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CRITICAL CARE

Extracorporeal treatment for acetaminophen poisoning: Recommendations from the EXTRIP workgroup

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Background. The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup was created to provide evidence-based recommendations on the use of extracorporeal treatments (ECTR) in poisoning and the results are presented here for acetaminophen (APAP). *Methods.* After a systematic review of the literature, a subgroup selected and reviewed the articles and summarized clinical and toxicokinetic data in order to propose structured voting statements following a pre-determined format. A two-round modified Delphi method was chosen to reach a consensus on voting statements, and the RAND/UCLA Appropriateness Method was used to quantify disagreement. Following discussion, a second vote determined the final recommendations. *Results.* Twenty-four articles (1 randomized controlled trial, 1 observational study, 2 pharmacokinetic studies, and 20 case reports or case series) were identified, yielding an overall very low quality of evidence for all recommendations. Clinical data on 135 patients and toxicokinetic data on 54 patients were analyzed. Twenty-three fatalities were reviewed. The workgroup agreed that N-acetylcysteine (NAC) is the mainstay of treatment, and that ECTR is not warranted in most cases of APAP poisoning. However, given that APAP is dialyzable, the workgroup agreed that ECTR is suggested in patients with excessively large overdoses who display features of mitochondrial dysfunction. This is reflected by early development of altered mental status and severe metabolic acidosis prior to the onset of hepatic failure. Specific recommendations for ECTR include an APAP concentration over 1000 mg/L if NAC is not administered (1D), signs of mitochondrial dysfunction and an APAP concentration over 700 mg/L (4630 mmol/L) if NAC is not administered (1D) and signs of mitochondrial dysfunction and an APAP concentration over 900 mg/L (5960 mmol/L) if NAC is administered (1D). Intermittent hemodialysis (HD) is the preferred ECTR modality in APAP poisoning (1D). *Conclusion.* APAP is amenable to extracorporeal removal. Due to the efficacy of NAC, ECTR is reserved for rare situations when the efficacy of NAC has not been definitively demonstrated.

Keywords Acetaminophen; Extracorporeal; Dialysis; Guidelines

Introduction

The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Table 1). Its mission is to provide evidence-based recommendations on the use of extracorporeal treatments (ECTR) for toxin removal in poisoning (www.extrip-workgroup.org). The rationale, background, objectives, complete methodology and other recommendations have been published.[1–4] This article presents the summary of a systematic review of the literature, data extraction, and voting results for the use ECTR in APAP poisoning.

With billions of doses taken annually, APAP is the most common analgesic used worldwide since it was introduced in 1955.[5] It is consistently one of the most commonly used medications in overdose, and the leading cause of drug-induced liver failure in the US, UK, and several other countries.[6–8] According to the 30th Annual Report of the American Association of Poison Control Centers' National Poison Data System, about one-fifth (18.9%) of single-substance fatal exposures in 2012 could be attributed to

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Table 1. Represented societies.

American Academy of Clinical Toxicology	European Renal Best Practice
American College of Emergency Physicians	European Society of Emergency Medicine
American College of Medical Toxicology	European Society of Intensive Care Medicine
American Society of Nephrology	French Language Society of Resuscitation
American Society of Pediatric Nephrology	German Society of Nephrology
Asia Pacific Association of Medical Toxicology	International Pediatric Nephrology Association
Australian and New Zealand Intensive Care Society	International Society of Nephrology
Australian and New Zealand Society of Nephrology	Latin American Society of Nephrology and Hypertension
Brazilian Association of Information Centres and Toxicologic Assistance	National Kidney Foundation
Brazilian Society of Nephrology	Pediatric Continuous Renal Replacement Therapy
Brazilian Society of Toxicology	Pediatric Critical Care Medicine
Canadian Association of Poison Control Centres	Quebec Association of Emergency Physicians
Canadian Association of Emergency Physicians	Quebec Association of Specialists in Emergency Medicine
Canadian Society of Nephrology	Quebec Society of Nephrology
Chinese College of Emergency Physicians	Renal Association
Chinese Medical Doctor Association	Society of Critical Care Medicine
European Association of Poison Centres and Clinical Toxicologists	Spanish Clinical Toxicology Foundation

APAP-containing drugs. Despite the availability of a well-known and highly efficacious antidote, N-acetylcysteine (NAC), patients with single acute ingestions still occasionally die even when they are treated within 8 h of ingestion.[9,10] These rare fatalities are usually the result of massive ingestions. Massive ingestions present rapidly with signs of mitochondrial dysfunction (metabolic acidosis and altered mental status) prior to the onset of severe liver injury and likely succumb either because the ingested dose overwhelms the protective effect of NAC, or NAC is unable to completely reverse the mitochondrial injury.[11] The remaining majority of fatalities usually result from delayed hospital presentation or other delays to initiating NAC therapy.

The current intravenous NAC dosing regimen that consists of a bolus of 150 mg/kg followed by 50 mg/kg over 4 h and 100 mg/kg over 16 h has been evaluated in large prospective studies.[12,13] This particular dosage was based on calculations aiming to provide protection from APAP toxicity during a decrease in five half-lives of no more than 4 h duration each (hence, 20 h) as well as predictions of how much toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), would be formed and the supplemental glutathione required to detoxify NAPQI. Initially, the discoverers of NAC therapy for APAP overdose wanted to incorporate the APAP concentration height into a decision on the duration of treatment but they were unable to do so.[14] Thus, it is possible that at very high APAP concentrations, insufficient NAC dosing explains some cases of apparent NAC failure.[9,10,15–18] Other treatment options have been explored, including ECTR. However, no randomized controlled trials of ECTR in APAP poisoning have been performed since the advent of NAC, and case reports suggest mixed results. We therefore sought to evaluate the evidence for the use of ECTR in APAP poisoning recognizing that the current antidote was not universally protective.

Pharmacology

APAP exerts its analgesic and antipyretic actions via indirect inhibition of cyclooxygenase (COX isoforms, mainly COX-2), thereby inhibiting central prostaglandin E2 synthesis.[19] After ingestion of a therapeutic dose, 60–95% of APAP is absorbed from the intestine. Absorption is generally complete by 4 h post ingestion. Sustained release preparations, large ingested amounts, and co-ingestion with other medications that reduce gastrointestinal motility can delay peak concentrations by several hours.[20–22] Protein binding is low at 10–30% and this has not been demonstrated to change in overdose.[23] The volume of distribution is 0.9–1.0 L/kg. Physicochemical and toxicokinetic properties are summarized in Table 2.

Overview of acetaminophen poisoning

APAP toxicity occurs when the amount of NAPQI formation exceeds available glutathione stores and turnover in the body. Free NAPQI, a strong electrophile and oxidant, reacts readily with many cellular targets in the absence of glutathione, including other thiol-containing compounds such as cysteine residues in cellular proteins. This occurs mainly in the centrilobular hepatocytes where oxygen content is lower and the concentration of CYP2E1 is higher. Eventually, cell necrosis occurs and hepatic function is impaired. The metabolism of APAP in therapeutic, overdose, and the clinical stages of poisoning are well described elsewhere.[24]

Table 2. Physical chemical and toxicokinetic parameters of acetaminophen.

