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Renal replacement therapy (RRT) in management of poisonings

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UFR de
Médecine

No conflicts of interest to declare

Outline

I Introduction

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Extracorporeal Kidney-Replacement Therapy for Acute Kidney Injury

Stéphane Gaudry, M.D., Ph.D., Paul M. Palevsky, M.D., and Didier Dreyfuss, M.D.

N ENGL J MED 386;10 NEJM.ORG MARCH 10, 2022

Table 2. Indications for KRT in Critically Ill Patients.*

Urgent indications in patients with AKI

Refractory, severe hyperkalemia†
Refractory, severe metabolic acidosis†
Refractory, severe pulmonary edema†
Uremic complications: pericarditis, bleeding, and encephalopathy‡

Nonurgent indications

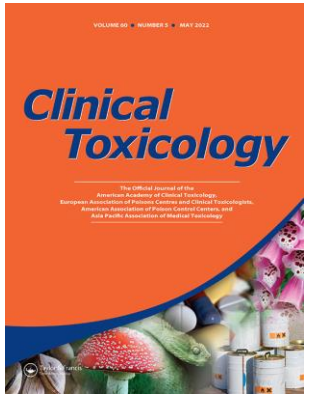
Persistent, severe AKI with blood urea nitrogen level >112 mg/dl, oliguria or anuria for more than 72 hr, or both§

No indications

Severe AKI (KDIGO stage 3) in the absence of complications¶
Sepsis in the absence of complicated AKI

Indications for RRT in the context of poisoning, apart from DETOXIFICATION, are the same as other critical states

I Introduction



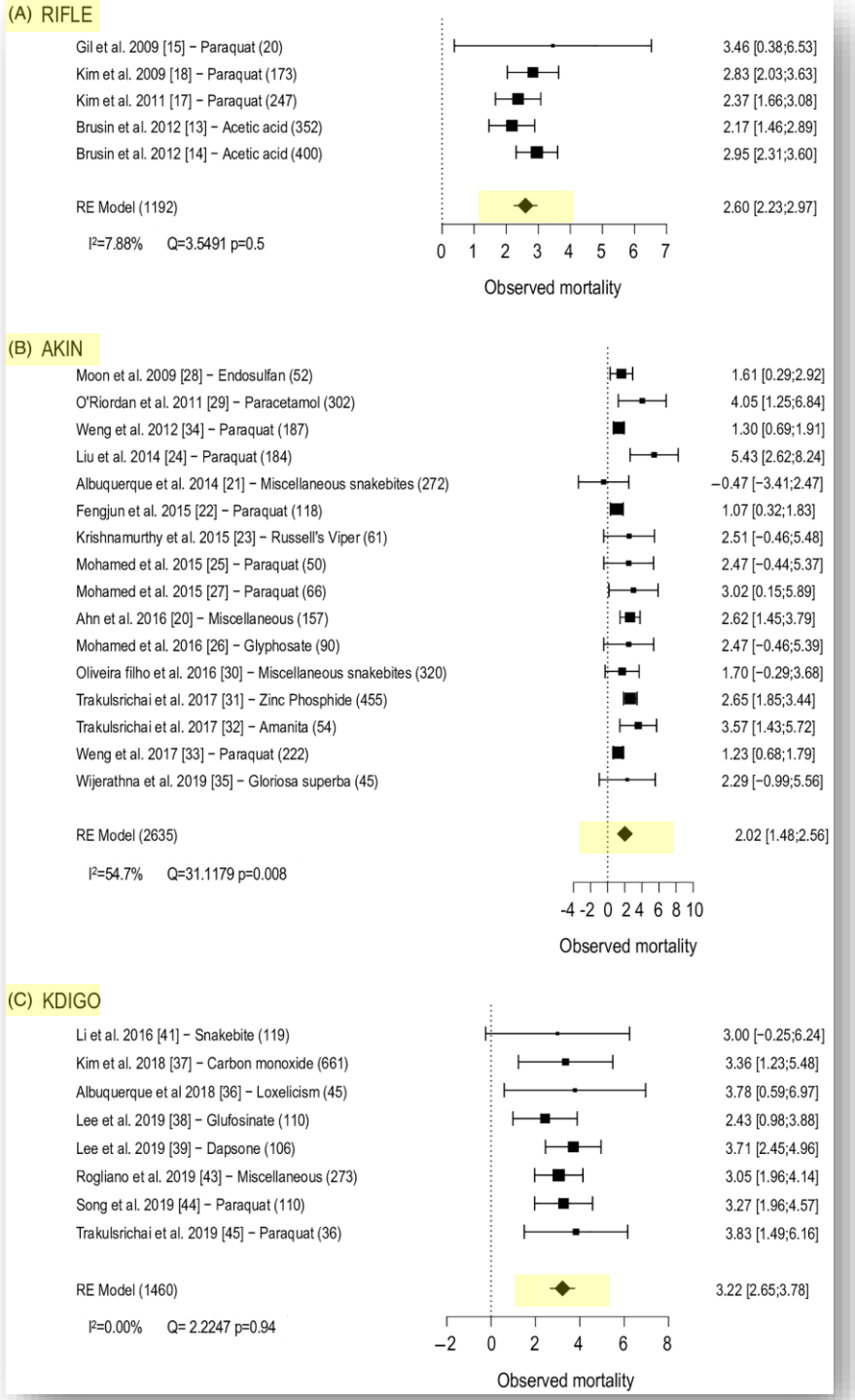
REVIEW

Relationship between acute kidney injury and mortality in poisoning – a systematic review and metanalysis

