonate, evidence for use of sodium acetate as a replacement therapy for salicylate toxicity is lacking. One report compared the use of sodium acetate with sodium bicarbonate for urinary alkalinization in methotrexate therapy when a urine pH of 8 or greater increases solubility and reduces toxicity of methotrexate (Alrabiah 2015). Thirty-one patient encounters using sodium acetate and 63 patient encounters using sodium bicarbonate were reviewed and found no difference in time from admission to achieving a urine pH of 8 or more (mean 16.7 hours vs. 15.5 hours, respectively [p=0.53]). Length of stay, time to serum methotrexate concentration, and increased SCr rates did not differ from baseline. Although this report was small and retrospective, it suggests that sodium acetate provides similar benefits when used for urinary alkalinization.

A case of sodium acetate use for urine alkalinization in salicylate toxicity was published in an abstract (Boyd 2013). Aspirin overdose was reported to a local poison center from a facility without sodium bicarbonate. Information provided in the abstract was limited; however, the patient received an infusion of sodium acetate 150 mEq/L (no initial bolus) and achieved serum and urinary alkalinization with no adverse effects. Although this was a single case report without comparison with sodium bicarbonate, it provides support that sodium acetate can generate alkaluria for salicylate toxicity.

Decompensation After Intubation

Severe salicylate toxicity is associated with respiratory alkalosis caused by direct respiratory stimulation in addition to late compensation after the development of metabolic acidosis. The typical teaching in salicylate toxicity is to avoid intubation, if possible, because of concern that serum pH will fall as the CO_2 in blood rises. With a pKa of 3.5, a greater portion of salicylates in the blood will become nonionized in the acidic environment and will cross biological membranes, exerting toxic effects. Intubation is commonly accomplished using a neuromuscular blocking agent, resulting in paralysis of the respiratory muscles, and is associated with a rapid rise in serum carbon dioxide because of the lack of expiratory capacity. In addition, there is concern that usual mechanical ventilation parameters will be insufficient to promote CO_2 clearance and will thus result in further Pco_2 increases and serum pH decreases.

Although providers are often cautioned against intubation in cases of severe salicylate toxicity, evidence for decompensation after intubation is limited. A previous study in cats found that hypercapnia was associated with an increased concentration of salicylates in the brain, whereas hypocapnia was associated with decreased concentrations (Goldberg 1961). In addition, a rat model showed that bicarbonate infusion was associated with a higher blood pH and decreased tissue concentrations of salicylates, whereas CO_2 inhalation lowered serum pH and caused increased salicylate uptake into tissues (Hill 1971).

Despite animal evidence showing the potential for hypercapnia and decreased serum pH to cause increased tissue uptake, human evidence of harmful effects is limited to case reports. A small retrospective case series from poison center records identified seven patients with a salicylate concentration of 50 mg/dL or greater who were intubated and placed on mechanical ventilation. All patients had a serum pH of less than 7.4 after intubation. Of these patients, two died within 3 hours of intubation, and another sustained severe neurologic injury requiring long-term care facility admission. The serum pH after initiating mechanical ventilation in these patients was reported as 7.14, 6.79, and 7.14, respectively (Stolbach 2008). A 58-year-old man with ingestion of aspirin in a suicide attempt had a salicylate serum concentration of 111 mg/dL, pre-intubation pH of 7.5, and a Pco_2 of 17 mm Hg. After intubation, the patient's serum pH fell to 7.07, and he died in 40 minutes (Greenberg 2003). Similarly, a 59-year-old man with a salicylate concentration of over 90 mg/dL had a pre-intubation pH of 7.37 with a Pco_2 of 19 mm Hg (Fernando 2017). The patient experienced a 4-minute apneic period during intubation, after which ventilator settings were increased to 25 breaths/minute with a tidal volume of 10 mL/kg total body weight in addition to administering 100 mEq of intravenous sodium bicarbonate. Despite these measures, a blood gas analysis 20 minutes post-intubation described a pH of 6.89 and a Pco_2 of 121 mm Hg; the patient sustained pulseless electrical activity shortly thereafter and ultimately died. Discussion from the authors describes the inability to maintain hypocapnia despite increased ventilator settings and suggests that mechanical ventilation cannot achieve the necessary minute ventilation in a patient with severe salicylate toxicity (Fernando 2017).