Molecular weight	151.2 Daltons
Volume of distribution	0.8–1.0 L/kg
Protein binding	25%
Oral bioavailability	60%–95%
Therapeutic range	8–20 mg/L (55–133 μmol/L)
Conversion factor	1 mg/L = 6.62 μmol/L
Toxic exposure	Single acute ingestion $>$150 mg/kg (adults) $>$200 mg/kg (children)
Half-life (therapeutic)	1–2 h
Lethal dose	$>$500 mg/kg

However, another pattern of APAP poisoning is both increasingly recognized and poorly described in the literature. In massive ingestions (above 500 mg/kg) patients can present with an altered level of consciousness and metabolic acidosis with elevated lactate concentrations. Typically, this occurs within 12 h post ingestion and often prior to biochemical or clinical evidence of hepatotoxicity. APAP concentrations in such cases are often extremely high ($>$ 750 mg/L or 5000 μmol/L) consistent with the ingestion of a massive dose. This clinical scenario represents mitochondrial failure and early cell death from overwhelming ROS and exhausted glutathione (GSH) reserves. Importantly, studies validating the efficacy of NAC for APAP overdoses included few such patients, and the clinical course and toxicokinetics of these patients are not well characterized.[25,26]

Changes in mitochondrial function are detected in the first hours after APAP overdoses and impairment of cellular respiration can lead to early mitochondrial failure. Doses of APAP in the range that is known to produce hepatotoxicity can cause functional changes in States 3 and 4 of mitochondrial respiration. In addition, when mitochondria are directly exposed to NAPQI, these same changes are reproduced. Thus, not only is the mitochondrial unit dependent on APAP metabolism for NAPQI to impair respiration, but it can also be affected by high doses of APAP itself. Mitochondrial dysfunction induces the formation of reactive oxygen species (ROS), and particularly in APAP poisoning, can be detected by high concentrations of glutathione disulphide. Mitochondrial dysfunction can be prevented to some extent by administration of NAC, which scavenges NAPQI. Studies have shown that ROS formation as a consequence of mitochondrial dysfunction occurs after glutathione depletion.[27–29] It is likely that following an exceedingly large APAP overdose the dose of NAC administered by the standard intravenous or oral protocols is insufficient to compete with massive amounts of APAP and/or NAPQI.

Additionally, many patients with severe APAP poisoning will also develop acute kidney injury (AKI) with or without associated hepatotoxicity.[30] This is usually a consequence of NAPQI production in the kidney, where CYP2E1 is expressed, rather than hepatorenal syndrome.[31] Moreover, renal prostaglandin synthetases produce NAPQI locally, which could explain some prostaglandin-mediated nephropathy that occurs in chronic APAP users.[30–33] Thus, patients with APAP-associated AKI may develop indications for ECTR other than acute toxin removal.

Initial management of an acute ingestion in the first 1–2 h post ingestion should include a detailed risk assessment to evaluate for potential co-ingestants, appropriateness of gastrointestinal decontamination and estimation of the amount of APAP ingested in mg/kg. APAP concentrations are typically obtained when absorption is thought to be complete at 4 h post ingestion or as soon as possible thereafter. However in the case of massive ingestions heralding early mitochondrial toxicity, APAP concentrations could be obtained earlier. The subsequent treatment decisions are guided by plotting the APAP concentration on the Rumack Matthew nomogram.[14] The management of patients with staggered and chronic supratherapeutic ingestions will not be reviewed here but are not amenable to guidance with the Rumack-Matthew nomogram.

Hemodialysis and hemoperfusion are seldom used in cases of APAP poisoning even if it is one of the most common toxins where dialysis is used.[34] This could be due to the fact that ECTR is used for other reasons than toxin removal, such as for AKI or hepatic failure. Currently, no guidelines exist to help identify patients who might benefit most from ECTR, or alternatively, which patients with acute large ingestions would be likely to develop mitochondrial failure and thus unlikely to recover with the current NAC dosing regimen alone.[35]

Methodology

The predetermined methodology incorporated guidelines from The Appraisal of Guidelines for Research and Evaluation (AGREE) and Grades of Recommendation Assessment, Development and Evaluation (GRADE) and it is described in detail elsewhere.[3] Literature search: Articles were obtained via EXTRIP's preliminary search database. Thereafter, two specific searches were conducted. One last accessed on July 10th 2012 for the voting process and another, last accessed on April 1st, 2014, retrieved other articles from Medline, Embase, Cochrane library (Review and Central), Conference proceedings/meeting abstracts of the European Association of Poison Centres and Clinical Toxicologists and North American Congress of Clinical Toxicology annual meetings, and Google Scholar. Finally, the bibliographies of all articles obtained were manually reviewed for completeness. The search strategy was as follows: [(acetaminophen* OR paracetamol) 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)].

The designated subgroup completed the literature search, reviewed articles, extracted data, summarized findings, and proposed structured voting statements following a pre-determined format, all of which were submitted to the workgroup. The benefits of ECTR were weighed against its cost, availability, complications, and alternative treatments. The appointed epidemiologist and the subgroup determined the level of evidence for clinical recommendations (Table 3). Dialyzability was determined by the workgroup following predefined criteria (Table 4). The strength of recommendations was determined through a two-round modified Delphi method for each proposed voting statement, using median vote and disagreement index (RAND/UCLA Appropriateness Method)[36] (Fig. 1, Table 3). Blinded votes with comments were compiled by the statistician and returned to each participant. The workgroup met in person in June 2012 to exchange ideas and debate statements. A second blinded vote was performed during the summer of 2012 and these final results reflect the core of EXTRIP recommendations.

Table 3. Strength of recommendation and level of evidence scale for clinical outcomes.

Strength of recommendation (consensus-based)	Level of evidence (based on GRADE system)
Level 1 = Strong recommendation (almost all experts would propose this course of action)	Grade A = High level of evidence (the true effect lies close to our estimate of the effect)
Level 2 = Weak recommendation (most experts would propose this course of action)	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 position (some experts would propose this course of action but non-compliance with the recommendation would be fully acceptable 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 (the 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)

Results

Results of the literature search and reasons for study exclusion are presented in Fig. 2. A total of 295 articles were identified. After screening for eligibility criteria, 24 articles were selected for extraction of clinical or toxicokinetic data. These include 1 randomized control trial (RCT) performed before NAC therapy was accepted, 1 observational study and 20 case report and case series. Two pharmacokinetic studies in patients receiving APAP while undergoing ECTR for ESRD were included for comparison. Animal or experimental in vitro studies were excluded. All case reports were acute APAP overdoses.

After the final votes were collected, the second search retrieved four new full text articles that would have been included following the criteria as for our previous search but only one new case report would have been included in analysis.[37] The subgroup reviewed this article and concluded that it is unlikely that voting results would have changed if it had been in the original search.

Clinical outcomes

The reported clinical outcomes are summarized in Table 5. Prior to the commercialization of NAC as an antidote for APAP poisoning in the 1980s, the fatality rate of APAP overdose was well documented.[38] However, in the 1970s Gazzard et al published the only RCT regarding ECTR in APAP poisoning. This study consisted of 16 patients assigned to either hemoperfusion or no therapy.[39] Baseline characteristics suggest that the ECTR group was sicker; peak concentrations in the hemoperfusion group were higher 305 mg/L (2019 μmol/L) versus controls 238 mg/L (1575 μmol/L) and the delay from time of ingestion to treatment was greater in the hemoperfusion group compared to the controls (5 h vs 3 h). However, clinical outcomes did not differ significantly (1 death in ECTR group versus none in control).

