FAKULTNÍ NEMOCNICE PLZEŇ
I. INTERNÍ KLINIKA
BIOMEDICÍNSKÉ CENTRUM

KDY INDIKUJI RRT U INTOXIKACÍ

Jaroslav Raděj
XIII. KONGRES ČESKÉ SPOLEČNOSTI INTENZIVNÍ MEDICÍNY 24. - 26. dubna 2019 v Praze

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2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report

Table 1A. AAPCC population served and reported exposures (1983–2017).

Year	No. of participating centers	Population served (in millions)	Human exposures	Exposures per thousand population
2015	55[g]	325.4[h]	2,168,371	6.7
2016	55	327.0[i]	2,159,032	6.6
2017	55	330.4[j]	2,115,186	6.4

Table 17D. Substance categories most frequently identified in drug identification calls (Top 25).

Substance (Major Generic Category)	All substances	%[a]
Analgesics	38,765	33.78
Sedative/Hypnotics/Antipsychotics	20,449	17.82
Unknown Drug	8,271	7.21
Cardiovascular Drugs	6,916	6.03
Antidepressants	5,704	4.97
Muscle Relaxants	5,069	4.42
Anticonvulsants	4,919	4.29

DD Gummin. Clinical Toxicology, 2018

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2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report

Therapy	ns by age. 6–12 y	13–19 y	>=20 y	Unknown child	Unknown adult	Unknown ag	Total
Hemodialysis		15	2,487	2	5		2,629
Hemoperfusion		1	36	0	0		38
Extracorp. procedure (other)		8	143	0	0		154

hemodialýza v 0,12% případů

DD Gummin. Clinical Toxicology, 2018

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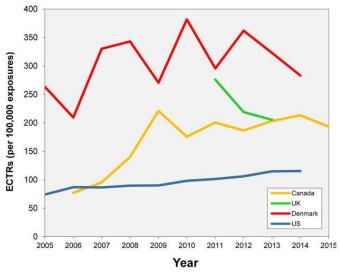
Practice Trends in the Use of Extracorporeal Treatments for Poisoning in Four Countries



M Ghannoum. Semin Dial, 2016

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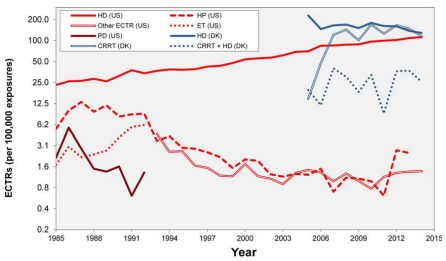
Practice Trends in the Use of Extracorporeal Treatments for Poisoning in Four Countries



M Ghannoum. Semin Dial, 2016

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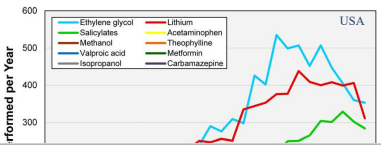
Practice Trends in the Use of Extracorporeal Treatments for Poisoning in Four Countries