Practice Points

Key points for pharmacists involved in managing acetaminophen and salicylate toxicities include:

- **Consultation with a toxicology consult service or a Poison Control center is recommended in patients with acetaminophen and salicylate toxicity.**
- **Traditional risk assessment using a modified Rumack-Matthew nomogram cannot be applied to all patients with elevated acetaminophen concentrations. Alternative techniques such as the psi nomogram, the acetaminophen x AT product, and mechanistic biomarkers may provide additional insight for patient care.**
- **The traditional intravenous acetylcysteine regimen given over 21 hours was never subject to randomized controlled trials to determine the appropriate dose in all patients. Although this dose is generally accepted as effective, adverse effects and medication errors are common. Moreover, questions remain whether 21 hours of therapy is necessary for all patients and whether the dose is sufficient to prevent hepatotoxicity in all patients. Alternative treatment regimens are currently under investigation.**
- **Although acidosis in the presence of acetaminophen toxicity is generally expected in patients with fulminant hepatic failure, acidosis can also develop from other clinical scenarios. Pyroglutamic acid accumulation may occur in patients with certain risk factors, even with therapeutic acetaminophen doses. In addition, massive ingestions of acetaminophen may lead to severe lactic acidosis early after ingestion.**
- **Certain laboratories may use tests resulting in a falsely elevated chloride concentration in the presence of high salicylate serum concentrations. This may lead to misinterpretation of the anion gap because it appears falsely low. Salicylate toxicity should not be ruled out in the presence of an unexplained metabolic acidosis without an anion gap, particularly with an elevated chloride concentration.**
- **Manufacturer drug shortages are common and have led to issues with sodium bicarbonate availability. Sodium acetate appears to achieve similar outcomes such as alkalinization and can generally be given at the same doses as sodium bicarbonate.**
- **Patients with severe salicylate toxicity tend to have significantly elevated minute ventilations because of direct respiratory stimulation and compensation for metabolic acidosis. These patients should be intubated with caution, given that this would be expected to cause CO_2 accumulation because of initial paralysis and failure to appropriately set the ventilator to mimic patient parameters. Hemodialysis should be considered in patients with salicylate toxicity requiring intubation.**

Current evidence suggests the potential for harm in patients with severe salicylate toxicity who are intubated and mechanically ventilated. For this reason, intubation should be avoided, if clinically feasible. Given the likelihood of patients accumulating Pco_2 and worsening acidosis if mechanical ventilation is set using traditional ventilator settings, ventilator settings that include hyperventilation to maintain alkalemia and prevent distribution of salicylates into tissues are warranted. At least one case report suggests that it will be challenging to match the patient's minute ventilation before intubation (Fernando 2017). Another potential strategy to mitigate deterioration with endotracheal intubation is the use of alkalinizing agents such as sodium bicarbonate or sodium acetate in the peri-intubation period. Initiating an infusion to maintain the serum pH at around 7.5 and considering the administration of bolus doses that may increase buffering capacity in the serum are reasonable interventions; however, none of these techniques has been studied to assess benefit or appropriate dose.

Hemodialysis is another potential intervention for patients with severe toxicity, and patients requiring intubation because of salicylate toxicity will likely meet the indications for extracorporeal removal. A retrospective review of poison center data previously evaluated the use of hemodialysis in patients with salicylate poisoning who received mechanical ventilation (McCabe 2017). In patients with a peak concentration greater than 50 mg/dL, survival was 83.9% if hemodialysis was done compared with 56% if it was not done. With concentrations over 80 mg/dL, no patients survived who did not receive hemodialysis compared with 83.3% of patients if hemodialysis was used. Although this study was small (n=56) and retrospective, it is hypothesis generating that hemodialysis appears beneficial for patients with severe salicylate toxicity requiring intubation.

CONCLUSION

Acetaminophen and salicylate toxicity is commonly encountered in clinical practice. Despite decades of published experience in managing these poisonings, questions remain regarding diagnosis and management in certain patient case scenarios. New literature aimed at addressing these clinical controversies may provide additional insight into managing challenging cases.