An observational study described a prospective evaluation of 73 patients presenting to a single hospital and who did not receive NAC within the first 15 h.[40] Fifty-one of these patients were treated with daily treatments of hemoperfusion, hemodialysis, or both based on the degree of encephalopathy, and their APAP concentration being above the "Helliwell line" drawn between concentrations of 140 mg/L (927 μmol/L) at 10 h and 25 mg/L (166 μmol/L) at 24 h. This line, which represents higher concentrations than the standard Rumack–Matthew nomogram was thought to identify patients with a high risk of severe liver damage.[41] Control groups were derived from patients with similar characteristics treated with supportive care with presentation before or after 42 h post ingestion. APAP half-life decreased during hemoperfusion, from 16.2 h (range: 9.2–20.3) to 3.2 h (range: 2.1–3.9). NAC was also administered in 39% of the study patients presenting within 42 h post-ingestion,

Table 4. Criteria used to define dialyzability.

Dialyzability[A]	Primary criteria % Removed[B]	Alternative criteria 1 CL_{EC}/CL_{TOT} (%)[C]	Alternative criteria 2 $t_{1/2\ EC}/t_{1/2}$ (%)	Alternative criteria 3 Re_{EC}/Re_{TOT} (%)[C]
D, Dialyzable	> 30	> 75	< 25	> 75
M, Moderately dialyzable	> 10–30	> 50–75	> 25–50	> 50–75
S, Slightly dialyzable	≥ 3–10	≥ 25–50	≥ 50–75	≥ 25–50
N, Not dialyzable	< 3	< 25	> 75	< 25

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[A]Applicable to all modalities of ECTR, including hemodialysis, hemoperfusion, and hemofiltration.
[B]Corresponds to % removal of ingested dose or total body burden in a 6-hour ECTR period.
[C]Measured during the same period of time.
*These criteria should only be applied if measured or calculated (*not reported*) endogenous half-life is greater 4 h (otherwise, ECTR is considered not clinically relevant). Furthermore, the primary criteria is preferred for poisons having a large Vd (> 5 L/Kg).

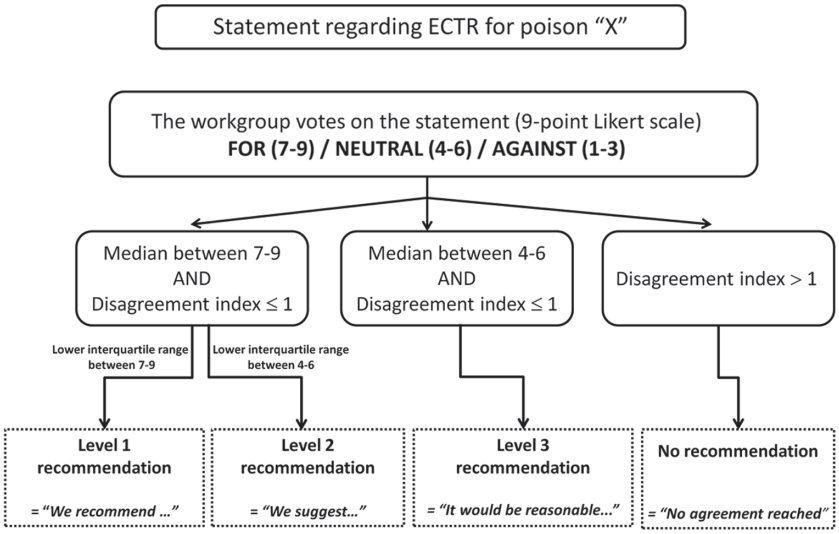

Fig. 1. Delphi Method (2 Rounds) for each recommendation.

40% after 42 h post ingestion and in 43% of those without ECTR. Other standard therapies at the time (such as vitamin K, low-protein diet, cimetidine, neomycin, lactulose, and fresh frozen plasma) were administered.

Reliable conclusions cannot be drawn from any of the case reports and case series. [15,16,41–58] The amount of APAP ingested, the delay between presentation and the time of ingestion, and the time to NAC therapy are not reported consistently enough to be able to classify any of these patients into a particular risk category and extrapolate what their clinical outcome would have been without ECTR. However, most had peak APAP concentrations well above the 150 mg/L Rumack–Matthew nomogram line. (Fig. 3) The majority of these case reports had metabolic acidosis and altered mental status both of which improved rapidly during the ECTR procedure. Unfortunately, with the limited information contained in the reports, their psi (ψ) parameter, a recently proposed predictor of toxicity taking into account the degree and duration of pretreatment exposure could not be calculated.[59,60]

Dialyzability

APAP is dialyzable (Level Evidence = C). Individual and summary of kinetic outcome is presented in Tables 6 and 7. Even by today's standards, the out-dated means of hemodialysis used in many of the papers cited provide evidence for the dialyzability of APAP. Two reports evaluated the clearance of APAP in patients with Stage 5 CKD undergoing HD.[61,62] In 6 patients given 650 mg of APAP 2 h before HD with a low blood flow rate (170–280 mL/min) and a dialysate flow rate (575–620 mL/min) a mean extraction ratio of 47.5% was achieved and a total of 11% of the ingested dose was removed.[62] This corresponds to moderate dialyzability according to the primary criteria reported in Table 4, even though the criteria were based on a 6-h

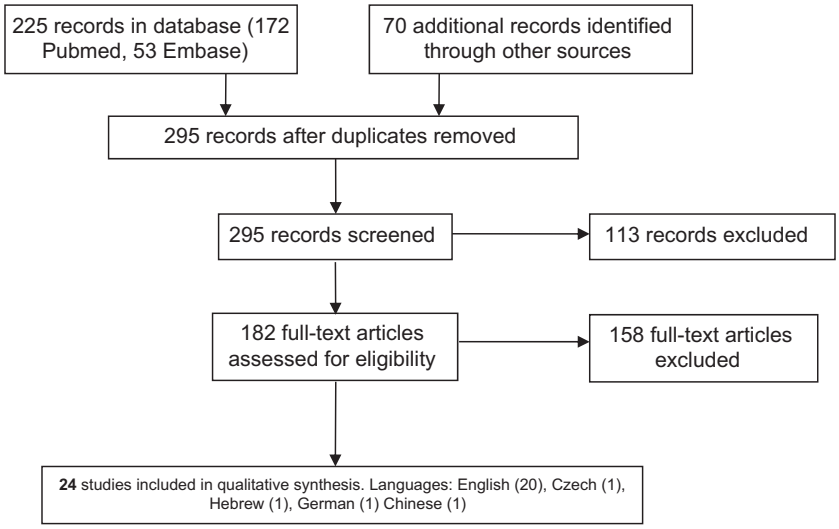

Fig. 2. Study selection flow diagram.

Table 5. Clinical outcomes reported in overdose studies.

