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;■:1-17.]

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

0196-0644/$-see front matter
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http://dx.doi.org/10.1016/j.annemergmed.2015.03.031

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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. Although other salicylates such as sodium salicylate and bismuth subsalicylate are also available, the most commonly

†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.

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 (≅0.5 L/kg) have been reported after overdose[4-6] (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 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]

Table 1. Salicylate physicochemical and toxicokinetic properties.

Physciochemical 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×0.072=mmol/L

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 hypoglycorrhachia), 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 to 60 mg/dL) are suggested to warrant extracorporeal

treatment in chronic poisoning. However, most sources acknowledge that clinical status is a more important factor than the salicylate concentration in the decision to initiate extracorporeal treatment.

MATERIALS AND METHODS

The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup is composed of international experts representing diverse specialties and professional societies (Figure 1). Its mission is to provide evidence-based recommendations on the use of extracorporeal treatment for toxin removal in poisoned patients (http://www.extrip-workgroup.org). The rationale, background, objectives, methodology, and other recommendations have been published previously.[23-32]

Predetermined methodology, incorporating guidelines from the Appraisal of Guidelines for Research and Evaluation[33] and Grades of Recommendation Assessment, Development and Evaluation,[34] is described in detail elsewhere.[25] The primary literature search was conducted on July 10, 2012, in MEDLINE, EMBASE, and the Cochrane Library (Reviews and Central).

The following search strategy was used: [(salicylate OR aspirin OR salicylic) AND (dialysis OR hemodialysis OR haemodialysis OR hemoperfusion OR haemoperfusion OR plasmapheresis OR plasma exchange OR exchange transfusion OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR extracorporeal therapy OR CRRT)].

A manual search of conference proceedings from the European Association of Poison Control Centres and Clinical Toxicologists and North American Congress of Clinical Toxicology annual meetings (from 2002 to 2012) and Google Scholar was performed, as was a review of the bibliography of each article obtained during the literature search.

Acute Dialysis Quality Initiative
American Academy of Clinical Toxicology
American College of Emergency Physicians
American College of Medical Toxicology
American Society of Nephrology
American Society of Pediatric Nephrology
Asia Pacific Association of Medical Toxicology
Association of Physicians of India
Australian and New Zealand Intensive Care Society
Australian and New Zealand Society of Nephrology
Brazilian Association of Information Centres and Toxicologic Assistance
Brazilian Society of Nephrology
Brazilian Society of Toxicology
Canadian Association of Poison Control Centres
Canadian Association of Emergency Physicians
Canadian Society of Nephrology
Chinese College of Emergency Physicians
Chinese Medical Doctor Association
European Association of Poison Centres and Clinical Toxicologists
European Renal Best Practice
European Society for Emergency Medicine
European Society of Intensive Care Medicine
French Society of Intensive Care
German Society of Nephrology
Indian Society of Critical Care Medicine
INDO-US Emergency & Trauma Collaborative
International Pediatric Nephrology Association
International Society of Nephrology
Latin American Society of Nephrology and Hypertension
National Kidney Foundation
Pediatric Continuous Renal Replacement Therapy
Pediatric Critical Care Medicine
Quebec Association of Emergency Physicians
Quebec Association of Specialists in Emergency Medicine
Quebec Society of Nephrology
Renal Association
Society of Critical Care Medicine
Spanish Clinical Toxicology Foundation

Figure 1. Societies represented in EXTRIP.

Table 2. Criteria used to define dialyzability.*

Dialyzability†	Primary Criteria, % Removed‡	Alternative Criteria, %		
		CL_{ECTR}/CL_{TOT}§	$T_{1/2\ ECTR}/T_{1/2}$	RE_{ECTR}/RE_{TOT}§
D	>30	>75	<25	>75
M	>10–30	>50–75	>25–50	>50–75
S	≥3–10	≥25–50	≥50–5	≥25–50
N	<3	<25	>75	<25

CL_{ECTR}, Extracorporeal clearance; CL_{TOT}, total clearance; $T_{1/2\ ECTR}$, half-life during ECTR; $T_{1/2}$, half-life off ECTR; RE_{ECTR}, extracorporeal removal; RE_{TOT}, total removal; *D*, dialyzable; *M*, moderately dialyzable; *S*, slightly dialyzable; *N*, not dialyzable.

*These criteria should be applied only if measured or calculated (not reported) endogenous half-life is greater than 4 hours (otherwise, ECTR is considered not clinically relevant). Furthermore, the primary criterion is preferred for poisons having a large volume of distribution (>5 L/kg). Reproduced with permission from *Clinical Toxicology*. Lavergne V, Nolin TD, Hoffman RS, et al. The EXTRIP (Extracorporeal Treatments in Poisoning) Workgroup: guideline methodology. *Clin Toxicol*. 2012;50:403-413.[25]

†Applicable to all modalities of extracorporeal treatment, including hemodialysis, hemoperfusion, and hemofiltration.

‡Corresponds to percentage removal of ingested dose or total body burden in a 6-hour extracorporeal treatment period.

§Measured during the same period.

A designated subgroup of EXTRIP completed the literature search, reviewed articles, extracted data, and summarized findings. Dialyzability was determined according to criteria listed in Table 2. The potential benefit of the procedure was weighed against its cost, availability, and alternative treatments, and its related complications. The level of evidence assigned to each clinical recommendation was determined by the subgroup and the appointed epidemiologist (Figure 2). This information was submitted to the entire workgroup for consideration, along with structured voting statements based on a predetermined format. The strength of recommendations was evaluated by a 2-round modified Delphi method for each proposed voting statement (Figure 3), and the RAND/UCLA Appropriateness Method was used to quantify disagreement between voters.[35] Anonymous votes with comments were compiled by the epidemiologist and returned to each participant. The workgroup met in person to exchange ideas and debate statements. A second vote was later submitted in the summer of 2012, and these results were used in developing the core EXTRIP recommendations. The literature search was updated on October 1, 2014, following the same methodology as described above. Any new articles were summarized and the data were then submitted to all participants, who updated their votes.

