HISTORY AND EPIDEMIOLOGY

The Ancient Egyptians recognized the pain-relieving effects of concoctions made from myrtle and willow leaves. Hippocrates may have been among the first to use willow bark and leaves from the Salix species to relieve fever, but it was not until 1829 that the glycoside salicin was extracted from the willow bark and used as an antipyretic. Seven years later, salicylic acid was isolated, and by the late 1800s, it was being used to treat gout, rheumatic fever, and elevated temperatures. The less irritating acetylated salicylate compound was first synthesized in 1833, and in 1899 acetylsalicylic acid was commercially introduced as aspirin by Bayer. With that, the modern era of aspirin therapy and salicylate toxicity began.

The American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) collects and reports annual exposure data in the United States. Analgesics, which include both aspirin and acetaminophen (APAP), continue to rank first among pharmaceuticals most frequently reported in human exposures (Chap. 136). Salicylate toxicity and fatalities have long been a major toxicological “concern.” From the 1950s to 1970s, salicylate was the leading cause of fatal childhood poisoning. The association with Reye syndrome; safer packaging; and the increased use of nonsteroidal antiinflammatory drugs (NSAIDs), APAP, and other alternatives to aspirin has decreased the incidence of unintentional salicylate poisoning. In the last 5 years of data available (2008–2012), there were 20 to 30 deaths per year reported (Chap. 136). Despite this decline in reported deaths and general use, it is still imperative that clinicians are adept at early recognition and swift management of patients with salicylate overdose.

Aspirin and other salicylate containing products continue to be some of the most common prescription and nonprescription xenobiotics used by the general public. Since landmark trials demonstrated the inhibition of platelet function by aspirin in the 1970s, its use became the standard of care for cardiovascular disease prevention and treatment. Subsequent investigations have demonstrated that aspirin can decrease the incidence of myocardial infarction, colon cancer, and transient ischemic attack. Its antiinflammatory properties have also continued to make it an active investigational xenobiotic for cancer.1

Bayer, a company once associated exclusively with aspirin, several years ago turned to making products containing ibuprofen or APAP. But in a very recent move of re-branding, Bayer is now marketing a return of aspirin for pain relief with three new products containing aspirin alone; aspirin with caffeine; and aspirin, caffeine, and APAP. Salicylates continue to be readily available and will continue to lead to significant morbidity and mortality in overdose.
PHARMACOLOGY

Aspirin and other salicylates have analgesic, antiinflammatory, and antipyretic properties, a combination of traits shared by all of the NSAIDs (Chap. 37). Most of the beneficial effects of NSAIDs result from their inhibition of cyclooxygenase (COX). This enzyme enables the synthesis of prostaglandins, which in turn mediate inflammation and fever. Contributing to the antiinflammatory effects and independent of the effects on prostaglandins, salicylates and other NSAIDs may also directly inhibit neutrophils. There are two types of salicylic acid esters, phenolic esters such as aspirin and carboxylic acid esters, including methyl salicylate, phenyl salicylate, and glycosalicylate. Most of the studies of salicylate metabolism involve aspirin. There is an implicit assumption that all members of the salicylate class have similar properties after being converted to salicylic acid.

Salicylates and NSAIDs are purportedly most effective in treating the pain accompanying inflammation and tissue injury. Such pain is elicited by prostaglandins liberated by bradykinin and other cytokines. Fever is also mediated by cytokines such as interleukin (IL)-1β, IL-6, α and β interferons, and tumor necrosis factor-α, all of which increase synthesis of prostaglandin E₂. In turn, this inflammatory mediator increases cyclic adenosine monophosphate (cAMP), which triggers the hypothalamus to elevate the body temperature set point, resulting in increased heat generation and decreased heat loss.

Because platelets cannot regenerate COX-1, a daily dose of as little as 30 mg of aspirin inhibits COX-1 for the 8- to 12-day lifespan of the platelet. Adverse effects of aspirin and some NSAIDs related to alteration of COX include gastrointestinal (GI) ulcerations and bleeding, interference with platelet adherence, and a variety of metabolic and organ-specific effects described later.

To achieve an antiinflammatory effect for patients with chronic conditions such as rheumatoid arthritis, salicylates are primarily prescribed in doses sufficient to achieve a serum salicylate concentration between 15 and 30 mg/dL, which is considered the therapeutic range. Concentrations higher than 30 mg/dL are typically associated with signs and symptoms of toxicity.

PHARMACOKINETICS

Aspirin is rapidly absorbed from the stomach. The pKₐ of aspirin is 3.5, and the majority is nonionized (ie, acetylsalicylic acid) in the strongly acidic stomach (pH 1–2). Although absorption of acetylsalicylate may be less efficient in the small bowel because of its higher pH, it is substantial and rapid because of the large surface area and the fact that the increase in pH increases the solubility of acetylsalicylate. After ingestion of therapeutic doses of immediate release acetylsalicylate, significant serum concentrations are achieved in 30 minutes, and maximum concentrations are often attained in less than 1 hour.

The plasma half-life of aspirin is about 15 minutes, because it is rapidly hydrolyzed to salicylate. The apparent half-life for salicylate is about 2 to 3 hours at antiplatelet doses and increases to 12 hours.
at antiinflammatory doses demonstrates dose dependent elimination. Aspirin undergoes biotransformation in the liver and is then eliminated by the kidneys. The apparent volume of distribution (Vd) increases from 0.2 L/kg at low concentrations to 0.3 to 0.5 L/kg at higher concentrations.

TOXICOKINETICS

In overdose, several factors contribute to significantly altered pharmacokinetics that can present very challenging obstacles to effectively managing patients poisoned with salicylates. The dose obviously is critical in contributing to the magnitude and duration of toxicity, but other important factors include the formulation, rate of gastric emptying, bezoar formation, hepatic and renal function, and both the serum and urine pH.

There is a decrease in protein (albumin) binding from 90% at therapeutic concentrations to less than 75% at toxic concentrations caused by saturation of protein binding sites. Salicylates have substantially longer apparent half-lives at toxic concentrations than at therapeutic concentrations, varying from 2 to 4 hours at therapeutic concentrations to as long as 20 hours at toxic concentrations. The dosage form of salicylates (eg, effervescent, enteric coated) influences the absorption rate. Therapeutic doses of enteric-coated tablets may not produce peak serum concentrations until 4 to 6 hours after ingestion, and in overdose the peak may not be reached until 24 hours after ingestion. Delayed absorption of aspirin may result from salicylate induced pylorospasm or pharmacobezoar formation.

Salicylates are conjugated with glycine and glucuronides in the liver and are eliminated by the kidneys. Approximately 10% of salicylates are excreted in the urine as free salicylic acid, 75% as salicyluric acid, 10% as salicylic phenolic glucuronides, 5% as acylglucuronides, and 1% as gentisic acid (Fig. 39–1). As the concentration of salicylates increases, two of the five pathways of elimination—those for salicyluric acid and the salicylic phenolic glucuronide—become saturated and exhibit zero-order kinetics. As a result of this saturation, overall salicylate elimination changes from first-order kinetics to zero-order kinetics (Chap. 9). In a healthy adult, these altered saturation kinetics may occur after as little as 1 to 2 g of acute aspirin ingestion.