Article	Study	ECTR	Peak [APAP] mg/L	[APAP] Time PI (h)	NAC received	Number	Survival	Deaths	Unknown
Gazzard, 1974[39]	RCT	HP	305	~ 5	No	8	7	1	0
		None	238	~3	No	8	8	0	0
Higgins, 1996[40]	Observational	HP, HD	NR	> 42	> 15 h PI (40%)	33	18	15	0
			NR	< 42	> 15 h PI (39%)	18	16	2	0
		None	NR	> 42	> 15 h PI (43%)	12	12	0	0
			NR	< 42	> 15 h PI (43%)	10	10	0	0
Farid, 1972[49]	Case Series	HD 3–12 h PI	10–575	< 12	No NAC	7	7	0	0
Rigby, 1978[55]	Case Report	HP 8 h PI	440	2	Cysteamine 6 h PI	1	1	–	–
Helliwell, 1980[50]	Case Report	HP	150	12	No	1	1	–	–
Helliwell, 1981[41]	Case Series	HP	150–262	11.5–24.5	No	7	5	2	–
Pond, 1982[54]	Case Report	HD	486	~20	NAC IV and PO	1	1	0	–
Raper, 1982[15]	Case Report	HP 17 h PI	1150	NR	NAC 17 h PI	1	0	1	–
Lederman, 1983[52]	Case Report	ET	150	16	No	1	0	1	–
Bentur, 1984[44]	Case Report	HP	86 m	20	IV NAC	1	1	0	–
Lieh-Lai, 1984[53]	Case Report	HD 12 h PI	863	5	IV NAC 8 h PI	1	1	0	–
Roberts, 1984[56]	Case Report	ET 12 h	100	6	No	1	1	–	–
Balikova, 1987[43]	Case Report	HP	43.7	NR	NR	1	–	–	1
Claass, 1993[45]	Case Report	ET	60	~8	No	1	1*	–	–
Eisele, 1995[48]	Case Report	HP	356	7	PO NAC not tolerated	1	1	0	–
Wu, 1999[58]	Case Report	HD	210	12	PO NAC 16 h PI not tolerated	1	1	0	–
Ash, 2002[42]	Case Series	LD	6–401	16–48	PO NAC	8	8	0	–
			171–310	8–12	PO NAC	2	2	–	–
Lai, 2004[51]	Case Report	HD	716	~16	IV NAC 16 h PI	1	1	0	–
Donovan, 2005[47]	Case Series	HD	NR	Late	IV NAC	3 acute 3 chronic	6	0	–
Patil, 2009[16]	Case Report	CVVHDF	714	22 post arrival	IV NAC Unknown time	1	0	1	–
de Geus, 2010[46]	Case Report	LD	400	7	IV NAC 8 h PI	1	1	0	–
Wiegand, 2010[57]	Case Report	CVVHDF	816	1.5	IV NAC	1	1	0	–

LD: liver dialysis, ET: exchange transfusion, HD: intermittent hemodialysis, CVVHDF: continuous veno-venous hemodiafiltration, HP: hemoperfusion. PI: post-ingestion * with permanent CNS sequelae.

ECTR and the 11% removal occurred during only 3 h of HD in these patients. In the other report, 4 patients with Stage 5 CKD were given APAP 1 g/1.73 m^2 once on an interdialysis day and again one month later on a dialysis day. Extraction ratios ranged from 46 to 78% and half-lives decreased 42–53%.[61] This corresponds to moderate dialyzability according to the alternative criteria 2 shown in Table 4. As

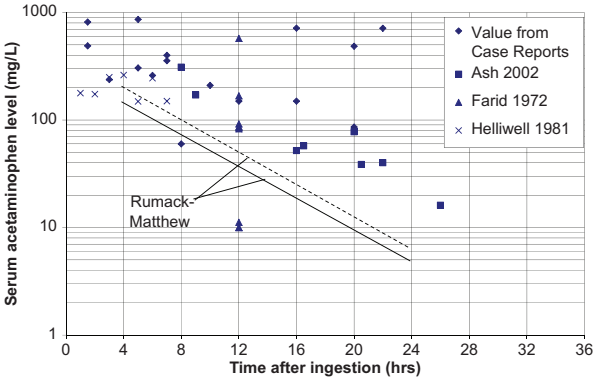

Fig. 3. Peak APAP concentrations of cases analyzed plotted on the Rumack–Matthew nomogram (colour version of this figure can be found in the online version at www.informahealthcare.com/ctx).

in the previous paper, these patients underwent HD on using an inefficient membrane with a somewhat low blood flow rate (250 mL/min), and therefore better clearance would be expected with modern techniques. A total of four case reports and case series provided sufficient data to evaluate dialyzability in 9 patients using one of the criteria in Table 4;[47,51,54,58] 7 of these patients met criteria for dialyzability and 2 met criteria for moderate dialyzability. Since the second round of voting was completed, two additional references were published with sufficient data to add to the discussion of APAP dialyzability. The first reference describes three adults with severe manifestations of massive APAP overdose who were being treated with HD using modern techniques including; filters (Optiflux 200, or RX18AX), blood flow rates (350–400 mL/min), and dialysate flow rate (500–800 mL/min). In this series, extraction ratios are reported as 73–87% and single 3 to 4-h runs of hemodialysis removed 10–20 grams of APAP, which correspond to a removal of between 48% and 80% of the drug remaining in the body.[63] The other report describes a single case of a woman with severe metabolic acidosis 1.5 h after ingesting 100 g of APAP (4 h APAP concentration 6496 μmol/L). She was treated with 7 h of hemodialysis 6 h post-ingestion (blood flow rate of

Table 6. Kinetic grading for individual patients included in the review.

Article	Study	ECTR	Peak [APAP]	*N*	Half-Life or Removal in grams	Clearance	Dialyzability
Gazzard, 1974[39]	RCT	HP	305 mg/L	8	8. h to 3. h in 2 h (37.5%)	N/R	M
					5.0 h to 2.5 h in 4 h (50%)		S
					6. h to 2. in 6 h (33.3%)		M
					8 h to 1.75 h in 4 h (21.8%)		D
					5.5 h to 2.5 h (45%)		M
					6. h to 1.5 in 3 h (25%)		D
					7.5 h to 2. h in 4 h (26.6%)		M
					9. h to 4. h in 9 h (44.4%)		M
Oie, 1975[61]	PK	HD	N/R	4	127 min to 69 min (54%)	112–215 mL/min	S
					147 min to 83 min (56%)	11% ingested dose	S
					120 min to 70 min (58%)		S
					128 min to 60 min (47%)		S
Marbury, 1980[62]	PK	HD	N/R	6	11% ingested dose	avg 112 mL/min	M
Rigby, 1978[55]	Case Report	HP	490 mg/L	1	6.7 h to 2.2 h (32.8%)	50–120 mL/min	M
Helliwell, 1980[50]	Case Report	HP	150 mg/L	1	41 h to 3.6 h (8.0%)	N/R	D
					4.75 g out of 8.89 g in 6 h		
Helliwell, 1981[41]	Case Series	HP	150–262 mg/L	7	4.3–2.3 (53%)	73–180 mL/min	S
					13.6–1.0 (7%)		D
					3.6–2.1 (58%)		S
					50–3.8 (7.6%)		D
					84–4 (4.7%)		D
					8.9–1.0 (11%)		D
					77–1.1 (1.4%)		D
Pond, 1982[54]	Case Report	HD	486 mg/L	1	14 h vs to 1.3 h to 3 h after (9%)	144 mL/min	D
Raper, 1982[15]	Case Report	HP	1150 mg/L	1	Calculated removal of 26.5 g (7%)	127–295 mL/min	D
Bentur, 1984[44]	Case Report	HP	86 mg/L	1	6.4 h vs 2.7 (42%)	176 mL/min	D
Lieh-Lai, 1984[53]	Case Report	HD	863 mgL	1	11.8 h to 2.6 h	600–2160 mL/min	D
					28% removed (2.8 g)		
Roberts, 1984[56]	Case Report	ET	260 mg/L	1	No change with ET		N
Claass, 1993[45]	Case Report	ET	60 mg/L	1	8 h vs 5.13 (64%)	N/R	M
Eisele, 1995[48]	Case Report	HP	356 mg/L	1	0.9 h HP vs 7.1 h before (12.6%)	N/R	D
Wu, 1999[58]	Case Report	HD	210 mg/L	1	7.2 h vs 2.6 h v 7.5 h after (36%)	109–163 mL/min	M
Ash, 2002[42]	Case Series	LD	6–310 mg/L	10	10% removed	140 mL/min	S
Lai, 2004[51]	Case Report	HD	716 mg/L	1	20 h vs 2.8 h (14%)	N/R	M
					9.75 g of 75 g (15%)		
Donovan, 2005[47]	Case Series	HD	NR	6	12.8 h vs 2.2 h (17.1%)	N/R	D
deGeus, 2010[46]	Case Report	LD	400 mg/L	1	3.4 vs 1.2 h (35%)	N/R	M
		MARS					
Wiegand, 2010[57]	Case Report	CVVH	816 mg/L	1	11.1 h on CVVH vs 5.6 h after	42 mL/min	S