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Self-Assessment Questions

1. A 23-year-old man presents to the ED with altered mental status after a presumed overdose. No history is available regarding the patient's exposure; his family reports he was normal when seen about 24 hours before arrival. Laboratory tests obtained at presentation return with an acetaminophen concentration of 43 mcg/mL and AST of 76 IU/L. Which one of the following is best to recommend for this patient?

   A. Start acetylcysteine because the acetaminophen x aminotransferase (AT) product (acetaminophen x AT) is greater than 1500 mcg/mL x IU/L.
   B. Start acetylcysteine for the supratherapeutic acetaminophen concentration and unreliable patient history.
   C. Start acetylcysteine, given the 24-hour concentration on the Rumack-Matthew nomogram.
   D. Recheck acetaminophen and transaminases in 8 hours to trend acetaminophen x AT.

2. A 15-year-old female adolescent (weight 52 kg) presents to the ED after reportedly ingesting 40 acetaminophen 500-mg tablets. A serum acetaminophen concentration 4 hours after ingestion is 202 mcg/mL and acetylcysteine is initiated at 6 hours post-ingestion. According to the psi nomogram for this patient, the risk of hepatotoxicity is less than 1%. Which one of the following is best to recommend for this patient?

   A. Discontinue acetylcysteine immediately because this patient is at low risk of hepatotoxicity.
   B. Discontinue acetylcysteine after completing the 21-hour protocol without rechecking laboratory test results because this patient is at low risk of hepatotoxicity.
   C. Discontinue acetylcysteine after completing the 21-hour protocol and confirming that the repeat acetaminophen concentration is negative and transaminases are not elevated.
   D. Change to oral acetylcysteine and discontinue therapy after 24 hours.

3. A 38-year-old man presents with 2 days of abdominal pain. The family reports a history of substance use disorder and states the patient took an entire bottle of acetaminophen with diphenhydramine two days prior for sleep. Initial laboratory evaluation is pertinent for acetaminophen concentration 3.1 mcg/mL, AST 16,405 IU/L, lactic acid 15.8 mmol/L, and anion gap 26 mEq/L. Which one of the following is best to recommend for this patient?

   A. Initiate hemodialysis because of lactic acidosis in the presence of acetaminophen toxicity.
   B. Obtain a urine organic acid screen to rule out pyroglutamic acid accumulation.
   C. Administer the intravenous acetylcysteine protocol at 2 times the normal dose because of high-risk exposure.
   D. Initiate the traditional intravenous acetylcysteine regimen and consult a transplant center if acidosis persists after resuscitation.

4. A 16-year-old male adolescent presents to the ED after ingesting "a handful" of acetaminophen 500-mg tablets. The acetaminophen concentration at 10 hours post-ingestion is 55 mcg/mL, and acetylcysteine is indicated, according to the modified Rumack-Matthew nomogram. The team is concerned because the patient reports a hypersensitivity reaction to acetylcysteine after a previous suicide attempt. Which one of the following is best to recommend for this patient?

   A. Do not start intravenous acetylcysteine because of the high risk of hypersensitivity reaction and the acetaminophen concentration below the original Rumack-Matthew nomogram line.
   B. Administer intravenous acetylcysteine at a dose of 200 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours.
   C. Initiate the traditional intravenous acetylcysteine regimen and alert the bedside nurse to monitor for hypersensitivity reaction symptoms.
   D. Administer the intravenous acetylcysteine protocol at 2 times the normal dose because of high-risk exposure.

Questions 5 and 6 pertain to the following case.

E.W. is a 24-year-old woman (weight 68 kg) who presents 2 hours after a reported ingestion of 48 g of acetaminophen in a suicide attempt. E.W. is noted to have a flat affect, though she is answering questions appropriately and denies ingesting other substances.