FIGURE 39–1.
Salicylic acid metabolism. At excessive doses, the four mechanisms of salicylic acid metabolism are overloaded, leading to increased tissue binding, decreased protein binding, and increased excretion of unconjugated salicylic acid. Asterisk indicates Michaelis-Menten kinetics; double asterisk indicates first-order kinetics.
At very high serum concentrations, salicylate elimination may again resemble first-order elimination as an increasing fraction undergoes renal clearance.

Free salicylic acid is filtered through the glomerulus and is both passively reabsorbed and actively secreted from the proximal tubules. More than 30% of an ingested salicylate dose may be eliminated in alkaline urine and as little as 2% in acidic urine. Salicylate conjugates (glycine and glucuronides) are filtered and secreted by the proximal tubules; salicylate conjugates are not reabsorbed across renal tubular cells because of limited lipid solubility, and the amount eliminated depends on the glomerular filtration rate and proximal tubule secretion but not urine pH. Protein-binding abnormalities, urine and plasma pH variations, and delayed absorption all influence both the maximum salicylate concentration and the rate of decline.

Other Forms of Salicylate
Topical Salicylate, Methyl Salicylate (Oil of Wintergreen), and Salicylic Acid.
Topical salicylates, which are used as keratolytics (salicylic acid) or as rubefacients (≤30% methyl salicylate), are rarely responsible for salicylate poisoning when used in their intended manner because absorption through normal skin is very slow. However, particularly in children, extensive application of topical preparations containing methyl salicylate may result in poisoning. After 30 minutes of contact time, only 1.5% to 2.0% of a dose is absorbed, and even after 10 hours of contact with the methyl salicylate, only 12% to 20% of the salicylate is systemically absorbed. Heat, occlusive dressings, young age, inflammation, and psoriasis all increase topical salicylate absorption. In a study of healthy volunteers, a profound effect of transdermal absorption of methyl salicylate was demonstrated from exercise and heat exposure, with a threefold increase in the systemic availability of salicylate.

Ingestion of methyl salicylate may be disastrous because 1 mL of 98% oil of wintergreencontains an equivalent quantity of salicylate as 1.4 g of aspirin. The minimum toxic salicylate dose of approximately 150 mg/kg body weight can almost be achieved with 1 mL of oil of wintergreen, which represents 140 mg/kg of salicylates for a 10-kg child. In Hong Kong, medicated oils containing methyl salicylate accounted for 48% of acute salicylate poisoning cases treated in one hospital. Methyl salicylate is rapidly absorbed from the GI tract, and much, but not all, of the ester is rapidly hydrolyzed to free salicylates. Despite rapid and complete absorption, serum concentrations of salicylates are much less than predicted after ingestion of methyl salicylate containing liniment compared with oil of wintergreen. Vomiting is common, along with abdominal discomfort. The onset of symptoms usually occurs within 2 hours of ingestion. Patients with methyl salicylate exposure have died in less than 6 hours, emphasizing the need for early determinations of salicylate concentrations in addition to frequent testing after such exposures.

Bismuth Subsalicylate.
Bismuth subsalicylate, which is available in several nonprescription formulations, releases the salicylate moiety in the GI tract, where it is subsequently absorbed. Each milliliter of common liquid preparations of bismuth subsalicylate contains 8.7 mg of salicylic acid. After a large therapeutic dose (60 mL), peak salicylate concentrations may reach 4 mg/dL at 1.8 hours after
ingestion. Patients with diarrhea and infants with colic using large quantities of bismuth subsalicylate may develop salicylate toxicity. Chronic use should also raise concerns for bismuth toxicity (Chap. 90).

PATHOPHYSIOLOGY

Because salicylic acid is a weak acid, at physiologic pH, it exists predominantly in a charged (ionized) state (Chap. 12). But in overdose as the serum pH falls, more salicylate shifts toward a nonionized (uncharged) salicylic acid form that is highly permeable, allowing swift movement across lipid bilayers and cell membranes. This is an important effect in that it allows salicylic acid to enter cells exerting its toxic effects across a wide variety of organs and is discussed later as a target for management.

Acid–Base and Metabolic Effects
Salicylate interferes with the Krebs cycle, which limits production of adenosine triphosphate (ATP). It also uncouples oxidative phosphorylation, causing accumulation of pyruvic and lactic acids and releasing energy as heat (Chaps. 12 and 13). Salicylate-induced increases in fatty acid metabolism generates ketone bodies, including β-hydroxybutyric acid, acetoacetic acid, and acetone. Toxic concentrations of salicylate impair renal hemodynamics, leading to the accumulation of inorganic acids. The net result of all of these metabolic processes is an anion gap metabolic acidosis (Chap. 19) in which the unmeasured anions include salicylate and its metabolites, lactate, ketoacids, and inorganic acids.

The salicylate effect on glucose metabolism is variable and may depend on the severity and phase of toxicity. Salicylate administration in mice increases glycogenolysis and can result in hyperglycemia. Early adrenergic effects of acute salicylate toxicity may stimulate epinephrine and glucagon release, enhancing glycogenolysis as well as gluconeogenesis. But salicylate can inhibit alanine and aspartate aminotransferase, and both enzymes provide key amino acid substrates for gluconeogenesis. Hypoglycemia may also occur because of the combined effect of increased energy demands, depletion of glycogen stores, and decreased gluconeogenesis.

Salicylate poisoned mice had dramatic increases in serum lactate concentration compared with control mice, likely because of increased glycogenolysis and anaerobic glycolysis to compensate partly for the energy loss caused by uncoupling of oxidative phosphorylation. There was also a marked increase in oxygen consumption in mice even with low salicylate concentrations, highlighting the importance of salicylate induced uncoupling of oxidative phosphorylation. Several investigations using intact or fragmented mitochondria demonstrate that increasing concentrations of salicylate result in decreased phosphate uptake and a concomitant decrease in the phosphate/oxygen (P/O) ratio. The impaired P/O ratio demonstrates the inefficiency of ATP production by illustrating that the rate of phosphate incorporation into ATP per molecule falls despite oxygen consumed during oxidative phosphorylation. Salicylates reduce lipogenesis by blocking the incorporation of acetate into free fatty acids and increase peripheral fatty acid metabolism as an energy source, resulting in
ketone formation. Salicylate-induced increased fatty acid metabolism generates ketone bodies, including β-hydroxybutyric acid, acetoacetic acid, and acetone.

**NEUROLOGIC EFFECTS**

The central nervous system (CNS) effects are the most visible and most consequential clinical effects in salicylate-poisoned patients. With increasing CNS salicylate concentrations, neuronal energy depletion likely develops as salicylate uncouples neuronal and glial oxidative phosphorylation. Several other mechanisms also likely contribute to the neurotoxic effects of salicylates. Salicylate also causes release of apoptosis inducing factor (AIF) or cytochrome C, triggers p38 mitogen, activated protein kinase, and activates glial caspase-3, which are responsible for programmed neuronal cell death. It is likely that these effects in addition to severe cellular acidosis lead to neuronal dysfunction and ultimately cerebral edema.

Salicylate poisoning may produce a clinical discordance between serum and cerebrospinal fluid (CSF) glucose concentrations. Despite normal serum glucose concentrations, CSF glucose concentration decreased 33% in salicylate-poisoned mice compared with control mice. In other words, the rate of CSF glucose use exceeded the rate of supply even in the presence of a normal serum glucose concentration. This hypoglycorrhachia demonstrates that altered glucose metabolism and transport may also play a role in the deleterious neurologic effects of salicylate poisoning. Salicylate-poisoned mice have lower CSF glucose concentrations compared with control mice but can maintain similar concentrations of ATP by enhanced glycolysis. Administration of dextrose in these salicylate-poisoned mice suppressed clinical signs of toxicity underlying the importance of providing supplemental glucose despite normal serum concentrations as discussed later in the management of toxicity.