S: slight, M: Moderate, D: dialyzable.

400 mL/min, dialysate flow rate of 1000 mL/min). An extraction ratio of 57% and an APAP clearance of 160 mL/min were reported to remove a total of 20.6 g of APAP.[37] These two cases highlight the benefits and modern hemodialysis techniques and only strengthen the evidence used to vote on APAP dialyzability.

In the one RCT noted above, 8 patients undergoing HP for APAP toxicity had sufficient data to evaluate dialyzability;[39]

Table 7. Summary of kinetic outcomes.

Total patients 54	TPE	PD	HP	HD	CRRT	ET	Liver dialysis
Number of TK patients graded:							
Dialyzable	–	–	11	8	–	–	–
Moderately dialyzable	–	–	6	2	–	1	1
Slightly dialyzable	–	–	3	–	1	–	10
Not dialyzable	–	–	–	–	–	1	–
Number of PK patients graded:							
Dialyzable	–	–	–	–	–	–	–
Moderately dialyzable	–	–	–	6	–	–	–
Slightly dialyzable	–	–	–	4	–	–	–
Not dialyzable	–	–	–	–	–	–	–

PK: pharmacokinetics, TK: toxicokinetics, TPE: Therapeutic plasma exchange, HD: Hemodialysis, HP: Hemoperfusion, CRRT: Continuous renal replacement therapy, ET: Exchange transfusion.

two met criteria for dialyzability, 5 for moderate dialyzability, and 1 for slight dialyzability. One case series and 5 case reports provided enough data to evaluate dialyzability in 12 patients undergoing HP for APAP overdose;[15, 41, 44, 48, 50, 55] 9 met criteria for dialyzability, 1 for moderate dialyzability, and 2 for slight dialyzability. Thus while some variability was noted, the EXTRIP work group voted overwhelmingly in support of the statement that with either HD or HP APAP met sufficient criteria to be assigned as dialyzable, but noted a low level of evidence.

Continuous renal replacement therapy (CRRT) is occasionally used in the setting of APAP poisoning, usually as support for AKI; liver support treatments, such as MARS and Prometheus, are also employed as a bridge for liver transplantation or spontaneous liver recovery. Unfortunately, an exceedingly small number of isolated reports included data on dialyzability. The workgroup therefore chose not to vote on the utility of these methods for other indications than our primary interest of toxin removal. Clinicians are encouraged to rigorously collect appropriate data when performing these modalities.

Fatalities

Overall 23 deaths were reviewed. One fatality was reported in the only RCT available for review. No patient received NAC. Peak APAP concentrations differed between both groups (305 mg/L vs 238 mg/L) and the HP group patients had higher AST concentrations ($p = 0.05$). The only observational study reports 17 deaths out of 73 patients. All deaths occurred in the ECTR-treated group and 15 in the group treated beyond 42 h. NAC treatment occurred in 39%, 40% and 43%, and of the early, late and control groups respectively. The timing of NAC therapy was not specified. Considering peak APAP concentrations were not reported, no conclusion can be drawn on the role of ECTR and these fatalities as those who did not receive ECTR were deemed to have a better prognosis. The deaths reported in the case reports are subjected to many confounding factors such as co-ingestants and thus no conclusions can be drawn.

Of the 28 patients in our review who did not receive or tolerate NAC but received some form of ECTR 11 survived. The 16 fatalities in this group underwent ECTR for APAP overdose on average within 10 h [5–20 h] post ingestion. All had ingested large amount of APAP and presented in metabolic acidosis. Multiple factors such as co-ingestants could have played a role in these fatalities and their demise cannot be attributed to the procedure.[39,45,48–50,52,54,56,58]

Adverse effects

A systematic review of complications associated with various extracorporeal removal techniques has not yet been published. In the studies reviewed for this present article, adverse effects of the procedures were inconsistently reported. Thrombocytopenia and hypotension were reported with hemoperfusion. One patient experienced a transient asymptomatic fall in serum calcium.[39]

Recommendations

1) General Statement: ECTR is suggested in severe acetaminophen poisoning (2D)

Rationale: NAC is the only treatment required for the vast majority of patients with acute APAP ingestion. In rare circumstances in which NAC is not available or serious concerns of allergy exist that might preclude use of NAC, ECTR should be considered. Other circumstances when APAP concentrations might be so high as to question whether or not the current NAC regimen is sufficient or when clinical evidence of mitochondrial failure is present warrant additional treatments. Additionally ECTR promptly corrects metabolic acidosis and perhaps also removes toxic metabolites such as NAPQI. Given the lack of knowledge regarding NAPQI kinetics or of its surrogate markers, any attempt to adjust NAC dosing regimen to match the amount of NAPQI production is arbitrary. NAPQI is an unstable molecule and not readily measurable in blood. Thus, calculating its dialyzability is virtually impossible. Surrogate markers of NAPQI quantity, such as protein adducts, require complex laboratory manipulations for their measurements and these are not commercial available. The knowledge on their clinical significance is also currently limited. In our review, APAP half-lives were reduced to less than 4 h in the majority of cases where concentrations before and after ECTR sessions were available, which likely indicates that enough APAP had been removed to restore previously saturated metabolic pathways to non-toxic conditions. It is thus reasonable to consider removal of the primary toxin by extracorporeal means to avoid progression of the toxicity and correction of the metabolic derangements. Despite the limited number of reports available, the group concluded there was sufficient evidence of efficacy of ECTR for APAP poisoning in certain circumstances. Also, considering the relatively inexpensive cost of the procedure as well as the low complication rate associated with a single session, ECTR presents a favorable risk benefit ratio in the rare APAP poisoning where doubt regarding the efficacy of NAC is important enough to justify removing the primary toxin.

