

Extracorporeal Treatment for Salicylate Poisoning: Systematic Review and Recommendations From the EXTRIP Workgroup

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Study objective: Salicylate poisoning is a challenging clinical entity associated with substantial morbidity and mortality. The indications for extracorporeal treatments such as hemodialysis are poorly defined. We present a systematic review of the literature along with evidence- and consensus-based recommendations on the use of extracorporeal treatment in salicylate poisoning.

Methods: The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup is a multidisciplinary group with international representation whose aim is to provide evidence-based recommendations on the use of extracorporeal treatments in poisoning. We conducted a systematic literature review followed by data extraction and summarized findings, following a predetermined format. The entire work group voted by a 2-round modified Delphi method to reach consensus on voting statements, using a RAND/UCLA Appropriateness Method to quantify disagreement. Anonymous votes were compiled, returned, and discussed in person. A second vote determined the final recommendations.

Results: Eighty-four articles met inclusion criteria, including 1 controlled clinical trial, 3 animal studies, and 80 case reports or case series, yielding an overall very low quality of evidence for all recommendations. Clinical data on 143 patients (130 sets of which could be analyzed for patient-level entry data), including 14 fatalities, were reviewed. Toxicokinetic data on 87 patients were also included. After the second round of voting, the workgroup concluded that salicylates are dialyzable by hemodialysis and hemoperfusion (level of evidence=B) and recommended extracorporeal treatment in patients with severe salicylate poisoning (1D), including any patient with altered mental status (1D), with acute respiratory distress syndrome requiring supplemental oxygen (1D), and for those in whom standard therapy is deemed to be failing (1D) regardless of the salicylate concentration. High salicylate concentrations warrant extracorporeal treatment regardless of signs and symptoms (>7.2 mmol/L [100 mg/dL] [1D]; and >6.5 mmol/L [90 mg/dL] [2D]), with lower thresholds applied for patients with impaired kidney function (>6.5 mmol/L [90 mg/dL] [1D]; >5.8 mmol/L [80 mg/dL] [2D]). Extracorporeal treatment is also suggested for patients with severe acidemia (pH ≤7.20 in the absence of other indications) (2D). Intermittent hemodialysis is the preferred modality (1D), although hemoperfusion (1D) and continuous renal replacement therapies (3D) are acceptable alternatives if hemodialysis is unavailable, as is exchange transfusion in neonates (1D).

Conclusion: Salicylates are readily removed by extracorporeal treatment, with intermittent hemodialysis being the preferred modality. The signs and symptoms of salicylate toxicity listed warrant extracorporeal treatment, as do high concentrations regardless of clinical status. [Ann Emerg Med. 2015;66:165-181.]

Please see page 166 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Despite improvements in supportive care, salicylate poisoning remains an important cause of poisoning-related mortality in the United States and around the world. Although comprehensive epidemiologic data are lacking, several deaths

related to acetylsalicylic acid (aspirin) toxicity are still reported to poison control centers each year in the United States alone.^{1,2} Although extracorporeal treatment is often considered for severe cases, their indications and specific applications are poorly defined. We present the results of a systematic review of the literature and clinical recommendations for the use of extracorporeal treatment in salicylate poisoning.

The term “salicylates” refers to all forms of salicylate, most commonly acetylsalicylic acid (aspirin) and methyl salicylate.

[†]All members are listed in the [Appendix](#).

Editor's Capsule Summary*What is already known on this topic*

Salicylate poisoning remains an important cause of poisoning-related morbidity. Specific indications for extracorporeal treatment are poorly defined.

What question this study addressed

This systematic review of 84 articles, including a single controlled clinical trial, derived consensus-based recommendations for extracorporeal treatment in salicylate poisoning.

What this study adds to our knowledge

Extracorporeal treatment is recommended for severe poisoning, including evidence of altered mental status, acute respiratory distress syndrome, or failure to respond to standard therapy. Asymptomatic patients with significantly elevated salicylate concentrations also merit consideration of extracorporeal treatment. Hemodialysis is the preferred extracorporeal treatment method.