RESULTS

Results of the literature search and reasons for study exclusion are presented in Figure 4. A total of 306 citations were identified. After full-text screening for eligibility criteria, 84 articles were selected for extraction of clinical or toxicokinetic data, including 1 controlled

Strength of Recommendation (Consensus Based)	Level of Evidence (Based on the GRADE System)
Level 1=strong recommendation="We recommend…" *The course of action is considered appropriate by the majority of experts, with no major dissension. The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.*	Grade A=high level of evidence *The true effect lies close to our estimate of the effect.*
Level 2=weak recommendation="We suggest…" *The course of action is considered appropriate by the majority of experts, but some degree of dissension exists among the panel. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects.*	Grade B=moderate level of evidence *The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different.*
Level 3=neutral recommendation="It would be reasonable…" *The course of action could be considered appropriate in the right context.*	Grade C=low level of evidence *The true effect may be substantially different from our estimate of the effect.*
No recommendation *No agreement was reached by the group of experts.*	Grade D=Very low level of evidence *Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect.*

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Figure 2. Strength of recommendation and level-of-evidence scale for clinical outcomes.

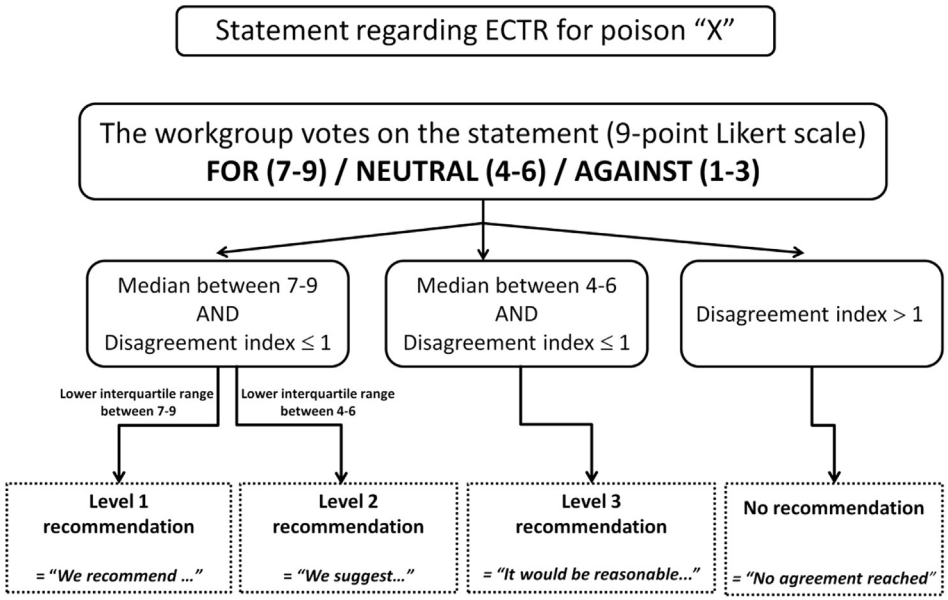

Figure 3. Delphi method (2 rounds) for each recommendation.

clinical trial,[36] 3 animal studies,[37-39] and 80 case reports or case series,[16,40-118] whereas in vitro studies were excluded.

The only controlled clinical trial of extracorporeal treatment in salicylate poisoning[36] was a very-low-quality study in which the design and risk of bias could not be reliably assessed. The study involved 13 young children with salicylate poisoning, including 10 who ingested acetylsalicylic acid and 3 who ingested methyl salicylate. All patients were treated with intravenous fluids and bicarbonate, whereas the intervention group underwent peritoneal dialysis with 5% albumin. Treatment was continued until clinical improvement was apparent and salicylate concentrations were approximately 2.2 mmol/L (30 mg/dL). No deaths were reported in either treatment arm. Treatment was shorter in patients allocated to extracorporeal treatment than standard care (7.9 versus 12.4 hours), but the clinical significance of this is uncertain. It is difficult to draw valid conclusions from this study in light of its low quality and small sample size.

The remaining evidence is composed of case reports and case series: A total of 143 patients were reported from the included studies, including 130 for whom sufficient patient-level data were available. Individual patients are presented in Table 3, whereas aggregate data are presented in Table 4. Because of their inherent limitations (lack of control group

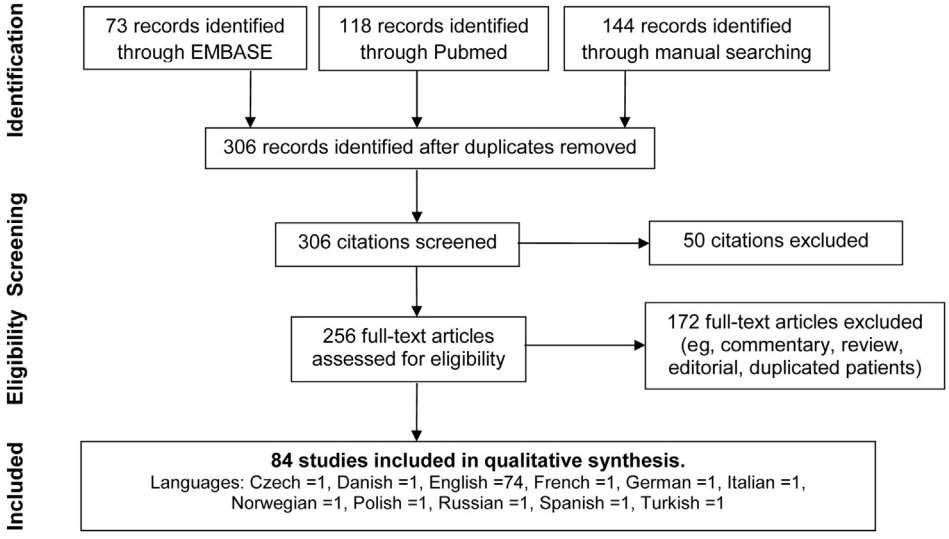

Figure 4. Study selection flow diagram (October 1, 2014).

Table 3. Individual clinical data reported after ECTR for salicylate poisoning.