**Hepatic Effects**

Hepatic injury from either acute or chronic overdose of salicylate is rare. Although the hepatocyte is the location of its toxic effects on several metabolic pathways such as glycogenolysis and the Krebs cycle, other concurrent co-ingestants and causes should be considered if there is a clinically significant elevation of aminotransferases or bilirubin concentration or signs of acute liver failure.

An unavoidable historical link exists between the hepatic encephalopathy in Reye syndrome and aspirin. A buildup of fatty acids in the hepatocyte resulting in microvesicular steatosis is characteristic of Reye syndrome. This may occur through salicylate depletion of intrahepatocyte coenzyme A (Co-A), where fatty acids entering the hepatocyte cytoplasm cannot be transported into the mitochondria for β-oxidation. Although there is no mechanism to explain why aspirin has a causal relationship in Reye syndrome, it is clear from epidemiologic evidence that aspirin is an essential cofactor among others in the development of this syndrome.

**Otolaryngologic Effects**

The molecular mechanism of salicylate ototoxicity is not completely understood but appears to be multifactorial. Inhibition of cochlear COX by salicylate increases arachidonate, enabling calcium flux
and neural excitatory effects of N-methyl-D-aspartic acid (NMDA) on cochlear spinal ganglion neurons.\textsuperscript{100,101,112} Also, the prevention of prostaglandin synthesis interferes with the Na\textsuperscript+-K\textsuperscript+-adenosine triphosphatase (ATPase) pump in the stria vascularis, and the vasoconstriction decreases cochlear blood flow.\textsuperscript{12,15,37,61} Membrane permeability changes cause a loss of outer hair cell turgor in the organ of Corti, which may impair otoacoustic emissions.\textsuperscript{100,102} A more complete description of the pathophysiology of salicylate-induced ototoxicity and sensorineural alterations as well as comparisons with the patterns of other ototoxic xenobiotics can be found in Chap. 26.

**Pulmonary Effects**

Salicylates have very potent stimulatory effects on respiratory drive via several mechanisms. Direct stimulation of the medullary respiratory neurons produces hyperpnea and tachypnea even at therapeutic concentrations. In fact, in a human trial, salicylates decreased the number and duration of apneic events in patients with sleep apnea.\textsuperscript{96} Increased sensitivity to PCO\textsubscript{2} and pH further increases ventilation. Carotid body and peripheral arterial chemoreceptor stimulation also contribute to salicylate-induced hyperventilation.\textsuperscript{81}

Patients with either acute or chronic salicylamism may develop acute respiratory distress syndrome (ARDS). It is often a sign of severe and advanced toxicity and can be lethal. One study\textsuperscript{4,5,51,122,128} that summarized data from nearly 400 consecutive cases of salicylate toxicity reported in the literature concluded that ARDS occurred in approximately 7\% of cases. The development of ARDS in salicylate poisoning is associated with a history of cigarette smoking, chronic overdose, metabolic acidosis, and neurologic symptoms at the time of arrival.\textsuperscript{90}

Although the exact etiology of salicylate-induced ARDS is unclear, as with other etiologies ARDS can result from increased pulmonary capillary permeability and subsequent exudation of high-protein edema fluid into the interstitial or alveolar spaces.\textsuperscript{57} Adrenergic excess in salicylate poisoning may injure the hypothalamus, leading to a shift in blood from the systemic to the pulmonary circulation because of a loss of left ventricular compliance with left atrial and pulmonary capillary hypertension (Chap. 17). Additionally, the resulting hypoxia produces pulmonary arterial hypertension and a local release of vasoactive substances, worsening ARDS.\textsuperscript{58} Unventilated salicylate-poisoned sheep were more likely to develop ARDS compared with a mechanically ventilated control group, suggesting that the mechanical stress of prolonged and severe hyperventilation is a significant contributing factor to this complication.\textsuperscript{78}

**Gastrointestinal Effects**

Salicylate disrupts the mucosal barrier that normally protects the gastric lining from the extremely acidic contents of the stomach. GI injury leading to ulcers or bleeding are among the most common adverse effects from therapeutic use of aspirin, but in acute overdose, the most common manifestations result from local gastric irritation presenting with nausea and vomiting. Emesis appears to be triggered both by local mucosal irritation and central stimulation of the chemoreceptor trigger zone.\textsuperscript{110} Hemorrhagic gastritis, decreased gastric motility, and pylorospasm result from the direct gastric irritant effects of salicylates.\textsuperscript{119}
Renal Effects
The kidneys play a major role in the excretion of salicylate and its metabolites. Although some believe that salicylates are nephrotoxic, the majority of experimental evidence does not strongly support this notion. Most of the adverse renal effects historically associated with salicylates occurred with use of combination products such as aspirin–phenacetin–caffeine (APC) tablets and appear to have been mostly caused by the phenacetin. Renal papillary necrosis and chronic interstitial nephritis, initially characterized by reduced tubular function and reduced concentrating ability, rarely occur in adults using salicylates unless they have chronic illnesses that already compromise renal function.

Volume losses in patients with salicylate toxicity that develop from hyperventilation and hyperthermia may also cause prerenal acute kidney injury (AKI). Rarely, salicylates may also induce a Fanconilike syndrome with generalized proximal tubular dysfunction characterized by glucosuria (despite normal serum glucose), proteinuria, aminoaciduria, and uric acid wasting.

Hematologic Effects
The hematologic effects of salicylate poisoning include hypoprothrombinemia and platelet dysfunction. The platelet dysfunction, caused by irreversible acetylation of COX-1 and COX-2, prevents the formation of thromboxane A₂, which is normally responsible for platelet aggregation. Although the platelets are numerically and morphologically intact, they are unresponsive to thrombogenic stimulation. At supratherapeutic doses, salicylate decreases the plasma concentration of the γ-carboxyglutamate containing coagulation factors and an accumulation of microsomal substrates for vitamin K dependent carboxylase in the liver and in the lung. The result of this interruption of vitamin K cycling is similar to that of warfarin, leading to hypoprothrombinemia (factor II) as well as decreases in factors VII, IX, and X (Chap. 60).

CLINICAL MANIFESTATIONS OF SALICYLATE POISONING
The following sections describe the typical clinical manifestations that follow toxic exposures to salicylates. The natural course of acute ingestions begins with nonspecific GI symptoms, early tachypnea caused by direct central respiratory stimulation, development of an anion gap metabolic acidosis, and several minor neurologic sequelae. As the acidosis worsens, symptoms progress and will invariably evolve to severe CNS toxicity. Hyperthermia, cerebral edema, coagulopathy, ARDS, and severe acidemia are the gravest clinical consequences and are often preterminal events. Cerebral edema is often seen at autopsy in those who succumb to salicylate toxicity.

The earliest signs and symptoms of salicylate toxicity, which include nausea, vomiting, diaphoresis, and tinnitus, typically develop within 1 to 2 hours of acute exposure. But the type of salicylate containing preparation, comorbidities, co-ingestants, and compromise in renal or hepatic function may alter the onset of symptoms that can be delayed up to 24 hours after exposure. Case reports of enteric-coated aspirin tablet ingestions have demonstrated delays in symptom onset and time to
initial detectable salicylate concentration, with peak salicylate concentrations reported to occur 2 to 3 days after initial exposure.