2) Indications for ECTR:

ECTR is suggested if any of the following conditions are present:

1. If NAC is **NOT** administered and the [APAP] more than 1000 mg/L (6620 μmol/L) (1D) or more than 800 mg/L (5300 μmol/L) (2D)
2. If NAC is **NOT** administered and the patient presents with altered mental status, metabolic acidosis, elevated lactate, and the [APAP] is more than 700 mg/L (4630 μmol/L) (1D) or more than 500 mg/L (3300 μmol/L) (2D)
3. If NAC **is** administered and the patient presents with altered mental status, metabolic acidosis, elevated lactate, and the [APAP] is more than 900 mg/L (5960 μmol/L) (1D) or more than 800 mg/L (5300 μmol/L) (2D)

ECTR is not suggested.

4. On the basis of the reported ingested dose alone even if NAC is **NOT** administered (2D).
5. Solely on the basis of the [APAP] if NAC is administered (2D).

ECTR is not recommended.

6. On the basis on the reported ingestion dose if NAC is administered (1D).

Rationale: NAC is the mainstay of therapy for patients with acute APAP poisoning and as such, the group did not vote in favor of ECTR based on reported APAP concentration alone. As discussed previously, cases of mitochondrial failure occurred early in the course of the patient's clinical evolution, usually within 12 h post ingestion, which leads us to believe that the current dosing regimen of NAC might be insufficient to either fully reverse mitochondrial failure or supplement the amount of glutathione required. Experimental animal studies demonstrate that mortality is high despite NAC administration when the ingested dose exceeds 350 mg/kg.[64, 65] It is unclear how these results can be applied to humans but they represent the only available evidence of the efficacy of NAC at for APAP ingested at high doses. However given the imprecision surrounding reported ingested doses in actual overdose scenarios, we do not suggest to perform ECTR on the basis of any reported ingestion dose, regardless of NAC administration, especially since APAP concentrations are usually available in a sufficient timeframe to confirm a massive ingestion. Various cut-off values are presented depending on the use of NAC or not. The degree of metabolic acidosis or the concentration of lactate required to initiate ECTR was insufficiently reported to be voted on. It was decided that the assessment of the presence of mitochondrial dysfunction be left to clinicians. The timing of the APAP concentration to confirm a massive ingestion has also not been specified. Rather it is thought that regardless of the delay between ingestion and a high APAP concentration, it is the presence of mitochondrial dysfunction and the amount of APAP in the blood at one given time that should support the decision to initiate ECTR. Both need to be present concurrently: simultaneous evidence of mitochondrial dysfunction and sufficient quantity of APAP present in blood for meaningful removal. If APAP concentrations were to be lower than the thresholds identified, it is unclear whether sufficient APAP would be removed to make a clinical difference in the outcome. Although one can argue that APAP half-life is of 4 h or less in therapeutic conditions, one cannot use this parameter to decide on the pertinence of ECTR as in toxic situations APAP kinetics are modified and APAP half-life is prolonged.[66]

3) Cessation of ECTR: ECTR is recommended until sustained clinical improvement is apparent (1D)

Rationale: In this systematic review the durations of ECTR vary considerably. Given that the goal of ECTR in patients with acute severe APAP poisoning is to remove enough APAP to prevent a large amount of NAPQI being produced, and to correct the metabolic acidosis, it seems reasonable to provide ECTR until clinical improvement is apparent. The workgroup preferred clinical endpoints instead of a specific target APAP concentration to determine the ECTR cessation. Since the second round of voting, a recent abstract recorded a rising serum APAP concentration at the end of HD.[67] While it is unclear whether this represents ongoing absorption or tissue redistribution it would be reasonable to confirm that the APAP concentration is zero or very low at the end of ECTR and assure that it is not rising. In our review, clinical improvement was apparent a few hours after the initiation of ECTR, with metabolic acidosis correcting earlier than the improvement in mental status. This observation might be biased by the fact that almost all these patients were intubated for airway protection and sedation was decreased after metabolic improvement was noted. Although seldom reported, the duration of ECTR sessions was between 2 and 9 h.

4) Choice of ECTR

Intermittent hemodialysis is the preferred ECTR in patients with APAP poisoning (1D). Intermittent hemoperfusion (1D) or continuous renal replacement modalities (3D) are valid alternatives if intermittent hemodialysis is not available. Exchange transfusion is an adequate alternative to HD in neonates (2D).

Rationale: There are insufficient human data to confidently advocate HP over HD. In general, in acute liver failure charcoal hemoperfusion is not associated with any benefit, irrespective of the underlying etiology including APAP overdose. It is unlikely that future direct comparison over a 2–6 h ECTR session would help to resolve this question, as high clearance limited to a short time might not necessarily be superior to a lower clearance over a longer time. Pragmatic considerations, such as the availability of charcoal cartridges, trained personal, the known side effects of HP on platelets and calcium in a patient prone to coagulopathy and/or co-existing fluid, and electrolyte abnormalities from AKI, will likely dictate the choice of modality. Continuous techniques offer lower clearances and thus should only be considered whether hemodialysis or hemoperfusion is not available. Clearances obtained with exchange transfusion are lower, and the evidence inconclusive. However exchange transfusion might be reserved for the rare neonate in whom this modality is technically easier. No cases with peritoneal dialysis were reviewed. Various reasons underline the preference of HD over HP; faster correction of acidosis, lack of availability of the HP cartridges, longer duration of sessions, lack of thrombocytopenia and potential effect on coagulation during coagulopathy are concerns with APAP-induced hepatic failure.

5) Miscellaneous: NAC should be continued during ECTR at an increased rate (1D)

Recent evidence has shown that NAC is also dialyzable and that the amount differs according to each ECTR modality. Up to 25% of NAC is extracted by CRRT and up to 50% with intermittent hemodialysis. In order to provide the same

Table 8. Executive summary of recommendations.

General Recommendation
- **ECTR is suggested in *severe* APAP poisoning (2D)**

ECTR is recommended:
- If the [APAP] more than 1000 mg/L (6620 µmol/L) and NAC is ***NOT*** administered (1D).
- If the patient presents with altered mental status, metabolic acidosis, with an elevated lactate, and an [APAP] is more than 700 mg/L (4630 µmol/L) and NAC is ***NOT*** administered (1D).
- If the patient presents with an altered mental status, metabolic acidosis, an elevated lactate, and an [APAP] is more than 900 mg/L (5960 µmol/L) even if NAC ***is*** administered (1D).

ECTR is not recommended
- On the basis of the reported ingested dose if NAC is administered (1D).

ECTR is not suggested
- On the basis of reported ingested dose alone even if NAC is ***NOT*** administered (2D).
- Solely on the basis of the [APAP] if NAC is administered (2D).

Cessation of ECTR
- ECTR is recommended until sustained clinical improvement is apparent (1D).