Citation	Type	N	Peak [SA], mg/dL	ECTR Modality	Time From Ingestion to ECTR	Alive	Dead
Summit, 1964[36]	RCT	6	—	PD	4.5–30	6	
		7	—	None		7	
Doolan, 1951[52]	Case report	1	55	ET	—		1
Leonards, 1955[80]	Case report	1	130	HD	—	1	
Schreiner, 1955[105]	Case report	1	90	HD	—	1	
Done, 1956[51]	Case report	1	86	ET	5.5	1	
Adams, 1957[40]	Case report	1	73	ET	28	1	
Diamond, 1958[49]	Case report	1	960	ET	—	1	
			115	HD	16.5		1
Schreiner, 1958[104]	Series	3	110	HD	5.3	1	
			101	HD	7	1	
Thomsen, 1958[111]	Case report	1	52	HD	48	1	
			100	ET	23	1	
Leikin, 1959[78]	Series	3	103	ET	CHR	1	
			102	ET	>8	1	
Rentsch, 1959[101]	Series	2	79	ET	14	1	
			69	ET	9	1	
Spritz, 1959[108]	Case report	1	62	HD	>48	1	
Sterne, 1959[109]	Case report	1	35	ET	CHR	1	
			38	PD	CHR	1	
Elliott, 1969[55]	Series	3	—	PD	CHR	1	
			74	PD	>8	1	
Leikin, 1960[77]	Series	7	78–160	ET	—	6	1
Etteldorf, 1961[57]	Series	7	41–62	PD	—	7	
Magness, 1961[85]	Case report	1	99	HD	27	1	
Millar, 1961[89]	Case report	1	70	ET	>19	1	
Caseley, 1962[46]	Case report	1	70	ET	CHR	1	
Etchart, 1965[56]	Case report	1	87	PD	>19	1	
Kallen, 1966[7]	Series	13	42–100	HD	—	11	2
Schlegel, 1966[103]	Series	5	45–100	PD	12–22	4	1
Kloss, 1967[73]	Case report	1	118	PD	—	1	
Levy, 1967[82]	Case report	1	114	HD	31	1	
Fine, 1968[60]	Case report	1	89	HD	1	1	
Zachau-Christiansen, 1968[117]	Series	2	86	PD	—	1	
			53	PD	—	1	
Halle, 1969[65]	Case report	1	121	PD	5	1	
Goulding, 1976[63]	Case report	1	66	HP	—	—	
Buselmeier, 1977[44]	Case report	1	96	HD	—	1	
Gelfand, 1977[62]	Series	2	58	HP	—	1	
			70	HP	—	1	
Koffler, 1978[75]	Case report	1	93	HP	—	1	
Sieniawska, 1978[106]	Case report	1	180	PD	—	1	
Knutsen, 1979[74]	Case report	1	137	HP	>2.5	—	1
Hampel, 1980[66]	Series	2	100	HP	—	1	
			68	HP	—	1	
Fantozzi, 1981[58]	Case report	1	48	HP	—	1	
Snodgrass, 1981[107]	Series	2	168	PD	CHR		1
			77	HD	CHR	1	
Todd, 1981[112]	Case report	1	58	PD	—	1	
Zimmerman, 1981[118]	Case report	1	97	HD	—	1	
Wanscher, 1986[114]	Case report	1	87	HD	4	1	
Montagnac, 1987[91]	Case report	1	150	HD	17	1	
Jacobsen, 1988[68]	Series	2	123	HP	6	1	
			95	HD	13	1	
Jimramovsky, 1988[69]	Case report	1	144	ET	—	1	
Kleinman, 1988[72]	Case report	1	81	HD	CHR	1	
Dmitriev, 1990[50]	Case report	1	—	HP	—	1	
Raschke, 1991[99]	Case report	1	44	HD	CHR	1	
Pec, 1992[96]	Case report	1	83	HD	19	1	
Lemesh, 1993[79]	Case report	1	82	HD	—	1	
Nawata, 1994[93]	Case report	1	91	HD, CRRT	—	1	
Watson, 1994[115]	Case report	1	120	HD	28	1	

Table 3. Continued.

Citation	Type	N	Peak [SA], mg/dL	ECTR Modality	Time From Ingestion to ECTR	Alive	Dead
Karabocuoglu, 1996[70]	Case report	1	67	HD	24	1	
Higgins, 1998[67]	Case report	1	72	HD	7	1	
Palatnik, 1998[95]	Case report	1	62	HD		1	
Reblin, 1998[100]	Case report	1	149	HP	12	1	
Varela, 1998[113]	Case report	1	73	HD	CHR	1	
Pertoldi, 1999[97]	Case report	1	70	HD	CHR	1	
Cohen, 2000[48]	Case report	1	54	HD	—	1	
Drummond, 2001[53]	Case report	1	71	HD	≅34	1	
Wrathall, 2001[116]	Series	3	97	HD, CRRT	CHR	1	
			117	HD, CRRT	19	1	
			86	CRRT	—	1	
Chase, 2002[47]	Case report	1	83	HD, CRRT	19	1	
Manikian, 2002[86]	Case report	1	85	ET	—	1	
Lund, 2005[84]	Case report	1	110	HD	14	1	
Birnbaum, 2006[43]	Case report	1	195	HD	10	1	
Levine, 2006[81]	Case report	1	59	HD	—	1	
Satar, 2006[102]	Series	2	227	HD	—	1	
			238	HD	—	1	
Aleguas, 2007[42]	Case report	1	87	HD	1	1	
Cannon, 2007[45]	Case report	1	152	CRRT	8	1	
Marquardt, 2007[87]	Case report	1	93	HD	CHR	1	
Kent, 2008[71]	Case report	1	152	HD, CRRT	—	1	
Kostic, 2008[76]*	Series	2	55	HD	CHR	1	
			46	HD	CHR		1
O'Shura, 2008[94]	Case report	1	176	HD	—	1	
Aleguas 2009[41]	Case report	1	78	HD, CRRT	—	—	
Lu, 2009[83]	Case series	6	75	HD	—	1	
			89	HD	—	1	
			101	HD	—	1	
			45	HD	—	1	
			90	HD	—		1
			94	HD	—		1
Meehan, 2009[88]	Case report	1	91	HD	>4	1	
Quintero, 2009[98]	Case report	1	68	HD	18	1	
Thomas, 2009[110]	Case report	1	92	HD	12	1	
Dulaney, 2010[54]	Case report	1	102	HD	28	1	
Grandey, 2010[64]	Series	2	99	HD	—	1	
			123	HD	—		1
French, 2011[61]	Case report	1	45	CRRT	—		1
Minns, 2011[90]	Case report	1	92	HD	9.5		1
Muniandi, 2012[92]	Case report	1	112	HD	>4	1	
Farmer, 2013[59]	Case report	1	104	HD	9	1	