**Acute Salicylate Toxicity**

Salicylates are extremely irritating to the GI lining; early vomiting after ingestion may be a warning sign of a clinically significant ingestion. Emesis occurs both by direct GI irritation and from salicylate-induced stimulation of the chemoreceptor trigger zone. Pylorospasm, delayed gastric emptying, and decreased GI motility can all be present, complicating toxicity by altering absorption kinetics. Hemorrhagic gastritis also occurs, likely as a consequence of severe emesis and alteration of protective GI barriers.

The initial evaluation of a patient suspected of salicylate poisoning must start at the bedside with a thorough assessment of the respiratory rate and depth. Subtle tachypnea or hyperpnea should not be overlooked because if missed, delays may occur in the initiation of appropriate laboratory analysis and management. Direct central stimulation of the respiratory center increases minute ventilation, determined by the product of respiratory rate and tidal volume. A primary respiratory alkalosis predominates initially, although an anion gap metabolic acidosis begins to develop early in the course of salicylate toxicity. By the time a symptomatic adult patient presents to the hospital after a salicylate overdose, a mixed acid–base disturbance is often prominent. This latter finding includes two primary processes, respiratory alkalosis and metabolic acidosis, and is discernible by arterial blood gas (ABG) or venous blood gas (VBG) and serum electrolyte analyses. In one study of 66 salicylate-poisoned adults, 22% had respiratory alkalosis, and 56% had mixed respiratory alkalosis and metabolic acidosis.

On presentation, salicylate poisoned adults who demonstrate respiratory acidosis should alert the clinician to the fact that systemic toxicity is severe. This patient may be late in the clinical course of poisoning and have salicylate induced ARDS, fatigue from hyperventilating for a prolonged period of time, or CNS depression (from either salicylate itself or co-ingestants). These broad variations of clinical toxicity can be divided into three general time frames based on rapidly available laboratory testing. Early, middle, and late salicylate poisoning are demonstrated in Table 39–1.

<table>
<thead>
<tr>
<th>TABLE 39–1. Acid-Base Stages of Salicylate Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>View Large</td>
</tr>
</tbody>
</table>

Mixed overdoses are common; in one study, one-third of patients with a presumed primary salicylate overdose had taken other xenobiotics. Benzodiazepines, barbiturates, alcohol, and cyclic antidepressants all blunt the centrally induced hyperventilatory response to salicylates, resulting in either actual respiratory acidosis (PCO₂>40 mm Hg) or metabolic acidosis without some respiratory compensation (PCO₂<40 mm Hg but inappropriately high for the concomitant degree of metabolic acidosis). In both adults and children, the development of respiratory acidosis may occur as salicylate poisoning progresses. The combination of metabolic and respiratory acidosis in a
salicylate poisoning results in severe and worsening acidemia that is an exceedingly grave situation and almost invariably is a preterminal event.  

When clinical and radiographic manifestations of ARDS are observed in the setting of salicylate toxicity, the following conditions should be considered: aspiration pneumonitis, viral and bacterial infections, neurogenic ARDS, and salicylate-induced ARDS (Chap. 29). In 111 consecutive patients with peak salicylate concentrations above 30 mg/dL, ARDS occurred in 35% of patients older than 30 years of age and none of the 55 patients younger than 16 years of age. Risk factors for developing ARDS included cigarette smoking, chronic salicylate ingestion, and the presence of neurologic symptoms on admission. The average arterial blood pH was 7.37 in the six adult patients with ARDS and 7.46 in the 30 adults without ARDS. There was no significant difference in salicylate concentrations, which were approximately 57 mg/dL in both groups. In a 2-year review of all salicylate deaths in Ontario, Canada, 59% of 39 autopsies revealed pulmonary pathology, mostly "pulmonary edema" (ARDS).  

Although hyperventilation is centrally mediated, patients may develop a spectrum of CNS abnormalities that includes confusion, agitation, and lethargy and then ultimately seizures and coma. Human and animal evidence suggests that hypoglycorrhachia despite euglycemia contributes to the neurotoxic effects. Stupor, coma, and delirium have been acutely reversed by the administration of dextrose in children and adults with salicylate toxicity and normal serum glucose concentrations. In one report, a child underwent lumbar puncture, and CSF analysis demonstrated no detectable glucose. The most severe neurologic clinical findings are likely associated with the development of cerebral edema and portend a poor prognosis. Excluding effects on ventilation, signs of neurologic toxicity, even if mild, should be of great concern.  

Tinnitus, a subjective sensation of ringing or hissing with or without hearing loss, loss of absolute acoustic sensitivity, and alterations of perceived sounds are the three effects resulting from exposure to large doses of salicylates. The pattern of salicylate-induced auditory sensorineural alterations is different than that of other ototoxic xenobiotics. Tinnitus should demonstrate to clinicians that CNS toxicity has occurred even without alterations in mental status. As CNS salicylate concentrations increase, tinnitus is rapidly followed by diminished auditory acuity that sometimes leads to deafness. As acute toxicity progresses, other CNS effects may include vertigo, hyperactivity, agitation, delirium, hallucinations, lethargy, seizures, and stupor. Coma is rare and is generally a late finding occurring in severe acute poisoning or mixed overdoses. Paratonia, extreme muscle rigidity, has been observed in severe salicylate poisoning pre- and postmortem, and in one case, it was even unresponsive to succinylcholine. Decreased ATP production, impaired glycolysis, increased lactate, and uncoupling of muscular oxidative phosphorylation likely contribute to this phenomenon. This excess neuromuscular activity may lead to rhabdomyolysis and most concerning hyperthermia that is typically a preterminal condition.  

**Chronic Salicylate Toxicity**
Chronic salicylate poisoning most typically occurs in elderly individuals as a result of unintentional overdosing on salicylates used to treat chronic conditions such as rheumatoid arthritis and osteoarthritis. Presenting signs and symptoms of chronic salicylate poisoning can be similar to those of acute toxicity and include nausea and vomiting, hearing loss and tinnitus, dyspnea and hyperventilation, tachycardia, hyperthermia, and neurologic manifestations such as confusion, delirium, agitation, hyperactivity, slurred speech, hallucinations, seizures, and coma. Although there is considerable overlap with acute salicylate poisoning, the slow, insidious onset of chronic poisoning in elderly individuals frequently causes delayed recognition of the true cause of the patient’s presentation.

Typically, ill patients who have chronic salicylate poisoning may be misdiagnosed as having delirium, dementia, or encephalopathy of undetermined origin, or diseases such as sepsis (fever of unknown origin), alcoholic ketoacidosis, respiratory failure, or cardiopulmonary disease. Unfortunately, many of the signs and symptoms of chronic salicylate toxicity may be mistakenly attributed to the illness for which the salicylates were administered. Despite an extensive evaluation during a first hospitalization for ARDS, chronic salicylism was not diagnosed until a second hospitalization for the same respiratory symptoms. This case highlights the need to include chronic salicylism in the differential for ARDS with or without neurologic symptoms.

In a study of 73 consecutive adults hospitalized with salicylate poisoning, 27% were not correctly diagnosed for as long as 72 hours after admission. These patients manifested toxicity with standard or excessive therapeutic regimens and had significant associated diseases without a history of previous overdoses. In this group, 60% of the patients had a neurologic consultation before the diagnosis of salicylism was established. When diagnosis is delayed in elderly individuals, the morbidity and mortality associated with salicylate poisoning are high. The mortality rate was reported to be as high as 25% in the 1970s, and there are no data to suggest that survival after delayed diagnosis is substantially better today.