Choice of ECTR
- Intermittent hemodialysis is the preferred ECTR in patients with APAP poisoning (1D).
- The following are acceptable alternatives if HD is not available:
  - Intermittent HP (1D)
  - CRRT (3D)
  - Exchange transfusion in neonates (2D)

Miscellaneous
1. NAC therapy should be continued during ECTR at an increased rate (1D).

concentration of NAC as that of the current NAC dosing regimen prescribed, the amount of NAC should be increased to match the expected NAC losses during ECTR.[37, 63, 68]

An executive summary of the recommendations is presented in Table 8.

Conclusions

APAP is one of the most common acute overdoses that clinicians will encounter and one of the most common drug-induced causes of acute fulminant liver failure. NAC is the mainstay of treatment of the vast majority of patients with acute APAP poisoning.

EXTRIP recommends ECTR for APAP removal when signs of early mitochondrial failure such as early coma, elevated lactate concentration, and metabolic acidosis are present prior to the onset of hepatic dysfunction and in the setting of a substantially elevated APAP concentration. When these conditions are met, ECTR seems to be a beneficial adjunct to NAC treatment as there is a high risk of liver failure and mortality and a suggestion that standard NAC regimens may be insufficient. As NAC is removed by ECTR, its dose should be increased during the duration of ECTR. Indications for the use of ECTR, other than removal of APAP, such as hepatic encephalopathy or AKI were not reviewed by EXTRIP.

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References

1. Ghannoum M, Nolin TD, Goldfarb DS, Roberts DM, Mactier R, Mowry JB, et al. Extracorporeal treatment for thallium poisoning: recommendations from the EXTRIP Workgroup. Clin J Am Soc Nephrol 2012; 7:1682–1690.
2. Ghannoum M, Nolin TD, Lavergne V, Hoffman RS. Blood purification in toxicology: nephrology's ugly duckling. Adv Chronic Kidney Dis 2011; 18:160–166.
3. Lavergne V, Nolin TD, Hoffman RS, Roberts D, Gosselin S, Goldfarb DS, et al. The EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup: guideline methodology. Clin Toxicol (Phila) 2012;50:403–413.
4. Yates C, Galvao T, Sowinski KM, Mardini K, Botnaru T, Gosselin S, et al. Extracorporeal treatment for tricyclic antidepressant poisoning: recommendations from the EXTRIP Workgroup. Semin Dial 2014; 27:381–389.
5. Josephy PD. The molecular toxicology of acetaminophen. Drug Metab Rev 2005; 37:581–594.
6. Mowry JB, Spyker DA, Cantilena LR Jr, Bailey JE, Ford M. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. Clin Toxicol (Phila) 2013; 51:949–1229.
7. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc 2014; 89:95–106.
8. Lopez AM, Hendrickson RG. Toxin-induced hepatic injury. Emerg Med Clin North Am 2014; 32:103–125.
9. Bourdeaux C, Bewley J. Death from paracetamol overdose despite appropriate treatment with N-acetylcysteine. Emerg Med J 2007; 24:e31.
10. Schwartz EA, Hayes BD, Sarmiento KF. Development of hepatic failure despite use of intravenous acetylcysteine after a massive ingestion of acetaminophen and diphenhydramine. Ann Emerg Med 2009; 54:421–423.
11. Shah AD, Wood DM, Dargan PI. Understanding lactic acidosis in paracetamol (acetaminophen) poisoning. Br J Clin Pharmacol 2011; 71:20–28.
12. Smilkstein MJ, Bronstein AC, Linden C, Augenstein WL, Kulig KW, Rumack BH. Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. Ann Emerg Med 1991; 20: 1058–1063.
13. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). N Engl J Med 1988; 319:1557–1562.
14. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol 2002; 40:3–20.
15. Raper S, Crome P, Vale A, Helliwell M, Widdop B. Experience with activated carbon-bead haemoperfusion columns in the treatment of severe drug intoxication. A preliminary report. Arch Toxicol 1982; 49:303–310.
16. Patil N, O'Donnell K, Salhanick S. Prolonged acetaminophen absorption secondary to a possible pharmacobezoar. Clin Toxicol 2009; 47:742.
17. Doyon S, Klein-Schwartz W. Hepatotoxicity despite early administration of intravenous N-acetylcysteine for acute acetaminophen overdose. Acad Emerg Med 2009; 16:34–39.
18. Beer C, Pakravan N, Hudson M, Smith LT, Simpson K, Bateman DN, Thomas SH. Liver unit admission following paracetamol overdose with concentrations below current UK treatment thresholds. QJM2007; 100:93–96.
19. Lucas R, Warner TD, Vojnovic I, Mitchell JA. Cellular mechanisms of acetaminophen: role of cyclo-oxygenase. FASEB J 2005; 19: 635–637.
20. Adams BK, Mann MD, Aboo A, Isaacs S, Evans A. Prolonged gastric emptying half-time and gastric hypomotility after drug overdose. Am J Emerg Med 2004; 22:548–554.
21. Stork CM, Rees S, Howland MA, Kaplan L, Goldfrank L, Hoffman RS. Pharmacokinetics of extended relief vs regular release Tylenol in simulated human overdose. J Toxicol Clin Toxicol 1996; 34:157–162.
22. Ho SY, Arellano M, Zolkowski-Wynne J. Delayed increase in acetaminophen concentration after Tylenol PM overdose. Am J Emerg Med 1999; 17:315–317.
23. Milligan TP, Morris HC, Hammond PM, Price CP. Studies on paracetamol binding to serum proteins. Ann Clin Biochem 1994; 31:492–496.
24. Hendrickson R. Acetaminophen. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, eds. Goldfrank's Toxicologic Emergencies. 9th ed. New York, NY: McGraw-Hil; 2013:483–499.
25. Jaeschke H, Bajt ML. Mechanisms of acetaminophen hepatotoxicity. In: McQueen CA, ed. Comprehensive Toxicology. 2nd ed. Elsevier Ltd. 2010:457–473.
26. Yarema MC, Johnson DW, Berlin RJ, Sivilotti ML, Nettel-Aguirre A, Brant RF, et al. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. Ann Emerg Med 2009; 54:606–614.
27. Jaeschke H, Bajt ML. Intracellular signaling mechanisms of acetaminophen-induced liver cell death. Toxicol Sci 2006; 89:31–41.
28. Donnelly PJ, Walker RM, Racz WJ. Inhibition of mitochondrial respiration in vivo is an early event in acetaminophen-induced hepatotoxicity. Arch Toxicol 1994; 68:110–118.
29. Hinson JA, Pike SL, Pumford NR, Mayeux PR. Nitrotyrosine-protein adducts in hepatic centrilobular areas following toxic doses of acetaminophen in mice. Chem Res Toxicol 1998; 11:604–607.
30. O'Riordan A, Brummell Z, Sizer E, Auzinger G, Heaton N, O'Grady JG, et al. Acute kidney injury in patients admitted to a liver intensive therapy unit with paracetamol-induced hepatotoxicity. Nephrol Dial Transplant 2011; 26:3501–3508.
31. Breen K, Wandscheer JC, Peignoux M, Pessayre D. In situ formation of the acetaminophen metabolite covalently bound in kidney and lung. Supportive evidence provided by total hepatectomy. Biochem Pharmacol 1982; 31:115–116.
32. Mohandas J, Duggin GG, Horvath JS, Tiller DJ. Metabolic oxidation of acetaminophen (Paracetamol) mediated by cytochrome P-450 mixed-function oxidase and prostaglandin endoperoxide synthetase in rabbit kidney. Toxicol Appl Pharmacol 1981; 61:252–259.
33. Walker RJ, Fawcett JP. Drug nephrotoxicity—the significance of cellular mechanisms. Prog Drug Res 1993; 41:51–94.
34. Holubek W, Kemp B, Goldfarb D, Nelson L, Hoffman R. The use of extracorporeal techniques in acute acetaminophen (paracetamol) poisoning (abstract). Clin Toxicol 2011; 49:248.
35. Holubek WJ, Hoffman RS, Goldfarb DS, Nelson LS. Use of hemodialysis and hemoperfusion in poisoned patients. Kidney Int 2008; 74:1327–1334.
36. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica, CA 2011. Available from: http://www.rand.org. Accessed July 1, 2014.
37. Grunbaum AM, Kazim S, Ghannoum M, Kallai-Sanfacon MA, Mangel R, Villeneuve E, et al. Acetaminophen and n-acetylcysteine dialysance during hemodialysis for massive ingestion. Clin Toxicol 2013;51:270–271.
38. Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, Williams R. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 1991; 303:1026–1029.
39. Gazzard BG, Willison RA, Weston MJ, Thompson RP, Williams R. Charcoal haemoperfusion for paracetamol overdose. Br J Clin Pharmacol 1974; 1:271–275.
40. Higgins RM, Goldsmith DJ, MacDiarmid-Gordon A, Taberner D, Venning MC, Ackrill P. Treating paracetamol overdose by charcoal