—, information unknown or unavailable.
ECTR, Extracorporeal treatment; *[SA]*, salicylate concentration; *PD*, peritoneal dialysis; *ET*, exchange transfusion; *HD*, intermittent hemodialysis; *HP*, hemoperfusion; *CHR*, chronic salicylate poisoning; *CRRT*, continuous renal replacement therapy.
*Same patient with 2 distinct poisonings.

and publication bias), reliable conclusions about clinical outcomes cannot be drawn from these reports, resulting in a very low quality of evidence for all recommendations. This is particularly true in light of variability in the amount ingested, differences in the acuity of poisoning, the interval from exposure to treatment, and the variable and uncontrolled nature of treatments used. Nevertheless, case reports occasionally note significant clinical improvement during or shortly after extracorporeal treatment.[85,89,108,111]

The review identified 14 fatalities in patients with extracorporeal treatment for salicylate poisoning, including 8 who received intermittent hemodialysis,[16,64,76,83,90,104] 1 treated with hemoperfusion,[74] 2 treated with peritoneal dialysis,[103,107] 2 treated with exchange transfusion,[52,77] and 1 with continuous venovenous hemodialfiltration.[61] In some of these reports, death occurred despite significant reductions in salicylate concentrations with extracorporeal treatment.[16,104] In most cases, death appeared to result from salicylate toxicity; in at least 1 case, however, extracorporeal treatment may have contributed to the outcome. Snodgrass et al[107] described the case of an 18-month-old with a peak salicylate concentration of

Table 4. Aggregate clinical data related to the 130 reported patients who received extracorporeal treatment for salicylate toxicity.*

Clinical Data	Result
Demographics	
Median age, y	14.5 (range 0.1–88)
Male, %	52
Poisoning exposure	
Acute exposure, %	77
Form	
Oral salicylate, %	86
Oral methyl salicylate, %	11
Rectal salicylate, %	1
Topical salicylate, %	2
Median salicylate exposure, g	28 (range 0.8–230)
Median exposure/body weight, mg/kg	798 (range 182–6,614)
Median peak salicylate concentration, mg/dL	86 (range 35–238)
Median delay between acute exposure and admission, h	9.8 (0.4–72)
Toxic manifestations†	
Altered consciousness, %	62
Seizure (≥1), %	11
Vomiting, %	22
Hyperthermia, %	43
Hypotension, %	15
Pulmonary edema, %	5
Median lowest arterial bicarbonate, mmol/L	12.9 (range 3.5–29)
Median arterial PCO_2, mm Hg	21 (9.6–71)
Median initial serum potassium, mmol/L	3.9 (range 2.1–7.2)
Acute kidney injury, %	15
Other treatments administered	
Gastric lavage, %	18
Activated charcoal, %	14
Intravenous bicarbonate, %	49
Mechanical ventilation, %	19
Vasopressors, %	10
Extracorporeal treatments	
Median time from admission to ECTR initiation, h	4.0 (range 0.5–150)
Hemodialysis, %	50
Hemoperfusion, %	9
Continuous renal replacement therapy, %	2
Peritoneal dialysis, %	18
Intermittent hemofiltration-hemoperfusion, %	1
Exchange transfusion, %	15
More than 1 ECTR, %	5
Outcome	
Death, %	11
Permanent sequelae, %	1

*These include only cases in which patient-level data could be extracted (patients from the controlled trial by Summit and Etteldorf[36] were not included).
†These data were often underreported in case reports, so the real incidence is likely higher.

12.2 mmol/L (168.4 mg/dL) who showed clinical improvement after peritoneal dialysis but deteriorated and died of peritonitis on the fourth hospital day. It is not otherwise possible to draw meaningful inferences from these reports, which represent only a small proportion of salicylate-related fatalities and offer little insight into the incidence of complications associated with extracorporeal treatment.

A systematic review of complications associated with various extracorporeal removal techniques for poisoning has not yet been published, to our knowledge. In the studies reviewed for this article, adverse effects of the procedures used were inconsistently reported, although many are expected complications related to the procedure used, including hypotension during hemodialysis,[16,41,107,118] bleeding from the catheter site,[16,114] peritoneal dialysis–associated peritonitis,[107] transfusion reaction during exchange transfusion,[77] and moderate thrombocytopenia during hemoperfusion sometimes related to bleeding (hemoperfusion).[62,66,75]

Multiple studies describe the use of various extracorporeal treatment modalities for the treatment of salicylate poisoning in animals. Hemoperfusion markedly decreases salicylate concentrations in rats.[119] In a canine model, peritoneal dialysis removed between 5.4% and 14% of intravenously administered sodium salicylate, whereas exchange transfusion removed approximately 20% and hemodialysis approximately 50%.[39] In another report, hemoperfusion removed 41% of orally administered acetylsalicylic acid (500 mg/kg).[120] In salicylate-poisoned dogs, approximately half of the administered dose was removed by dialysis during a 4-hour period compared with 17% recovered in the urine of control animals.[37]

Several human case reports and case series also demonstrate efficient removal of salicylate by both hemodialysis[16,52,68,85] and hemoperfusion (Table 5).[58,66,68] Where documented, the extent of removal is typically on the order of 50% to 60% of the ingested dose, although it is considerably lower with peritoneal dialysis compared with hemoperfusion or hemodialysis.[44,56,73,117] For example, in one report, only approximately 5% of the reported amount of acetylsalicylic acid ingested was recovered in dialysate after 16 hours of peritoneal dialysis.[56] Although a few case reports describe continuous extracorporeal treatment in patients with salicylate toxicity,[47,61,116] the clearance of salicylate by these methods (7.5 mL/min) is several-fold inferior to hemodialysis or hemoperfusion.[61] Several reports describe the use of exchange transfusion in very young children with salicylate poisoning.[40,46,51,77,78,86,89] In these, the amount of salicylate removed typically represented 20% to 25% of the estimated dose that was reportedly ingested, and salicylate concentrations decreased by approximately 50% of values obtained before exchange. The rationale for exchange transfusion rests in the very low volume of distribution of salicylate.

Table 5. Toxicokinetic results and grading in humans.