**EVALUATION AND DIAGNOSTIC TESTING**

The most commonly reported route of salicylate exposure is from the acute ingestion of aspirin, which, as mentioned earlier, has a very short serum half-life of about 15 minutes during which time it is rapidly converted to salicylate. The symptoms of toxicity are due to the systemic effects of salicylate and not the parent compound. Systemic toxicity is concerning after the following exposures: ingestions of 150 mg/kg or 6.5 g of aspirin, whichever is less; ingestion of greater than a lick or taste of oil of wintergreen (98% methyl salicylate) by children younger than 6 years of age; and more than 4 mL of oil of wintergreen by patients 6 years of age and older. These patients as
well as those with significant topical exposures and signs of toxicity should be promptly evaluated for salicylate toxicity.

The initial approach to a patient suspected of salicylate toxicity should obviously include a serum salicylate concentration. But it is very important to recognize that other laboratory assays such as an ABG or VBG, electrolytes to determine anion gap, the presence of serum or urine ketones, and a lactate concentration can be critical in uncovering an unrecognized salicylate poisoning. It also may be important to evaluate renal and hepatic function because dysfunction in either will exacerbate toxicokinetic effects in patients with acute or chronic exposures.

As aspirin or other parent compounds are metabolized to salicylate, there should be a drop in serum bicarbonate, leading to an increase in the anion gap. Elevated anion gaps are caused by increases in unmeasured anions that are primarily salicylate but also related to increases in lactic acid, ketoacids, and daily endogenous dietary acids. Volume loss from vomiting and excess metabolic energy can cause AKI, which will decrease the elimination of dietary acids.

Several studies have suggested that empiric serum salicylate concentrations are not required as part of a general toxicologic evaluation in patients with acute self-poisoning. Routine salicylate testing is likely unnecessary without a positive history of salicylate ingestion, an inability to obtain a valid history (altered mental status), or clinical features of salicylate poisoning. One retrospective study also suggested that screening for salicylism is not needed in the absence of an elevated anion gap. Although an anion gap metabolic acidosis is likely found in most cases of salicylate toxicity, severe salicylism may falsely elevate serum chloride, bringing the anion gap closer to a normal range.

Although it may be wise to curtail empiric testing, clinicians should likely err on the side of ordering a salicylate assay if there is any clinical concern because the morbidity and mortality are significantly increased with delays in recognition and management. Many of the signs and symptoms of salicylate toxicity are vague and may be mistakenly attributed to another illness with disastrous consequences. In the review of all salicylate deaths in Ontario, Canada, in 1983 and 1984, the author noted that in six of the 23 (26%) patients who arrived alert, no salicylate determination appears to have been made and that probably neither the diagnosis nor the severity of the salicylate poisoning was recognized.

Salicylate Analysis

Serum salicylate concentrations are relatively easy to obtain in most hospital laboratories today. Several methods are available for determining serum salicylate concentrations. The Trinder assay is the most popular method for the measurement of salicylate in serum by using spectrophotometric analysis. Trinder’s reagent contains mercuric chloride and hydrochloric acid used to precipitate serum proteins. The measured absorbance at 540 nm of a ferric ion–salicylate complex allows for accurate determination of the serum salicylate concentration. Historically there have been several bedside urine qualitative tests (ie, mercuric chloride, ferric chloride) used to assess for the presence of salicylate. They have no clinical utility today because of poor specificity and chemical hazards and
are no longer permissible under the federal Clinical Laboratory Improvement Amendments (CLIA) in the United States.

Serum salicylate concentrations are commonly reported in mg/dL in the United States, but confusion can arise because values can also be reported in mg/L and µg/mL. Analyzing and reporting salicylate concentrations as mg/L when the clinician is accustomed to receiving results as mg/dL or inadvertently reporting actual mg/L (before internal laboratory conversion) produces erroneous results. These may suggest a toxic salicylate concentration in a patient whose serum salicylate concentration is actually within the therapeutic range (eg, “165 mg/L” instead of “16.5 mg/dL”). Most errors can be eliminated before initiation of aggressive therapy, such as hemodialysis (HD), by determining whether the reported salicylate concentration is consistent with the clinical presentation and ABG or VBG results and, when time permits, repeating the salicylate determination with appropriate consideration for methodology and conversion calculations. Using the earlier example, a patient with a serum salicylate concentration of 165 mg/dL would undoubtedly show clinical signs of salicylate toxicity and have a profound acid–base abnormality, but a patient with a concentration of 165 mg/L would likely be asymptomatic.

It should also be noted that several clinical scenarios and xenobiotic exposures are recognized to cause false-positive or falsely elevated true salicylate concentrations. Medications that may interfere with the assay include thioridazone, promethazine, prochlorperazine, chlorpromazine, acetylcysteine, and cysteamine. Significantly falsely elevated serum salicylate concentrations are well recognized after diflunisal overdose. Hyperbilirubinemia can create clinically significant false-positive results in neonates and adults. Interestingly, hyperlipidemia can also cause significant interference and false elevation of serum salicylate concentrations. If there is concern for false salicylate concentrations, clinicians should contact laboratory personnel, who often have information regarding instrument-specific recognized interferences for each assay as published by the manufacturer. Several techniques may be used to determine a true salicylate concentration in the setting of a known interference. One of the most sensitive and specific assays now available is an automated immunoassay based on specific antisalicylate antiserum with fluorescence polarization immunoassay (FPIA) detection technology.

**Interpretation of Serum Salicylate Concentrations and Correlation with Toxicity**

The recommended therapeutic concentration of salicylate is 10 to 30 mg/dL, but this varies by indication. Antiinflammatory dosing usually is advised to be on the higher end of this spectrum, but analgesic effects can be observed as low as 5 to 10 mg/dL. Values above 30 mg/dL are usually not found unless there is a supratherapeutic, acute, or chronic toxic exposure.

The correlation of serum salicylate concentrations and clinical toxicity is often poor and dependent on several factors. A concurrent arterial or venous blood pH should be determined when a serum salicylate concentration is obtained because in the presence of acidemia, more salicylic acid leaves the blood and enters the CSF and other tissues (Fig. 39–2), increasing the toxicity. A decreasing serum salicylate concentration may be difficult to interpret because it may reflect either an increased tissue distribution with increasing toxicity or an increased clearance with decreasing toxicity. A
decreasing serum salicylate concentration accompanied by a decreasing or low blood pH should be presumed to reflect a serious or worsening situation, not a benign or improving one. Patients with chronic toxicity demonstrate more significant clinical effects at lower concentrations compared with acute toxicity given the increased distribution over time into tissue compartments and specifically the CNS.

**FIGURE 39–2.**
Rationale for alkalinization. Alkalinization of the plasma with respect to the tissues and alkalinization of the urine with respect to plasma shifts the equilibrium to the plasma and urine and away from the tissues, including the brain. This equilibrium shift results in “ion trapping.”