How this is relevant to clinical practice

Although clinical data were limited, the consensus recommendations provide specific guidance for extracorporeal treatment use in the management of these patients with complex disease.

Although other salicylates such as sodium salicylate and bismuth subsalicylate are also available, the most commonly encountered salicylate in clinical practice is acetylsalicylic acid, which is a small organic acid with a mass of 180 Da. It is extensively bound to albumin (90%), but this process is saturable and can decrease to 30% after overdose.³ After ingestion, acetylsalicylic acid is rapidly absorbed and hydrolyzed to salicylic acid (the negative logarithm of the acid dissociation constant, pK_a 2.98), which exists primarily in the dissociated (salicylate) form at physiologic pH. Acetylsalicylic acid has a low volume of distribution (0.2 L/kg), although higher values (\cong 0.5 L/kg) have been reported after overdose⁴⁻⁶ (Table 1).

The pathophysiology and clinical manifestations of acetylsalicylic acid poisoning are described in detail elsewhere.⁷⁻¹¹ Briefly, salicylates uncouple oxidative phosphorylation, liberating heat while interfering with the generation of adenosine triphosphate.^{12,13} A metabolic acidosis with accumulation of lactate and ketoacids ensues as glucose is rapidly but inefficiently consumed and mitochondrial

Table 1. Salicylate physicochemical and toxicokinetic properties.

Physicochemical characteristic	Result
Molecular mass, Da	180 (acetylsalicylic acid)
Volume of distribution, L/kg	0.2 (up to 0.5 in overdose)
Protein binding, %	90 (30 in overdose)
Oral bioavailability, %	68 (acetylsalicylic acid)
Therapeutic range, mmol/L (mg/dL)	0.4–1.8 (5–25)
Toxic exposure, mg/kg	>150
Lethal exposure, mg/kg	>500
Half-life (therapeutic), h	2–4
Conversion factor	mg/dL \times 0.072 = mmol/L

adenosine triphosphate synthesis fails.^{10,12,14} Many organ systems are subject to injury in patients with severe salicylism. However, death is typically associated with cerebral edema resulting from entry of salicylate into the central nervous system, a process heavily influenced by systemic pH.^{10,11,15}

The early features of salicylate poisoning are nonspecific and include nausea and vomiting, although unexplained tinnitus or primary respiratory alkalosis are suggestive of the diagnosis. Other features of salicylate poisoning include volume depletion, tachycardia, acute respiratory distress syndrome, hypoglycemia (with or without hypoglycorrachia), hypoprothrombinemia, hyperthermia, acute kidney injury, and, rarely, rhabdomyolysis. In the absence of another explanation, agitation and altered mental status in the setting of salicylate toxicity are features of severe poisoning.

Salicylate poisoning is a medical emergency and is easily underestimated. Treatment should proceed with the involvement of a clinical toxicologist or regional poison center. The cornerstones of therapy include good supportive care, gastrointestinal decontamination in selected patients after acute overdose, repletion of intravascular volume, and bicarbonate administration. Bicarbonate produces alkalemia, which minimizes passage of salicylate into the central nervous system, and alkaluria, which reduces renal tubular reabsorption and thus promotes renal excretion of salicylate, particularly when urinary pH values reach 7.5 to 8.^{7,16}

Existing recommendations differ in regard to the indications for extracorporeal treatment in patients with salicylate poisoning.¹⁷⁻²² Most recommend hemodialysis in patients with altered mental status, evidence of acute respiratory distress syndrome or cerebral edema, fluid overload that precludes administration of sodium bicarbonate, or clinical deterioration despite good supportive care. High salicylate concentrations are often given as a potential indication for extracorporeal treatment; quoted thresholds include 5.8 mmol/L (81 mg/dL),¹⁸ 6.5 mmol/L (90 mg/dL),¹⁷ 7.2 mmol/L (100 mg/dL),^{19,20,22} and 9.4 mmol/L (130 mg/dL), and concentrations greater than 3.6 to 4.2 mmol/L (50

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