Article	ECTR	Exposure, Grams	Peak [SA], mg/dL	Amount Removed by ECTR (Approximate %, Where Applicable)	Apparent Half-life, Hours	ECTR Clearance, mL/min	Kidney Clearance, mL/min	Dialyzability Grading
Doolan, 1951[52]	HD	42	55	1,300 mg in 60 min (3.1)	—	39	—	MD
	HD (volunteer, ESRD)	3.1	11	1,000 mg in 180 min (32.6)	—	64	—	D
	HD (volunteer, ESRD)	3.1	13	1,326 mg in 180 min (43.2)	—	76	—	D
Leonard, 1955[80]	HD	—	130	9,500 mg in 360 min	—	32	1.9	D
Schreiner, 1955[105]	HD	210	90	9,400 mg in 450 min (3.9)	4.1 h during HD	43	—	MD
Done, 1956[51]	ET (1.4 L total)	28	86	542 mg in 214 min (1.9)	—	3.8	1.8	SD
Adams, 1957[40]	ET (1 volume)	7	73	—	7.2 h during HD vs 24 h post-HD	—	D	D
Schreiner, 1958[104]	HD	42	110	3,500 mg in 180 min (8.3)	1.6 h during HD	25.9	—	MD
Leikin, 1959[78]	ET	5.8 (during 3 days)	103	752 mg (13.0)	—	5.1	—	MD
		7.3	150	1,940 mg (26.6)	—	9.8	—	D
Spritz, 1959[108]	HD	—	62	2,000 mg in 300 min	3.4 h during HD	23.8	—	D
Leikin, 1960[77] (3 of 7 patients are duplicates from Leikin, 1959[78]; the other 4 are shown here)	ET double volume	12.8	104	—	—	—	—	—
	ET double volume	>5	140	1,676 mg	—	9.4	—	D
	ET double volume	>8	160	1,826 mg	—	8.9	—	D
Etteldorf, 1961[57]	Albumin PD	—	41	310 mg in 360 min	9.1 h during PD	5.0	0.6	D
	Albumin PD	—	62	771 mg in 420 min	11.5 h during PD*	7.3	0.8	D
	Albumin PD	—	51	602 mg in 660 min	9.5 h during PD*	3.6	0.7	MD
	Albumin PD	—	45	441 mg in 570 min	11 h during PD*	3.0	0.6	MD
	Albumin PD	—	40	393 mg in 360 min	8.9 h during PD*	7.7	0.9	D
	Albumin PD	—	52	1,085 mg in 600 min	10.9 h during PD*	7.7	1.6	D
	Albumin PD	—	42	419 mg in 360 min	7.6 h during PD*	4.8	1.0	MD
Magness, 1961[85]	HD	32.5	99	3,200 mg in 120 min (9.8)	3.8 h on HD*	37.6	—	D
Millar, 1961[89]	ET double volume	21	70	852 mg in 180 min (4.1)	3.3 h during ET*	8.9	—	SD
Caseley, 1962[46]	ET	9 during 4 days	70	—	5.8 h during ET vs 22 h post-ET	—	—	M
Etchart, 1965[56]	PD	65	87	3,000 mg in 960 min (4.6)	—	5.6	4.7	ND
Fine, 1968[60]	HD	5.6	89	—	7.3 h during HD vs 14.9 h post-HD	—	—	S
Fantozzi, 1981[58]	HP	—	48	4,677 mg in 180 min	4.4 h during HP	100	—	D
Jacobsen, 1988[68]	HD	—	123	9,000 mg in 190 min	5.9 h during HD vs 1.9 h during HD	86	2	D
	HP	60–70	95	16,900 mg in 300 min (24.4 to 28.2)	6.2 h during HP	81	25	D

Table 5. Continued.

Article	ECTR	Exposure, Grams	Peak [SA], mg/dL	Amount Removed by ECTR (Approximate %, Where Applicable)	Apparent Half-life, Hours	ECTR Clearance, mL/min	Kidney Clearance, mL/min	Dialyzability Grading
Pec, 1992[96]	HD	–	83	–	7.5 h during HD vs 13.6 post-HD	–	–	D
Watson, 1994[115]	HD	227.5	120	–	26.6 h pre-HD vs 1.3 h during HD*	–	–	D
Reblin 1998[100]	CRRT	50	149	7,312.5 mg in 600 min (14.6)	8 h during CRRT	5.5	–	SD
Manikian, 2002[86]	ET double volume	–	85	–	35 h pre-ET vs 8.2 h during ET vs 12.5 h post-ET	–	–	SD
Lund, 2005[84]	HD, SLED	32.5	110	–	6.2 h during HD vs 7.4 h during SLED vs 12.3 h post-ECTR	–	1.7	M for HD, SD for SLED
Kent, 2008[71]	HD-CRRT	–	152	–	2 h during HD-CRRT vs 16 h post-HD-CRRT	–	–	D

–, unknown.
SLED, sustained low-efficiency dialysis; *HD-CRRT*, hemodialysis with continuous renal replacement therapy; *PD*, peritoneal dialysis.
*Based on 2 points only (all data available).

Table 6. Summary of kinetic outcomes for salicylate poisoning (n=35).*

TK/PK Grading	PD, n	HP, n	HD, n	CRRT, n	ET, n	SLED, n	HD-CRRT, n
D: Dialyzable	4	2	8	0	4	0	1
M: moderately dialyzable	3	0	4	0	2	0	0
S: Slightly dialyzable	0	0	1	1	3	1	0
N: not dialyzable	1	0	0	0	0	0	0

TK, Toxicokinetic; *PK*, pharmacokinetic.
*Some patients received more than 1 ECTR and so their data can appear at more than 1 place.

In accordance with the individual pharmacokinetic and toxicokinetic grading (Table 6), the group agreed that salicylates are dialyzable by the most efficient extracorporeal treatment techniques (level of evidence B). Many of these reports describe older extracorporeal treatment technologies, and removal is likely to be considerably greater with present-day techniques that use more efficient filters (ie, with higher surface area) and higher blood flow rates.

One study suggested that urinary alkalinization and hemodialysis were equally effective at removing salicylate.[67] However, because the investigators quantified neither removal nor clearance, the 2 interventions could not be directly compared. In a pediatric series in which salicylate removal was quantified, peritoneal dialysis (a low-efficiency technique) was comparable to urinary alkalinization.[36] In another report, high-efficiency extracorporeal treatment provided at least 3 times the clearance generated by intravenous alkalinization when studied in the same patient.[68]

Figure 5 summaries our recommendations.