5. Which one of the following is best to recommend for E.W.'s initial evaluation?

   A. Administer a dose of activated charcoal, and obtain an acetaminophen concentration.
   B. Obtain laboratory tests immediately, including acetaminophen and lactic acid concentrations.
   C. Do not administer activated charcoal because the patient has presented more than 1-hour post-ingestion.
   D. Initiate acetylcysteine before reviewing laboratory test results.

6. E.W.'s laboratory test results show a 4-hour acetaminophen concentration of 486 mcg/mL, lactic acid 2.1 mmol/L, and AST 43 IU/L. Which one of the following is best to recommend for E.W.?

   A. The patient's acetaminophen concentration is above the modified Rumack-Matthew nomogram treatment line. Use the traditional intravenous acetylcysteine regimen.
   B. The patient is considered to have had a massive acetaminophen overdose. Consult nephrology for emergency hemodialysis and administer the intravenous acetylcysteine protocol at 2 times the normal dose.
   C. The patient's ratio of acetaminophen concentration at 4 hours to the modified Rumack-Matthew nomogram concentration at 4 hours is 3.24. Initiate acetylcysteine using a 200-mg/kg dose over 16 hours for the last infusion.
   D. The patient ingested about 705 mg/kg of acetaminophen. Initiate intravenous acetylcysteine with an infusion rate of 19.5 mg/kg/hour.

7. A 49-year-old man presents unresponsive after a suspected drug overdose. Initial laboratory tests show an acetaminophen concentration of 1216 mcg/mL, lactic acid 21 mmol/L, pH 6.95, and anion gap 34 mEq/L. Which one of the following is best to recommend for this patient?

   A. Initiate a sodium bicarbonate infusion in addition to intravenous acetylcysteine using a 200-mg/kg dose over 16 hours for the last infusion.
   B. Initiate emergency hemodialysis and administer intravenous acetylcysteine at 2 times the normal dose.
   C. Initiate a sodium bicarbonate infusion in addition to the traditional intravenous acetylcysteine regimen.
   D. Obtain a urine organic acid screen to evaluate for pyroglutamic acid accumulation and initiate the traditional intravenous acetylcysteine regimen.

8. A 56-year-old woman with a history of diabetes mellitus, osteoarthritis, and chronic kidney disease is admitted to the hospital after a fall at home. The patient is initiated on acetaminophen 1000 mg three times daily with hydromorphone 2 mg by mouth as needed for severe pain. Two days after admission, the patient has altered mental status and tachypnea. The rapid response team evaluates the patient and obtains laboratory test results that include pH 7.1, Pco_2 15 mm Hg, HCO_3 6 mEq/L, anion gap 20 mEq/L, lactate 2.3 mmol/L, acetaminophen 11 mcg/mL, and AST 34 IU/L. The team is concerned that acetaminophen is contributing to her acidosis and discontinues therapy. Which one of the following is best to recommend for this patient?

   A Initiate a sodium bicarbonate infusion in addition to intravenous acetylcysteine using a 200-mg/kg dose over 16 hours for the last infusion.
   B. Initiate emergency hemodialysis, and administer intravenous acetylcysteine at 2 times the normal dose.
   C. Initiate a sodium bicarbonate infusion in addition to the traditional intravenous acetylcysteine regimen.
   D. Obtain a urine organic acid screen to evaluate for pyroglutamic acid accumulation, and initiate the traditional intravenous acetylcysteine regimen.

9. Which one of the following patients is most likely to benefit from hemodialysis?

   A. 73-year-old man after abdominal surgery who develops acute kidney injury and metabolic acidosis while taking acetaminophen 1000 mg three times daily.
   B. 27-year-old woman initiated on intravenous acetylcysteine after acute ingestion of acetaminophen with a concentration of 906 mcg/mL.
   C. 38-year-old man with altered mental status and lactic acidosis after acetaminophen ingestion with a concentration of 816 mcg/mL.
   D. 42-year-old woman presenting several days after acetaminophen overdose with hepatotoxicity and lactic acidosis.

10. A 46-year-old man presented to the ED after his family called 911 for altered mental status. On examination, the patient was lethargic and diaphoretic with a respiratory rate of 22 breaths/minute. Initial laboratory results are significant for Na 140 mEq/L, Cl 120 mEq/L, and HCO_3 10 mEq/L. His family is concerned for overdose and states the patient has recently been depressed after the death of his wife. Which one of the following is best to recommend for this patient?