Although impractical clinically, salicylate concentrations in the CSF are likely the most accurate measure of toxicity, directly correlating with death in a rat model. Animals that were lethally poisoned with salicylate were comatose and died from seizures. The time to death after salicylate administration varied greatly as did the blood, muscle, and liver salicylate concentrations. However, regardless of the time of death and the concentrations in blood, muscle, or liver, all animals died with a consistent range of CSF salicylate concentrations. Inhalation of CO₂ (lowering serum pH) in a rat resulted in a precipitous decrease in serum salicylate concentrations, which returned to baseline rapidly after the discontinuation of CO₂. This suggests that the salicylate redistributed into tissue during the period of induced respiratory acidosis and reequilibrated after its correction. After administration of radiolabeled salicylate to cats, autoradiographs of the brain visually and objectively documented the profound effect that acidemia has on the distribution of salicylate into the brain.

Before serum assays were readily available, physicians who prescribed aspirin would advise patients to take repeated doses until tinnitus occurred and then “back off” a little to maintain this “steady state.” Tinnitus and the subsequent reversible hearing loss typically occur at serum salicylate concentrations of 20 to 45 mg/dL. This prompted investigations into whether salicylate-induced tinnitus could be used as an indicator of serum salicylate concentration and toxicity. Unfortunately, some patients with therapeutic concentrations of salicylates had tinnitus, and many with higher or toxic concentrations had no tinnitus. In a study of 94 patients with salicylate concentrations above 30 mg/dL on one or more occasions, tinnitus only correlated with serum salicylate concentrations in 30%; 55% had no tinnitus, although audiologic testing results were usually abnormal regardless of the patient’s perception of presence or absence of tinnitus. Thus, although symptomatic ototoxicity may be a helpful warning sign of salicylate toxicity when present, it is too nonspecific and too insensitive to serve as an indicator of serum salicylate concentrations.

**MANAGEMENT**
The management of patients with salicylate toxicity is aimed at supporting vital signs and organ function, preventing or limiting ongoing exposure from the gut or skin, and enhancing elimination of salicylate that has already entered the systemic circulation. It is imperative to understand that there is no true antidote for salicylate toxicity; no xenobiotic can combat the clinical toxicity demonstrated in consequential exposures. HD, as discussed later, aims to remove salicylate from the tissues but may not correct severe organ toxicity such as ARDS or cerebral edema and can therefore not guarantee survival after severe toxicity occurs. Rather, all therapies are better at preventing tissue injury than treating it.

It is imperative to understand that the primary toxicity of salicylate is on the CNS, and the amount of salicylate in the brain is a function of pH with acidemia enhancing CNS penetration of the drug. Management strategies strive to create concentration gradients and pH conditions that favor exit of salicylate from the CNS and other tissues and enhanced renal elimination.

Gastrointestinal Decontamination and Use of Activated Charcoal and Catharsis
The use of orogastric lavage and activated charcoal (AC) is discussed in Chap. 8 and Antidotes in Depth: A1. Their effects on the absorption and elimination of salicylates have been extensively studied. In vitro studies suggest that each gram of AC can adsorb approximately 550 mg of salicylic acid. In humans, AC reduces the absorption of therapeutic doses of aspirin by 50% to 80%, effectively adsorbing aspirin released from enteric-coated and sustained-release preparations in addition to immediate-release tablets. Presumably, the sooner AC is given after salicylate ingestion, the more effective it will be in reducing absorption. A 10:1 ratio of AC to ingested salicylate appears to result in maximal efficacy but is often impractical given the fact that ingestions of salicylate often reach 20- to 30-g amounts or more. Although peak serum concentrations are markedly decreased from predicted concentrations, aspirin desorption from the aspirin–AC complex in the alkaline milieu of the small bowel may diminish the impact of AC on total absorption. The addition of a cathartic to the initial dose of AC has been questioned and largely abandoned for most xenobiotics, but a benefit of adding sorbitol to AC in preventing salicylate absorption was demonstrated in one study. A single dose may still therefore be acceptable.

Repetitive or multiple-dose AC (MDAC) is necessary to achieve desired ratios of activated charcoal to salicylate (and probably limits desorption), which may reduce the concentration of initially absorbed salicylate to only 15% to 20%. MDAC appears to increase the elimination of unabsorbed salicylates over that achieved by single-dose AC. Thus, the use of MDAC to decrease GI absorption of salicylates is warranted, barring contraindications particularly if a pharmacobezoar or extended-release preparation is suspected (Antidotes in Depth: A1).

The value of MDAC in enhancing salicylate elimination through GI dialysis is controversial and is not generally warranted. In one volunteer study of a 2800-mg dose of aspirin followed by 25 g of AC at 4, 6, 8, and 10 hours after ingestion, the total amount of salicylate excreted from the body increased by 9% to 18% but was not considered statistically significant. The efficacy is likely greater in an overdose situation, when more unbound salicylate is available because of decreased protein binding. However, in another study of the effects of MDAC on the clearance of high-dose
intravenous (IV) aspirin in a porcine model, MDAC did not enhance the clearance of salicylates under conditions when the venous bicarbonate was kept at 15 mEq/L or less and urine pH kept at 7.5 or less. In contrast to the findings of both of these studies, two children with salicylate overdoses were successfully treated with MDAC given every 4 hours for 36 hours. Overall, extensive use of MDAC is currently discouraged, but the administration of two to four properly timed doses is reasonable. The administration of AC or MDAC must be balanced against risks of vomiting and aspiration, especially in patients with altered mental status and unprotected airways (Chap. 8).

Theoretical support may be found for the use of whole-bowel irrigation (WBI) with polyethylene glycol electrolyte lavage solution (PEG-ELS) in addition to AC to reduce absorption, particularly for enteric-coated aspirin preparations. However, because the addition of WBI to MDAC does not increase the clearance of absorbed salicylate in an experimental model, it is not routinely recommended.

**Fluid Replacement**

There is a need to differentiate between restoration of fluid and electrolyte balance in salicylate-poisoned patients and increasing the fluid load presented to the kidneys in an attempt to achieve “forced diuresis.” Fluid losses in patients with salicylate poisoning are prominent, especially in children, and can be attributed to hyperventilation, vomiting, fever, a hypermetabolic state, cathartic administration, and perspiration. The kidneys also respond to salicylate poisoning by excreting an increased solute load, including large quantities of bicarbonate, sodium, potassium, and organic acids. For all of these reasons, the patient’s volume status must be adequately assessed and corrected if necessary along with any glucose and electrolyte abnormalities. As in other cases, accurate management of volume status in poisoned patients may require invasive or noninvasive monitoring of central venous pressures, especially in patients with cardiac disease, ARDS, or AKI.

Increasing fluids beyond restoration of fluid balance to achieve forced diuresis is a practice that was inappropriately promoted in the past. Although forced diuresis theoretically increases renal tubular flow and reduces the urine tubular cell diffusion gradient for reabsorption, renal excretion of salicylate depends much more on urine pH than on flow rate, and use of forced diuresis alone is not effective regardless of whether diuretics, osmotic agents, or large fluid volumes are used to achieve the diuresis. Although renal salicylate clearance varies in direct proportion to flow rate, its relation to pH is logarithmic. In summary, although fluid imbalance must be corrected, forced diuresis does little more than oral fluids to enhance elimination over a 24-hour period and subjects the patient to the hazards of fluid overload.