Extracorporeal treatment is recommended in severe salicylate poisoning (1D). The rationale is that, with the exception of urinary alkalinization, extracorporeal treatment is the only intervention that convincingly and rapidly reduces the burden of circulating salicylate. It does so efficiently (extracorporeal treatment clearance can surpass 100 mL/min[68]) and also allows correction of acidemia, which will lessen the delivery of salicylate to the brain. In some instances, the availability of alternative means of enhanced elimination (such as multiple-dose activated charcoal and urinary alkalization) may erroneously lead clinicians to delay implementation of extracorporeal treatment.[121] Considering the relatively low cost and infrequent complications of extracorporeal treatment, the significant morbidity and mortality associated with severe salicylate poisoning, and the lack of an antidote or other definitive therapies, the group concluded that there was sufficient justification to use

GENERAL RECOMMENDATION

ECTR is recommended in severe salicylate poisoning (1D).

INDICATIONS FOR ECTR

ECTR is recommended if any of the following are met:

- If [salicylate] >7.2 mmol/L (100 mg/dL) (1D)
- If [salicylate] >6.5 mmol/L (90 mg/dL) in the presence of impaired kidney function (1D)
- In the presence of altered mental status (1D)
- In the presence of new hypoxemia requiring supplemental oxygen (1D)

If standard therapy (supportive measures, bicarbonate, etc) fails (1D), ECTR is suggested if any of the following are met:

- If [salicylate] >6.5 mmol/L (90 mg/dL) (2D)
- If [salicylate] >5.8 mmol/L (80 mg/dL) in the presence of impaired kidney function (2D)
- If the systemic pH is ≤7.20 (2D)

ECTR CESSATION

ECTR cessation is indicated if

- Clinical improvement is apparent (1D) *and*
- [salicylate] <1.4 mmol/L (19 mg/dL) (1D) *or* ECTR has been performed for a period of at least 4–6 h when salicylate concentrations are not readily available (2D)

CHOICE OF ECTR MODALITY

- Intermittent HD is the preferred modality in patients with salicylate poisoning (1D)
- The following are acceptable alternatives if HD is not available:
  - Intermittent HP (1D)
  - CRRT (3D)
  - Exchange transfusion in neonates (1D)
- **Miscellaneous: It is recommended to continue intravenous bicarbonate therapy between ECTR sessions (1D)**

Figure 5. Summary of recommendations.

extracorporeal treatment in patients with severe salicylate poisoning. Despite the paucity of convincing data about the effect of extracorporeal treatment on clinical outcomes and the impracticability of a controlled clinical trial, this conclusion was unanimously supported by all 28 participants. However, the group also acknowledged that salicylate removal is a surrogate measure; the challenge rests in identifying patients with salicylate toxicity for whom extracorporeal treatment is likely to favorably influence the more meaningful outcomes of morbidity and mortality. The available literature does not confidently identify these patients. Extracorporeal treatment affords several advantages over urinary alkalinization, including more rapid clearance of salicylate and more predictable correction of acidemia.

Salicylate poisoning is a medical emergency and patients may die with or without receiving extracorporeal treatment.[121,122] However, when a decision is made to proceed with extracorporeal treatment, it should be implemented promptly because this will give the best chances of survival. This is particularly important for patients with acute salicylate poisoning, who often appear relatively well in the hours shortly after overdose despite substantially elevated salicylate concentrations. Prompt implementation of extracorporeal treatment in these patients may limit the entry of salicylate into the central nervous system, from where it is less rapidly cleared.

Extracorporeal treatment is recommended if the salicylate concentration is greater than 7.2 mmol/L (100 mg/dL) after acute salicylate poisoning (1D).

Extracorporeal treatment is suggested if the acetylsalicylic acid concentration is greater than 6.5 mmol/L (90 mg/dL) (2D).

The rationale is as follows: Unlike patients with chronic salicylate poisoning, those with acute poisoning may have elevated salicylate concentrations despite few other signs or symptoms, particularly in the early period after ingestion. Existing data do not identify a salicylate concentration threshold predictive of a poor outcome. Although its interpretations were contested,[123] the study by Done[124] reported a significantly higher median salicylate concentration in patients who died than in those who did not (7.3 mmol/L [100 mg/dL] versus 4.3 mmol/L [60 mg/dL]). Other studies observed no statistical difference in peak salicylate concentrations between fatal (6.5 mmol/L [90 mg/dL]) and nonfatal cases (6 mmol/L [83 mg/dL]).[125] A review of all salicylate-related fatalities in the United States during a 17-year period found that the mean salicylate concentration was 6.9 mmol/L (96 mg/dL) but

was lower in patients older than 50 years.[126] Other investigators observed that in approximately one quarter of deaths the patients had a salicylate concentration below 5.8 mmol/L (80 mg/dL), but the timing of this concentration is unclear.[127] Finally, yet another abstract suggested that salicylate concentration was predictive of hemodialysis requirement.[128] The workgroup noted that the interpretation of salicylate concentrations without an understanding of the delay postingestion and concomitant acid-base status of the patient may bias these conclusions because pH modulates salicylate partitioning into the brain. Despite the controversy, the workgroup suggested that extracorporeal treatment be administered regardless of clinical status in any patient with a salicylate concentration greater than 6.5 mmol/L (90 mg/dL). This was unanimously recommended when the concentration was greater than 7.2 mmol/L (100 mg/dL). Over this threshold, the likelihood of a fatal outcome was considered significant.[122]

In patients with very elevated salicylate concentrations, the workgroup advocates extracorporeal treatment even in the absence of clinical signs and symptoms because subsequent deterioration is common, because salicylate concentrations may increase unpredictably as the result of ongoing gastrointestinal absorption, and because removal from the vascular compartment before distribution into the central nervous system is likely to be an important determinant of a patient's subsequent course.

Extracorporeal treatment is recommended if: acetylsalicylic acid concentration is greater than 6.5 mmol/L (90 mg/dL) in patients with impaired kidney function (1D).

Extracorporeal treatment is suggested if acetylsalicylic acid concentration is greater than 5.8 mmol/L (80 mg/dL) in patients with impaired kidney function (2D).