	United States	Canada	Denmark	United Kingdom
1	Ethylene glycol (n = 7831; 3.9%)	Methanol (n = 413; 5.7%)	Salicylates (n = 140)	Ethylene glycol[b] (n = 150; 24.0%)
2	Lithium (n = 7315; 4.1%)	Ethylene glycol (n = 315; 5.9%)	Lithium (n = 109)	Acetaminophen (n = 30; 0.2%)
3	Salicylates (n = 4551; 0.4%)	Salicylates (n = 254; 1.8%)	Barbiturates (n = 48)	Ethanol (n = 23; 0.3%)
4	Acetaminophen (n = 2668; 0.1%)	Lithium (n = 251; 7.6%)	Valproic acid (n = 39)	CCBs (n = 23; 1.4%)
5	Methanol (n = 1749; 2.2%)	Acetaminophen (n = 96; 0.1%)	Ethanol (n = 36)	Valproic acid (n = 20; 2.1%)
6	Theophylline (n = 1235; 1.6%)	Valproic acid (n = 68; 1.5%)	Metformin (n = 26)	Salicylates (n = 18; 0.7%)
7	Ethanol (n = 770; 0.0%)	Ethanol (n = 51; 0.3%)	Carbamazepine (n = 16)	Benzodiazepines (n = 22; 0.6%)
8	Valproic acid (n = 701; 0.3%)	Benzodiazepines (n = 44; 0.2%)	Pregabalin (n = 16)	Lithium (n = 15; 2.7%)
9	Cardiac glycosides (n = 690; 0.5%)	Metformin (n = 41; 1.2%)	Lamotrigine (n = 13)	Metformin (n = 15; 1.3%)
10	Metformin (n = 633; 0.5%)	Carbamazepine (n = 21; 0.6%)	Magnesium (n = 12)	Methanol (n = 15; 2.8%)

M Ghannoum. Semin Dial, 2016

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diagnostika

zábrana expozice

antidotum

zvýšení eliminace

podpůrná opatření

symptomatická léčba

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ACETYLSALICYLIC ACID INTOXICATION

A PROPOSED METHOD OF TREATMENT

Lieutenant (jg) Paul D. Doolan, Medical Corps, United States Navy,
William F. Walsh, M.D., Laurence H. Kyle, M.D.
and
Henry Wibinsky, M.S., Washington, D. C.

Fatalities resulting from acetylsalicylic acid (aspirin) intoxication are rare,[1] but when sufficient amounts are taken the drug is an effective suicidal agent. The exact lethal dose is unknown, but death has followed doses of as little as 2 Gm.[2] However, adults must ordinarily ingest 15 to 30 Gm. before a fatality will ensue. Salicylates inflict pathological lesions of an irreversible nature in the central nervous system, and treatment, in the absence of a specific antidote, depends on rapid removal from the body. Normally, the kidney is the chief route of excretion. When suicidal amounts are ingested, severe renal impairment may occur, and this complication or the presence of antecedent renal disease imposes formidable obstacles to treatment.[3]

REPORT OF A CASE

A 39 year old white man was first admitted, in coma, to another hospital at 6:45 p. m. It was learned from his wife that he had consumed 140 five grain (0.30 Gm.) acetylsalicylic acid tablets that day, in addition to an unknown quantity during the preceding 24 hours. He was drenched with perspiration. The respirations, although only 26 per minute, were extremely deep. The tendon reflexes were absent, and the right pupil reacted sluggishly to light. The prothrombin time was 17.5 seconds, or 50 per cent prothrombin content. Because of the patient's moribund condition, he was transferred to Georgetown University Hospital for treatment with the artificial kidney. He arrived at this hospital about 11 p. m. on the same day, his condition remaining unchanged except for extreme restlessness. Lumbar puncture revealed clear fluid, and the electrocardiogram did not show any changes suggestive of alkalosis. He was given dextrose in water, ascorbic acid and vitamin K oxide before the artificial kidney was used. Great technical difficulty was encountered with the dialysis because of the patient's restlessness, and the procedure had to be terminated at the end of one hour. Barbiturates and paraldehyde were used in very small doses, since sedatives have been reported to potentiate the toxic effects of the salicylates on the central nervous system.[4] His condition remained critical; slight cyanosis appeared, and he died at 5 a. m. the following day, apparently of respiratory failure. Necropsy disclosed petechial hemorrhages throughout the cerebrum, brain stem, visceral peritoneum and mesentery. Further history obtained after the patient's death revealed that he had been consuming acetylsalicylic acid tablets by the bottle for the preceding 12 days. Signs and symptoms of salicylism had appeared three days prior to admission, when he began to complain of nausea, vomiting, tinnitus and deafness.