**Serum and Urine Alkalinization**

The cornerstone of the management of patients with salicylate toxicity is to shift salicylate out of the brain and tissues into the serum, where elimination through the kidneys can then occur. Alkalinization of the serum with respect to the tissues and alkalinization of the urine with respect to the serum accomplishes this goal by facilitating the movement and “ion trapping” of salicylate into the serum and the urine (Fig. 39–2). Alkalinization of the serum by a substance that does not easily cross the blood–brain barrier such as intravenously administered sodium bicarbonate reduces the
fraction of salicylate in the nonionized form and increases the pH gradient with the CSF. This both prevents entry and helps remove salicylate from the CNS. 47, 52, 53, and 54

Alkalinization with IV sodium bicarbonate should be considered for all symptomatic patients whose serum salicylate concentrations exceed the therapeutic range and for clinically suspected cases of salicylism until a salicylate concentration and simultaneously obtained blood pH are available to guide treatment. Patients on therapeutic regimens of salicylates who feel well with salicylate concentrations of 30 to 40 mg/dL and who do not manifest toxicity do not require intervention.

Alkalinization may be achieved with a bolus of 1 to 2 mEq/kg of sodium bicarbonate IV followed by an infusion of 3 ampules of sodium bicarbonate (132 mEq) in 1 L of 5% dextrose in water (D5W), administered at 1.5 to 2.0 times the maintenance fluid range. Urine pH should be maintained at 7.5 to 8.0, and hypokalemia must be corrected (see later discussion) to achieve maximum urinary alkalinization. Volume load should remain modest while previous losses are repleted (Antidotes in Depth: A5).

Oral bicarbonate administration should never be substituted for IV bicarbonate to achieve alkalinization because the oral route may increase salicylate absorption from the GI tract by enhancing dissolution. Hyperventilation alone should not be relied upon, and intravenous sodium bicarbonate should be used for alkalinization.

Urine Alkalinization
Because salicylic acid is a weak acid (pKₐ 3.0), it is ionized in an alkaline milieu and theoretically can be “trapped” there. This occurs because there is no specific uptake mechanism in the kidney for salicylate ion, and passive reabsorption of a charged molecule is very limited. Thus, alkalinization of the urine (defined as pH ≥7.5) with sodium bicarbonate results in enhanced excretion of the ionized salicylate ion.

Alkalinization of the urine should be considered as a first-line treatment for patients with moderately severe salicylate poisoning who do not meet the criteria for HD. 99, 123 It should also be administered to salicylate-poisoned patients who require HD while preparations are being made to perform HD. Although salicylic acid is almost completely ionized within physiologic pH limits, small changes in pH obtained by alkalinization may have substantial changes in the relative amount of salicylate in the charged form.

Regardless of the reason for the change in serum pH, renal excretion of salicylate is very dependent on urinary pH. 45-57, 127 Alkalinization increases free salicylate secretion from the proximal tubule but does not affect renal elimination of salicylate conjugates. Alkalinizing the urine from a pH of 5 to 8 logarithmically increased renal salicylate clearance from 1.3 to 100 mL/min 62, 66 (Fig. 39–3). Assuming an overdose Vd of 0.5 L/kg, this increased clearance would decrease salicylate half-life from 310 to 4 hours. However, in reality alkalinizing the urine from a pH of 5 to 8 has a more modest effect on serum salicylate clearance. 62

FIGURE 39–3.
The relationship between urine pH and urine salicylate clearance. This curve was adapted from a logarithmic relationship determined by Kallen in patients with salicylate poisoning. It illustrates the need to substantially increase urine pH above 7 to impact elimination.

Although the administration of acetazolamide, a noncompetitive carbonic anhydrase inhibitor, results in the formation of bicarbonate-rich alkaline urine, it also causes a metabolic acidosis and acidemia.\textsuperscript{41, 52, 53} This latter effect of acetazolamide is usually self-limited and mild but nevertheless increases the concentration of freely diffusible nonionized molecules of salicylic acid, thereby increasing the Vd and most probably enhancing the penetrance of salicylate into the CNS.\textsuperscript{53, 73}

Hypokalemia is a common complication of salicylate poisoning and sodium bicarbonate therapy and can prevent urinary alkalinization unless corrected. In the presence of hypokalemia, the renal tubules reabsorb potassium ions in exchange for hydrogen ions, preventing urinary alkalinization. If urinary alkalinization cannot be achieved easily, hypokalemia, excretion of organic acids, and salt and water depletion should be considered possible reasons. Calcium concentrations should be monitored because decreases in both ionized\textsuperscript{43} and total serum calcium\textsuperscript{43} are also complications of bicarbonate therapy.

**Glucose Supplementation**

As discussed earlier, salicylate poisoning may significantly alter glucose metabolism, transport, and relative requirements. Clinically, this is relevant in that the presence of a normal serum glucose concentration may not be reflective of a normal CSF glucose concentration. It is suggested that the neurotoxicity of salicylism may be partly caused by this hypoglycorrhachia. Dextrose administration alone has reversed acute delirium associated with salicylate toxicity.\textsuperscript{23, 69} It is therefore wise to liberally administer dextrose to all patients with altered mental status in salicylate toxicity regardless of their serum glucose concentration. A bolus of 0.5 to 1 g/kg of dextrose with additional or even continuous infusion should be considered in patients being treated for severe salicylate toxicity.

**Extracorporeal Removal**

Extracorporeal measures are indicated if the patient has severe signs or symptoms, a very high serum salicylate concentration regardless of clinical findings, severe fluid or electrolyte disturbances, cerebral edema, or ARDS or is unable to eliminate the salicylates because of AKI (Table 39–3). It should also be considered when a patient cannot tolerate the increased solute load that results from alkalinization or large-volume infusions necessary. Failure to tolerate such therapy can be anticipated if the patient has initial symptoms that are consistent with severe salicylate toxicity or has a history congestive heart failure or chronic kidney disease.

**Table 39–3. Indications for Hemodialysis in Salicylate Poisoned Patients**
In most instances, HD is the extracorporeal technique of choice, not only to clear the salicylate but also to rapidly correct fluid, electrolyte, and acid–base disorders that will not be corrected by hemoperfusion (HP) alone. The combination of HD and HP in series is feasible and theoretically may be useful for treating patients with severe or mixed overdoses, but it is rarely used. A rapid reduction of serum salicylate concentrations in severely poisoned patients has been described with the use of continuous renal replacement therapy, a technique that may be valuable for patients who are too unstable to undergo HD or when HD is unavailable (Chap. 10). There is only one published clinical experience with sustained low-efficiency dialysis (SLED) for salicylate toxicity, which demonstrated similar clearance rates to other continuous extracorporeal therapies. Its role still requires further investigation.

While the patient is awaiting HD, alkalinization of serum and urine should be aggressively achieved with sodium bicarbonate therapy. During HD, it is unnecessary to continue bicarbonate therapy because it will be provided by HD. It is prudent to reinstitute bicarbonate therapy after HD has been completed, especially if patients are still symptomatic or serum salicylate concentrations are pending.

Nephrology consultation should be sought early and liberally to anticipate and prevent avoidable morbidity and mortality. Despite the well-recognized benefit of extracorporeal removal of salicylates in severe toxicity, delays in initiating HD remain a potentially preventable cause of death despite repeated calls over many years for prompt HD for patients with salicylate poisoning. The initiation of HD should not be considered definitive treatment because patients may still have a significant GI burden of salicylate, resulting in continued absorption, and even with early and multiple runs of HD, patients may still succumb to this poisoning.

**Chemical Sedation, Intubation, and Mechanical Ventilation Risks**

Salicylate-poisoned patients have a significantly increased minute ventilation rate brought about by both tachypnea and hyperpnea, often exceeding 20 to 30 L/min. Any decrease in minute ventilation increases the PCO₂ and decreases the pH. This shifts salicylate into the CNS, exacerbating toxicity. Thus, extreme caution must be used when considering chemical sedation, intubation, and initiating mechanical ventilation.