The rationale is the following: The EXTRIP nephrology subcommittee proposed a general definition of impaired kidney function relevant to toxin clearance, including any of the following:

1) Advanced stage 3b, 4, or 5 chronic kidney disease (ie, estimated glomerular filtration rate, (eGFR) <45 mL/min per 1.73 m^2)
2) Stage 2 or 3 acute kidney injury from the Kidney Disease Improving Global Outcomes classification
3) In the absence of a baseline serum creatinine concentration, 176 μmol/L (2 mg/dL) in adults or 132 μmol/L (1.5 mg/dL) in the elderly or patients with low muscle mass
4) In children with no baseline creatinine concentration, a serum creatinine greater than twice the upper limit of normal for age and sex
5) The presence of oligo/anuria for more than 6 hours, regardless of serum creatinine concentration

The workgroup advocates a lower threshold for the implementation of extracorporeal treatment in patients with impaired kidney function because the kidney is the primary route of elimination for salicylate and its metabolites. A recommendation was set at 6.5 mmol/L (90 mg/dL) and a suggestion is made for 5.8 mmol/L (80 mg/dL). All other factors being equal, decreased salicylate clearance is likely to be associated with worse clinical outcomes. In formulating this recommendation, the workgroup acknowledged that these factors would influence clinical decisions on a case-by-case basis.

Extracorporeal treatment is suggested if the blood pH is less than or equal to 7.20 (2D). The rationale is as follows: The work group acknowledged that even mild acidemia is of concern in patients with salicylate poisoning, regardless of whether the primary disorder is metabolic (reflecting the metabolic effects of salicylate) or respiratory (the converse of the expected respiratory response to salicylate poisoning, reflecting respiratory fatigue, coingestion of a respiratory depressant, or the development of acute respiratory distress syndrome). In the setting of salicylate poisoning, acidemia not only reflects serious organ dysfunction but also favors the formation of nonionized salicylic acid, which crosses readily into the central nervous system. In its discussions, the group recognized that dialysis based on pH alone would apply primarily to patients with acute salicylate poisoning and high anion gap metabolic acidosis because patients with chronic salicylate poisoning who are acidemic would invariably meet other criteria. The target pH chosen by the workgroup (pH $\leq$7.2) is one associated with poor outcomes in salicylate poisoning.[125] The group also acknowledged that most patients with this degree of acidemia would most likely have other indications for extracorporeal treatment.

Extracorporeal treatment is recommended in the presence of altered mental status (1D).

The rationale is as follows: In patients with salicylate poisoning, altered mental status reflects end-organ toxicity and is a sign of serious toxicity. Even subtle cognitive abnormalities or agitation can reflect accumulation of salicylate into the central nervous system and may be a harbinger of profound toxicity and death. Removal of salicylate by extracorporeal treatment is expected to reduce the burden of salicylate in the central nervous system and may prevent the development of cerebral edema, a common finding at autopsy. Coingestants and other comorbidities can influence mental status and obfuscate the contribution of salicylate, and it is important to consider all factors when implementing extracorporeal treatment solely on the basis of altered mental status.

Extracorporeal treatment is recommended in the presence of new hypoxemia requiring supplemental oxygen (1D).

The rationale is as follows: The acute respiratory distress syndrome (ARDS) (formerly known as acute lung injury) is a well-described manifestation of end-organ toxicity of salicylates and as such is indicative of severe poisoning. Although ARDS can develop after acute overdose, it occurs most commonly in patients with chronic salicylate poisoning.[19] In addition, the development of ARDS complicates other elements of supportive care (such as the administration of crystalloid and bicarbonate), and the associated respiratory fatigue can interfere with the protective hyperventilation of salicylate poisoning. As noted earlier, salicylate poisoning is generally accompanied by tachypnea, hyperpnea, and hyperventilation, and these findings in isolation are not necessarily reflective of acute respiratory distress syndrome. Consequently, the workgroup agreed that in this context the development of new hypoxemia requiring supplemental oxygen (with or without parenchymal infiltrates) be considered presumptive evidence of salicylate-induced ARDS and an independent indication for extracorporeal treatment. Our recommendation is supported by the observation that hypoxemia predicts a poor outcome; in one study, the mean PaO_2 was 99 mm Hg in survivors and 80 mm Hg in fatalities.[125]

Extracorporeal treatment is recommended if standard therapy (supportive measures, bicarbonate, etc) fails (1D).

The rationale is as follows: Although many patients with salicylate poisoning can be managed with supportive care and urinary alkalinization, in more severe cases these interventions alone often fail. The consensus opinion of the workgroup was that extracorporeal treatment should be implemented in the event that supportive care is deemed to be failing. Given the complexity of salicylate poisoning, the determination that supportive care is failing can be a difficult one to establish but might include a rapidly increasing salicylate concentration despite gastrointestinal decontamination and urinary alkalinization. Timely involvement of a clinical toxicologist is advisable in all cases.

It is suggested not to perform extracorporeal treatment on the basis of acetylsalicylic acid ingestion history alone (2D).

The rationale is as follows: The workgroup recognized that in patients with acute salicylate poisoning, the manifestations of toxicity (and, by extension, the appropriateness of extracorporeal treatment) would increase with the reported amount ingested. However, the workgroup agreed that in light of uncertainty surrounding the ingested dose,[129] the availability of salicylate assays in most institutions, and the many other factors that influence severity and prognosis of individual poisoning cases, a dose threshold alone is insufficient justification for extracorporeal treatment. Moreover, patients with very large ingestions are likely to meet at least 1 other criterion for the initiation of extracorporeal treatment, and prompt communication and possible transfer to a center that provides extracorporeal treatment is advisable for such patients, even in the absence of an existing indication for extracorporeal treatment.

Extracorporeal treatment cessation is indicated when clinical improvement is apparent (1D) *and* a salicylate concentration is less than 1.4 mmol/L (19 mg/dL) (1D) *or* extracorporeal treatment has been performed for a period of at least 4 to 6 hours when salicylate concentrations are not readily available (2D).