Despite the fact that only one hour of dialysis was accomplished, 1,300 mg. of salicylic acid were removed in the bath, the blood containing 57.5 mg. per 100 cc. Consequently, further test of the procedure appeared worth while. Salicylates were determined by the method of Keller with slight modifications.[5] The type of artificial kidney used was a modified Kolff model.[6]

PD Doolan. JAMA, 1951

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George E Schreiner

Benefit vs. riziko ECTR u intoxikace

- ✓ závažný průběh intoxikace
- ✓ intoxikace je vysoce riziková absorbovaným množstvím toxinu
- ✓ absence možného účinného konzervativního postupu nebo antidota

Zejména je metoda ECTR indikována, pokud se zdravotní stav pacienta zhoršuje přes vyčerpaná podpůrná a konzervativní opatření.

- ✓ předpoklad účinného zvýšení eliminace noxy

V ideálním případě nízká endogenní clearance toxinu vs. vysoká účinnost eliminace extrakorporální metodou.

- ✓ poškozen přirozený mechanismus eliminace toxické látky

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Benefit vs. riziko hemodialýzy u intoxikace

- ✓ závažný průběh intoxikace, zejména špatně reagující na podpůrná a konzervativní opatření
- ✓ intoxikace je vysoce riziková absorbovaným množstvím toxinu
- ✓ absence možného účinného konzervativního postupu nebo antidota
- ✓ zkrácení doby nutných podpůrných opatření, monitorace, léčby antidotem

- ✓ předpoklad účinné difuze semipermiabilní membránou:
  high-flux high-efficiency dialyzátor (M_r do 15 kDa; V_D < 1 l/kg; PPB < 80 %

- ✓ poškození funkce ledvin
- ✓ těžká metabolická acidóza, iontové poruchy, hyperhydratace

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hemodialýza je indikována u závažné intoxikace:

alkoholy a glykoly; lithium; metformin; salicylová kyselina; theofylin; valproová kyselina

hemodialýza může být použita u závažné intoxikace:

acebutolol; antimikrobiální léky (některé); atenolol; baklofen; barium; boritá kyselina; bromidy; cyklofosfamid; dabigatran; dapson; fenobarbital; fenytoin; gabapentin; chloralhydrát; jod; kalcium; kalium; karbamazepin; lisinopril; magnézium; meprobamat; methotrexat; mexiletin; nadolol; paracetamol; pregabalin; primidon; prokainamid; sotalol; těžké kovy a jejich chelátové komplexy

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EXTRIP

THE EXTRACORPOREAL TREATMENTS IN POISONING WORKGROUP

Blood Purification in Toxicology: *Reviewing the Evidence and Providing Recommendations*

OBJECTIVES | PUBLICATIONS | RECOMMENDATIONS | NEWS & EVENTS | PARTICIPANTS | REPRESENTED SOCIETIES

REPRESENTED SOCIETIES

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
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 of Emergency Medicine
European Society of Intensive Care Medicine
French Language Society of Resuscitation
German Society of Nephrology
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

EXTRIP, The Extracorporeal Treatments In Poisoning workgroup
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Table 7. Summary of the effect for dialyzability.

Dialyzability[&]	Primary criteria % Removed*	Alternative criteria 1 CL_{EC}/CL_{TOT} (%)[#]	Alternative criteria 2 $T_{1/2\,EC}/T_{1/2}$ (%)	Alternative criteria 3 Re_{EC}/Re_{TOT} (%)[#]
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

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

Type of statements for proposal:

1) *Toxicokinetic statement*: Poison X is (Dialyzable, Moderately dialyzable, Slightly dialyzable, Not dialyzable) by ECTR (GRADE equivalent). EXAMPLE: Salicylates are moderately dialyzable by ECTR (A).
2) *General statement*: (We recommend/ We suggest/ it would be reasonable/ no agreement reached) to (perform/not perform) ECTR in severe poisoning with "X" (GRADE). EXAMPLE: We recommend performing ECTR in severe salicylate poisoning (1D).
3) *Specific statements*: If there is support for performing ECTR, other statements (with grade) will be submitted; indications of initiating ECTR (ingestion, level, special population, symptoms, clinical markers), when to discontinue ECTR, preferable ECTR modality, particularities of ECTR with the particular poison (timing, special population, technical).