Although induced hyperventilation may effectively increase the blood pH in certain patients, endotracheal intubation followed by assisted ventilation of a salicylate-poisoned patient poses particular risks if it is not meticulously performed. Although early endotracheal intubation to maintain hyperventilation may aid in the management of patients whose respiratory efforts are faltering, health care providers must maintain appropriate hypocarbia through hyperventilation. Ventilator settings that result in an increase in the patient’s PCO₂ relative to premechanical ventilation will produce relative respiratory acidosis even if serum pH remains in the alkaline range.
In a search of a poison center database of patients with salicylate poisoning between 2001 and 2007, seven patients were identified with salicylate concentrations above 50 mg/dL who had both premechanical ventilation and postmechanical ventilation data. All seven had postmechanical ventilation pH values below 7.4, and five of the six for whom recorded PCO$_2$ values were available had postmechanical ventilation PCO$_2$ values above 50 mm Hg, suggesting substantial underventilation. Two of the seven patients died after intubation, and one sustained neurologic injury. Inadequate mechanical ventilation of patients with salicylate poisoning was associated with respiratory acidosis, a decrease in the serum pH, and an abrupt clinical deterioration. Even when achieved, however, respiratory alkalosis sustained by hyperventilation (assisted or unassisted) alone should never be considered a substitute for use of either sodium bicarbonate (to achieve both alkalemia and alkalinuria) or HD (when indicated).

If chemical sedation is required, although there is no clear choice of preferred sedative, the goals are to minimize respiratory depression and use the minimum amount required for desired sedation. If intubation is deemed necessary, which it often may be in situations of severe toxicity or multdrug ingestions, the following steps should be taken to optimize before, during, and after intubation conditions. The goal should be to maintain or exceed minute ventilation rates that were present before intubation. Before intubation, an attempt should be made to optimize serum alkalinization by administering a 2-mEq/kg bolus of sodium bicarbonate. Preparations should be made to minimize the period of time the patient will spend with apnea or decreased ventilation by considering an awake intubation. The provider most experienced in intubation should be present as well as any adjunct materials to increase first-pass success. An intensivist, respiratory technician, or other mechanical ventilator expert should be consulted to help match preintubation minute ventilation. After mechanical ventilation has begun, frequent blood gas monitoring should be obtained and ventilator settings adjusted as needed. An emergent nephrology consult is indicated for HD if not previously obtained. One recent report suggested the use of ketamine for awake intubation, thereby minimizing the hypoventilation associated with rapid-sequence intubation.

**Serum Salicylate Concentration and pH Monitoring**
Careful observation of the patient, correlation of the serum salicylate concentrations with blood pH, and repeat determinations of serum salicylate concentrations every 2 to 4 hours are essential until the patient is clinically improving and has a low serum salicylate concentration in the presence of a normal or high blood pH. In all cases, after a presumed peak serum salicylate concentration has been reached, at least one additional serum concentration should be obtained several hours later. Analyses should be obtained more frequently in managing seriously ill patients to assess the efficacy of treatment and the possible need for HD.

**Pediatric Considerations**
The predominant primary respiratory alkalosis that initially characterizes salicylate poisoning in adults may not occur in young children. This likely results from the limited ventilatory reserve of small children that prevents the same degree of sustained hyperpnea as occurs in adults. The typical acidemia noted in seriously poisoned children led some investigators in the past to incorrectly
suggest that pediatric salicylate poisoning produces only metabolic acidosis. Although after a significant salicylate exposure, some children present with a mixed acid–base disturbance and a normal or high pH, most present with acidaemia, suggesting the need for more urgent intervention because the protective effect of alkalemia on CNS penetration of salicylate is already lost. Although not routinely recommended, exchange transfusion may effectively remove large quantities of salicylate in infants too small to undergo emergent HD without extensive delays.  

Pregnancy
Considered a rare event, salicylate poisoning during pregnancy poses a particular hazard to fetuses because of the acid–base and hematologic characteristics of fetuses and placental circulation. Salicylates cross the placenta and are present in higher concentrations in a fetus than in the mother. The respiratory stimulation that occurs in the mother after toxic exposures does not occur in the fetus, which has a decreased capacity to buffer acid. The ability of a fetus to metabolize and excrete salicylates is also less than in the mother. In addition to its toxic effects on the mother, including coagulation abnormalities, acid–base disturbances, tachypnea, and hypoglycemia, repeated exposure to salicylates late in gestation displaces bilirubin from protein binding sites in the fetus, causing kernicterus.

A case report described fetal demise in a woman who claimed to ingest 50 aspirin tablets per day for several weeks during the third trimester of pregnancy. This raises concerns that a fetus is at greater risk from salicylate exposures than is the mother. Emergent delivery of near-term fetuses of salicylate-poisoned mothers should be considered on a case-by-case basis (Chap. 31).

SUMMARY
- The clinical presentation of a patient with a salicylate overdose may be characterized by an early onset of nausea, vomiting, abdominal pain, tinnitus, and lethargy.
- The combination of a primary respiratory alkalosis and a primary metabolic acidosis with net alkalemia constitutes the classic acid–base abnormality of salicylate poisoning in the adult.
- Initial efforts in managing patients with salicylate poisoning include restoration of intravascular volume, the use of AC to limit absorption, and urinary alkalinization to enhance renal elimination of salicylate.
- HD is indicated in patients with significantly elevated salicylate concentrations, altered mental status, ARDS, and or AKI.
- It is essential to maintain alkalemia to prevent CNS penetration of salicylate. As such, sedation and mechanical ventilation can be rapidly lethal, if they impair minute ventilation, causing rises in $\text{PCO}_2$ and a fall in pH.

Acknowledgment
Neal E. Flomenbaum, MD, Eddy A. Bresnitz, MD, Donald Feinfeld, MD (deceased), and Lorraine Hartnett, MD, contributed to this chapter in previous editions.
References


CrossRef [PubMed: 14066150]


CrossRef [PubMed: 8397891]


CrossRef [PubMed: 10817258]


CrossRef [PubMed: 8699558]


CrossRef [PubMed: 10880852]


CrossRef [PubMed: 8880210]


CrossRef [PubMed: 19031386]


CrossRef [PubMed: 10434224]


CrossRef


42. Filippone GA, Fish SS, Lacouture PG et al.: Reversible adsorption (desorption) of aspirin from activated charcoal. *Arch Intern Med.* 1987;147:1390–1392. [CrossRef] [Archives of Internal Medicine Full Text]


46.


47.


48.


49.


50.


51.


52.


53.


54.


55.


CrossRef [PubMed: 18632935]

113.


114.


CrossRef [PubMed: 8765104]

115.


CrossRef [PubMed: 13149788]

116.


CrossRef [PubMed: 18821862]

117.

Swintosky JV: Illustrations and pharmaceutical interpretations of first order drug elimination rate from the bloodstream. *J Am Pharm Assoc Am Pharm Assoc (Baltim).* 1956;45:395–400.

CrossRef [PubMed: 13319145]

118.


CrossRef [PubMed: 10999592]

119.


CrossRef [PubMed: 7469627]

[Archives of Internal Medicine Full Text]

120.


CrossRef [PubMed: 1277769]

121.


CrossRef [PubMed: 3287090]

122.


CrossRef [PubMed: 3591255]


134.