    A. Consider other medical causes because the patient's presentation is not consistent with a toxidrome.
    B. Initiate sodium bicarbonate because the patient has a non-gap metabolic acidosis.
    C. Consult nephrology because of unexplained electrolyte abnormalities.
    D. Obtain acetaminophen and salicylate concentrations to rule out ingestion of these medications.

11. A 23-year-old woman presents 12 hours after ingesting "a bottle" of aspirin tablets. Initial laboratory test results are pertinent for Na 135 mEq/L, Cl 118 mEq/L, HCO_3 15 mEq/L, and salicylate 86 mg/dL. Which one of the following is best to recommend for this patient?

    A. Administer an intravenous fluid bolus with a normal saline maintenance infusion.
    B. Administer an intravenous fluid bolus with a maintenance infusion of sodium bicarbonate.
    C. Consult nephrology for emergency hemodialysis.
    D. Continue workup for causes of hyperchloremic acidosis.

12. A 33-year-old man is admitted to the ICU for the treatment of salicylate toxicity. Initial laboratory tests show a salicylate concentration of 76 mg/dL, serum pH 7.5, and urine pH 8. Sodium bicarbonate is on national shortage, and the hospital has restricted its use in order to conserve the supply. Which one of the following is best to recommend for this patient's initial treatment?

    A. Consult nephrology for emergency hemodialysis.
    B. Administer an intravenous fluid bolus with normal saline maintenance infusion.
    C. Administer an intravenous fluid bolus with maintenance infusion of sodium acetate.
    D. Administer a sodium bicarbonate 1- to 2-mEq/kg intravenous bolus.

Questions 13 and 14 pertain to the following case.

J.J. is a 16-year-old male adolescent who presents after reportedly ingesting several bottles of aspirin in a suicide attempt. On initial presentation, he is alert and responsive to questions while maintaining a respiratory rate of 32 breaths/minute. Laboratory evaluation is significant for serum pH 7.5, Pco_2 15 mm Hg, HCO_3 15 mEq/L, and salicylate 82 mg/dL. The treatment team is concerned that J.J. will be unable to maintain this respiratory rate for a prolonged time.

13. Which one of the following interventions is best to recommend as J.J.'s initial treatment?

    A. Initiate sodium bicarbonate and continue close monitoring of airway/breathing.
    B. Initiate sodium bicarbonate and intubate.
    C. Consult nephrology for emergency hemodialysis and intubate.
    D. Initiate sodium bicarbonate and consult nephrology for emergency hemodialysis.

14. Soon after arrival, J.J. becomes unresponsive. Repeat blood gas analysis shows serum pH 7.25, Pco_2 30 mm Hg, and HCO_3 10 mEq/L. A repeat salicylate concentration is 96 mg/dL. Nephrology has been consulted for emergency hemodialysis. Which one of the following is best to recommend for J.J.?

    A. Continue sodium bicarbonate with close monitoring of airway/breathing.
    B. Administer a sodium bicarbonate 1- to 2-mEq/kg intravenous bolus with continued monitoring of airway/breathing.
    C. Administer a sodium bicarbonate 1- to 2-mEq/kg intravenous bolus and intubate, followed by mechanical ventilation with increased minute ventilation.
    D. Increase sodium bicarbonate infusion rate and administer a dose of activated charcoal because of the increasing salicylate concentration.

15. Which one of the following patients is most likely to benefit from hemodialysis?

    A. 17-year-old male adolescent with a salicylate concentration of 72 mg/dL, serum pH of 7.3, normal renal function, and normal mental status before receiving sodium bicarbonate.
    B. 36-year-old woman with a salicylate concentration of 92 mg/dL with normal renal function before receiving sodium bicarbonate.
    C. 44-year-old woman with a salicylate concentration of 88 mg/dL with acute kidney injury before receiving sodium bicarbonate.
    D. 28-year-old man receiving sodium bicarbonate with a salicylate concentration of 86 mg/dL, normal renal function, and altered mental status requiring intubation.