V Lavergne. Clin Toxicol (Phila), 2012

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EXECUTIVE SUMMARY OF RECOMMENDATIONS

SALICYLATES POISONING

Lithium
Salicylates
Thallium
Theophylline
Valproic Acid

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EXECUTIVE SUMMARY OF RECOMMENDATIONS

SUBSTANCES

Acetaminophen
Barbiturates
Carbamazepine
Digoxin
Lithium
Metformin
Methanol
Phenytoin
Salicylates
Thallium
Theophylline
Tricyclic Antidepressants
Valproic Acid

GRADE A až D (vysoká až velmi nízká úroveň evidence)
síla konsenzuálního doporučení: 1= silné doporučení (doporučují…)
2= slabé doporučení (navrhují…)
3= neutrální doporučení (bylo by rozumné…).

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	zvýšený osmolální gap		metabolická acidóza se zvýšeným anion gapem	
dietylenglykol	ADH	2-hydroxy-ethoxyacet-aldehyd	ALDH	kyselina 2-hydroxyethoxyoctová/HEacetát kyselina diglykolová/diglykolát
etylenglykol	ADH	glykolaldehyd	ALDH	kyselina glykolová/glykolát kyselina glyoxalová/glyoxalát kyselina šťavelová/oxalát
metanol	ADH	formaldehyd	ALDH	kyselina mravenčí/formiát
propylenglykol	ADH	laktaldehyd	ALDH	kyselina mléčná/laktát kyselina pyrohroznová/pyruvát

ADH alkoholdehydrogenáza, ALDH aldehyddehydrogenáza

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Use of extracorporeal treatments in the management of poisonings

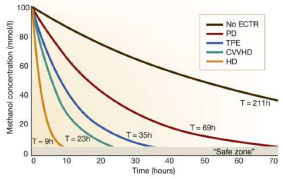

Figure 3 | Simulation of the effect of different extracorporeal treatments for methanol poisoning. Theoretical model of a methanol-poisoned patient with an initial concentration of 100 mmol/l (320 mg/dl) treated with fomepizole and either nothing, hemodialysis (HD), continuous venovenous hemodialysis (CVVHD), therapeutic plasma exchange (TPE), or peritoneal dialysis (PD). The time (T) to achieve a safe plasma concentration is shown. Assumptions are V_D = 0.6 l/kg, weight = 70 kg, endogenous body clearance of methanol with fomepizole = 10 ml/min, HD methanol clearance = 240 ml/min, CVVHD methanol clearance = 80 ml/min, TPE methanol clearance = 50 ml/min, and PD methanol clearance = 20 ml/min.[32]

M Ghannoum. Kidney Int., 2018

clearance [ml/min]	IHD	CRRT
metanol	208,0	36,7
karbamazepin	59,6	18,5
lithium	106,9	43,1
metformin	148,0	34,0
salicyláty	41,0	5,5
theofylin	82,8	64,2
valproát	87,5	11,0

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Intermitentní hemodialýza vs. CVVHD

IHD

- ✓ **účinnější clearance noxy**
- ✓ **rychlejší korekce vnitř. prostředí**

Q_d 30 l/hod

- ✓ kratší doba antikoagulace, popř. proplachy mimotělního okruhu
- ✓ kratší doba nutné monitorace vnitř. prostředí, imobilizace,…
- ✓ 3-4x nižší cena

CVVHD (CRRT)

- ✓ **lepší hemodynamická tolerance ? vs. 4,8 l/hod**

Co je významná hemodynamická nestabilita?
↓ lepší hemodynamická tolerance
pokles TK 10-70 % při IHD; 40-60 % při SLED; do 50 % při CRRT