The rationale is as follows: The workgroup recognized the challenges associated with defining meaningful clinical improvement and with the interpretation of salicylate concentrations in isolation. Clinical improvement is typically characterized by normalization of mental status, resolution of hyperventilation and reduced oxygen requirements, and correction of acid-base abnormalities; these changes are generally (but not always) accompanied by a decline in salicylate concentrations. The possibility of a rebound in salicylate concentrations, either from ongoing absorption or redistribution from the intracellular compartment, was noted in several reports. For this reason, although the workgroup acknowledged that toxicity would be reduced when the salicylate concentration decreased to 2.2 mmol/L (30 mg/dL), a lower threshold was preferred (<1.4 mmol/L [19 mg/dL]). This would offer some security in light of the potential for rebound. Alternatively, if salicylate concentrations were not readily available, the workgroup concluded that at least 4 to 6 hours of high-efficiency extracorporeal treatment would be empirically reasonable. This is based on the assumption that with high-efficiency extracorporeal treatments and optimal operational parameters,[130] a salicylate half-life of 2 hours will be achieved during extracorporeal treatment.[71,115] As mentioned, the possibility of rebound warrants close monitoring of the patient's clinical status and salicylate concentration. Therefore, it is generally advisable to leave the dialysis catheter in place until it is clear that the patient will not require a subsequent treatment.

For choice of extracorporeal treatment, intermittent hemodialysis is the preferred modality of extracorporeal treatment (1D); hemoperfusion (1D) and continuous renal replacement techniques (3D) are acceptable alternatives if hemodialysis is not available.

Exchange transfusion is an acceptable alternative to hemodialysis in neonates (1D).

The rationale is as follows: Hemodialysis rapidly enhances salicylate clearance, corrects acidemia, and is widely available, easily implemented in most settings, and associated with a favorable risk profile. In contrast, hemoperfusion is encumbered by the low availability of charcoal cartridges,[131,132] the need to replace them during treatment, and the potential for thrombocytopenia, which is typically mild but may be of greater significance in patients who have received anticoagulation or whose platelet function is impaired by acetylsalicylic acid. Continuous renal replacement techniques provide lower salicylate dialysance than hemodialysis and should be implemented only if intermittent modalities are not available. The workgroup favored hemodialysis over continuous renal replacement techniques, even in the context of hypotension. The theoretical advantage of continuous renal replacement techniques with hypotension is unproven in situations in which net ultrafiltration (eg, fluid removal) is not required, such as in most cases of poisoning. The workgroup prefers the more efficient intermittent techniques even in the presence of hypotension. The available evidence about exchange transfusions is limited, but this remains a practical consideration in neonates because the technique is used in neonatal and pediatric critical care units and is technically easier to perform. There are no justifications for therapeutic plasma exchange, peritoneal dialysis, or liver support therapies in acetylsalicylic acid poisoning.

The composition of the dialysis bath should account for the metabolic abnormalities typical of salicylate-poisoned patients, which differ from those of patients with end-stage kidney disease. In particular, the bicarbonate and potassium dialysate concentration need to be tailored to the patient's requirement. Phosphate can also be added to the bath,[133] if required, and the need for heparinization and ultrafiltration should be carefully considered according to clinical parameters.

It is recommended to continue intravenous bicarbonate therapy between extracorporeal treatment sessions (1D). The rationale is as follows: Administration of intravenous bicarbonate is relatively safe and promotes alkalemia (if not already present) and alkaluria. The former minimizes entry of salicylate into the central nervous system,[11] whereas the latter reduces renal tubular reabsorption and significantly increases renal excretion of salicylate when urine pH exceeds 7.5 or 8.[16] For these reasons, intravenous bicarbonate is recommended between extracorporeal treatment sessions. Although, extracorporeal treatment enhances salicylate clearance and achieves alkalemia far more efficiently than bicarbonate, no agreement was reached about the ongoing administration of bicarbonate during extracorporeal treatment.

Salicylates are capable of causing serious toxicity. The workgroup agreed that salicylates are dialyzable by high-efficiency extracorporeal treatments and unanimously recommended extracorporeal treatments in severe poisoning despite the absence of high-quality evidence. Indications for extracorporeal treatment include changes in mental status, new-onset hypoxemia, failure of supportive therapy, and very elevated salicylate concentrations regardless of clinical status. Emergency physicians should recognize these indications promptly and rapidly contact a dialysis unit for patients with significant salicylate poisoning.

The authors acknowledge the tremendous work of our dedicated translators: Marcela Covica, Alexandra Angulo, Ania Gresziak, Samantha Challinor, Monique Cormier, Martine Blanchet, Gunel Alpman, Joshua Pepper, Lee Anderson, Andreas Betz, Tetsuya Yamada, Nathalie Eeckhout, Matthew Fisher, Ruth Morton, Denise Gemmellaro, Nadia Bracq, Olga Bogatova, Sana Ahmed, Christiane Frasca, Katalin Fenyvesi, Timothy Durgin, Helen Johnson, Martha Oswald, Ewa Brodziuk, David Young, Akiko Burns, Anna Lautzenheiser, Banumathy Sridharan, Charlotte Robert, Liliana Ionescu, Lucile Mckay, Vilma Etchart, Valentina Bartoli, Nathan Weatherdon, Marcia Neff, Margit Tischler, Sarah Michel, Simona Vairo, Mairi Arbuckle, Luc Ranger, Nerissa Lowe, Angelina White, Salih Topal, John Hartmann, Karine Mardini, Mahala Bartle Mathiassen, Anant Vipat, Gregory Shapiro, Hannele Marttila, and Kapka Lazorova; and the important contribution from our librarians and secretarial aides: Marc Lamarre, David Soteros, Salih Topal, Henry Gaston, and Brenda Gallant.

Supervising editor: Matthew D. Sztajnkrycer, MD, PhD

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Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist and provided the following details: Funding for EXTRIP was obtained from industry in the form of unrestricted educational grants. These funds were used solely for expenses related to literature retrieval and translation of publications, and for reimbursement of conference calls and travel expenses for attendance at EXTRIP meetings. A list of EXTRIP sponsors can be found at http://www.extrip-workgroup.org.

Publication dates: Received for publication December 21, 2014. Revision received March 9, 2015. Accepted for publication March 25, 2015.

There was no industry input into meeting organization, scientific content, development, or publication of the recommendations. Furthermore, industry presence at meetings was not allowed, nor was industry awareness or comment on the recommendations sought or accepted.

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APPENDIX

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