haemoperfusion and long-hours high-flux dialysis. QJM 1996; 89:297–306.
41. Helliwell M, Essex E. Hemoperfusion in "late" paracetamol poisoning. Clin Toxicol 1981; 18:1225–1233.
42. Ash SR, Caldwell CA, Singer GG, Lowell JA, Howard TK, Rustgi VK. Treatment of acetaminophen-induced hepatitis and fulminant hepatic failure with extracorporeal sorbent-based devices. Adv Ren Replace Ther 2002;9:42–53.
43. Balikova M, Monhart V, Tlustakova M. Scorption efficiency of Czechoslovak haemoperfusion columns 'Hemasorb' in toxicological indications. [Czech]. Vnitrni Lekarstvi 1987; 33:772–776.
44. Bentur Y, Zonis Z. Charcoal hemiperfusion in acetaminophen poisoning. [Hebrew]. Harefuah 1984; 107:333–334.
45. Claass A, Gaude M, Schroder H. [Paracetamol poisoning in infancy]. Dtsch Med Wochenschr 1993; 118:898–902.
46. de Geus H, Mathot R, van der Hoven B, Tjoa M, Bakker J. Enhanced paracetamol clearance with molecular adsorbents recirculating system (MARS®) in severe autointoxication. Blood Purif 2010; 30:118–119.
47. Donovan JW, Burkhart KK, O'Donnell S, Shaer A. Hemodialysis for acetaminophen-induced acute liver failure [abstract]. Clin Toxicol (Phila) 2005; 43:433.
48. Eisele G, Bailie GR. Charcoal haemoperfusion to increase paracetamol elimination after overdose. Clin Drug Invest 1995; 10:123–125.
49. Farid NR, Glynn JP, Kerr DN. Haemodialysis in paracetamol self-poisoning. Lancet 1972; 2:396–398.
50. Helliwell M. Severe barbiturate and paracetamol overdose: the simultaneous removal of both poisons by haemoperfusion. Postgrad Med J 1980; 56:363–365.
51. Lai MW, Friedman D, Kalmowitz BD, Niemann P, Curry MP, Burns MM, et al. Extracorporeal Removal of Acetaminophen [abstract]. Clin Toxicol (Phila) 2004;42:748.
52. Lederman S, Fysh WJ, Tredger M, Gamsu HR. Neonatal paracetamol poisoning: treatment by exchange transfusion. Arch Dis Child 1983; 58:631–633.
53. Lieh-Lai MW, Sarnaik AP, Newton JF, Miceli JN, Fleischmann LE, Hook JB, Kauffman RE. Metabolism and pharmacokinetics of acetaminophen in a severely poisoned young child. J Pediatr 1984; 105:125–128.
54. Pond SM, Tong TG, Kaysen GA, Menke DJ, Galinsky RE, Roberts SM, Levy G. Massive intoxication with acetaminophen and propoxyphene: unexpected survival and unusual pharmacokinetics of acetaminophen. J Toxicol Clin Toxicol 1982;19:1–16.
55. Rigby RJ, Thomson NM, Parkin GW, Cheung TP. The treatment of paracetamol overdose with charcoal haemoperfusion and cysteamine. Med J Aust 1978;1:396–399.
56. Roberts I, Robinson MJ, Mughal MZ, Ratcliffe JG, Prescott LF. Paracetamol metabolites in the neonate following maternal overdose. Br J Clin Pharmacol 1984; 18:201–206.
57. Wiegand TJ, Margaretten M, Olson KR. Massive acetaminophen ingestion with early metabolic acidosis and coma: treatment with IV NAC and continuous venovenous hemodiafiltration. Clin Toxicol (Phila) 2010; 48:156–159.
58. Wu ML, Tsai WJ, Deng JF, Yang CC. Hemodialysis as adjunctive therapy for severe acetaminophen poisoning: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 1999; 62:907–913.
59. Sivilotti ML, Good AM, Yarema MC, Juurlink DN, Johnson DW. A new predictor of toxicity following acetaminophen overdose based on pretreatment exposure. Clin Toxicol (Phila) 2005; 43: 229–234.
60. Chomchai S, Chomchai C, Anusornsuwan T. Acetaminophen psi parameter: a useful tool to quantify hepatotoxicity risk in acute acetaminophen overdose. Clin Toxicol (Phila) 2011; 49:664–667.
61. Oie S, Lowenthal DT, Briggs WA, Levy G. Effect of hemodialysis on kinetics of acetaminophen elimination by anephric patients. Clin Pharmacol Ther 1975; 18:680–686.
62. Marbury TC, Wang LH, Lee CS. Hemodialysis of acetaminophen in uremic patients. Int J Artif Organs 1980; 3:263–266.
63. Sivilotti ML, Juurlink DN, Garland JS, Lenga I, Poley R, Hanly LN, Thompson M. Antidote removal during haemodialysis for massive acetaminophen overdose. Clin Toxicol (Phila) 2013; 51:855–863.
64. Cohen SD, Khairallah EA. Selective protein arylation and acetaminophen-induced hepatotoxicity. Drug Metab Rev 1997; 29:59–77.
65. Miners JO, Drew R, Birkett DJ. Mechanism of action of paracetamol protective agents in mice in vivo. Biochem Pharmacol 1984; 33: 2995–3000.
66. Prescott LF, Roscoe P, Wright N, Brown SS. Plasma-paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. Lancet 1971; 1:519–522.
67. Orozco BS, Gray Iii T, Setzer SC, Cole JB. Redistribution of acetaminophen following hemodialysis in the setting of massive overdose. Clin Toxicol 2013; 51:608.
68. Hernandez SH, Howland MA, Schiano T, Hoffman RS. Pharmacokinetics of N-acetylcysteine during renal replacement therapies (RRTs). Clin Toxicol 2013;51:579.