- ➢ isovolemické napojení
- ➢ start s nižším krútokem krve
- ➢ D-Na ≥ 145 mmol/l, modelování
- ➢ nižší teplota dialyzátu (start např. 36 °C)
- ➢ vyřazení netto ultrafiltrace
- ➢ bikarbonátový roztok

A Douvris. Crit Care, 2018
F Schortgen. Am J Respir Crit Care Med, 2000

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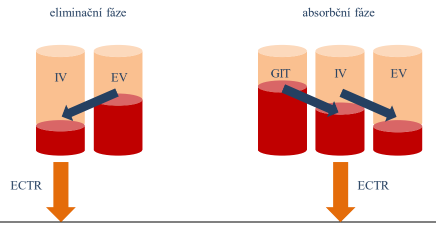
Rebound fenomén



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Metformin-associated lactic acidosis, MALA
Metformin-induced lactic acidosis, MILA

Endogenní clearance metforminu při normální funkci ledvin je 500-600 ml/min.

- ✓ eliminace kumulovaného léku/toxinu a **korekce vnitřního prostředí**
- ➢ **dávka ECTR** vs. hemodynamická nestabilita (IHD, SLED, CRRT)
- ✓ **dávka ECTR** vs. riziko disekvilibria (hypernatremie při alkalizaci, zvýšení D-Na)
- ✓ **intolerance citrátové antikoagulace je pravděpodobná**

Nephrol Dial Transplant. 2004 Aug;19(8):2157-8.
Combination of intermittent haemodialysis and high-volume continuous haemofiltration for the treatment of severe metformin-induced lactic acidosis.
Panzer U, Kluge S, Kreymann G, Wolf G.

Nephrol Dial Transplant. 2006 Jul;21(7):2038-9. Epub 2006 Jan 31.
Combined renal replacement therapy for severe metformin-induced lactic acidosis.
Friesecke S, Abel P, Kraft M, Gerner A, Runge S.

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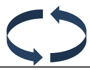
Hemoperfuze na ústupu

- ✓ M_w 5-10 kDa; PPB < 90 %; **lipofilní**
- ✓ extrakční poměr mnohdy = 1, CL až rovná Q_b
- ✓ **NÚÚ**: trombocytopenie, leukopenie, hypokalcemie, hypofosfatemie, hypoglykemie, hypofibrinogenemie a koagulopatie
- ✓ při Q_b nad 350 ml/min hrozí hemolýza
- ✓ vyšší nároky na antikoagulaci
- ✓ saturace adsorbéru á 2-4 hodin s nutnou výměnou
- ✓ cena 10x vyšší než IHD
- ✓ **nemožnost korekce vnitřního prostředí a volémie**
- ✓ **klesají zkušenosti**

nepoužívaná



nedostupná

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EXTRIP — THE EXTRACORPOREAL TREATMENTS IN POISONING WORKGROUP

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

Indications
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)

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)

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

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Shrnutí

- ✓ Léčíme pacienta, ne jed.
- ✓ ECTR indikuji podle klinického vývoje a reakce na léčbu, nebo ve snaze předejít katastrofickému vývoji.
- ✓ Pro efekt správně indikované ECTR u intoxikace je rozhodující dávka metody.
- ✓ V nasazení dominuje IHD, podle dostupnosti metody a zkušenosti.
- ✓ Hemodynamická nestabilita není absolutní kontraindikací IHD.
- ✓ Absence toxokinetických předpokladů noxy ještě nevylučuje úspěšné zvýšení eliminace metodou IHD při masivní intoxikaci.

Toxikologické informační středisko (TIS) Kliniky pracovního lékařství VFN a 1. LF UK v Praze

EXTRIP, www.extrip-workgroup.org

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Národní program udržitelnosti I (NPU I) č. LO1503 poskytovaný Ministerstvem školství, mládeže a tělovýchovy

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