Dominique Vodovar[a,b,c], Hugo Peyre[c,d,e] and Bruno Mégarbane[b,c,f]

CLINICAL TOXICOLOGY
2021, VOL. 59, NO. 9, 771–779

International classifications linking AKI severity with mortality are also valid in the context of poisoning



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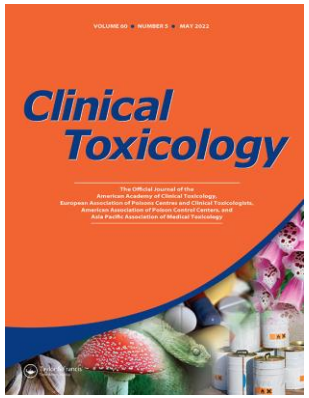

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N ENGL J MED 386;10 NEJM.ORG MARCH 10, 2022

The remainder of this presentation

will focus on the indications for RRT, in the context of poisoning, with the aim of ExtraCorporeal Toxin Removal (ECTR)

Outline

I Introduction

II Do I need ExtraCorporeal Toxin Removal (ECTR)

III Will ECTR using RRT benefit my patient?

IV Which RRT method(s) for ECTR?

V Who should be dialyzed?

VI Conclusion

II Do I need ExtraCorporeal Toxin Removal (ECTR)

1

Can exposure or poisoning lead to serious complications or even death?

Patient *40 years - 70 kg*

Medical history *Epilepsy treated with immediate-release sodium valproate*

Context *Therapeutic error with double intake of sodium Valproate (2g) 7 hours ago*

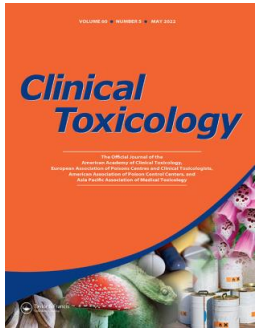
Presentation *No symptoms*

Suspected ingested dose : 30 mg/kg

Suspected Ingested Dose < 50 mg/kg

No symptom at H+6

No indication for extracorporeal toxin removal (ECTR)



PRACTICE GUIDELINE

Valproic acid poisoning: An evidence-based consensus guideline for out-of-hospital management

Clinical Toxicology (2008) **46**, 661–676

II Do I need ExtraCorporeal Toxin Removal (ECTR)

2 Can the toxicity be prevented/reversed by administering an antidote?

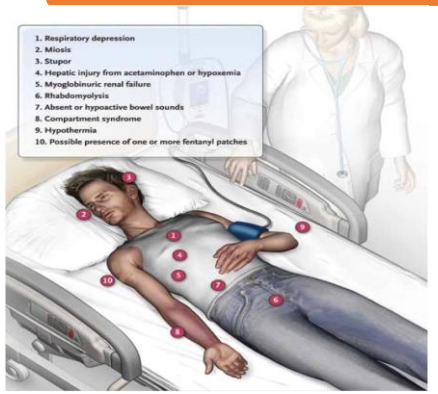
Patient *32 years - 72 kg*

Medical History *Unknown*

Context *Found on the street, a syringe at his side*

Presentation *Myosis - Calm coma - Bradypnea at 11/minute*

Opioid syndrome



No indication for extracorporeal toxin removal (ECTR)

Oxygen therapy
Naloxone titration and recovery after 0.2 mg

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Management of Opioid Analgesic Overdose

Edward W. Boyer, M.D., Ph.D.

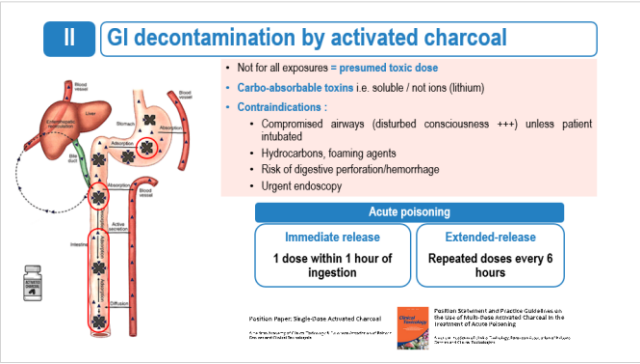
N ENGL J MED 367;2 NEJM.ORG JULY 12, 2012

II Do I need ExtraCorporeal Toxin Removal (ECTR)

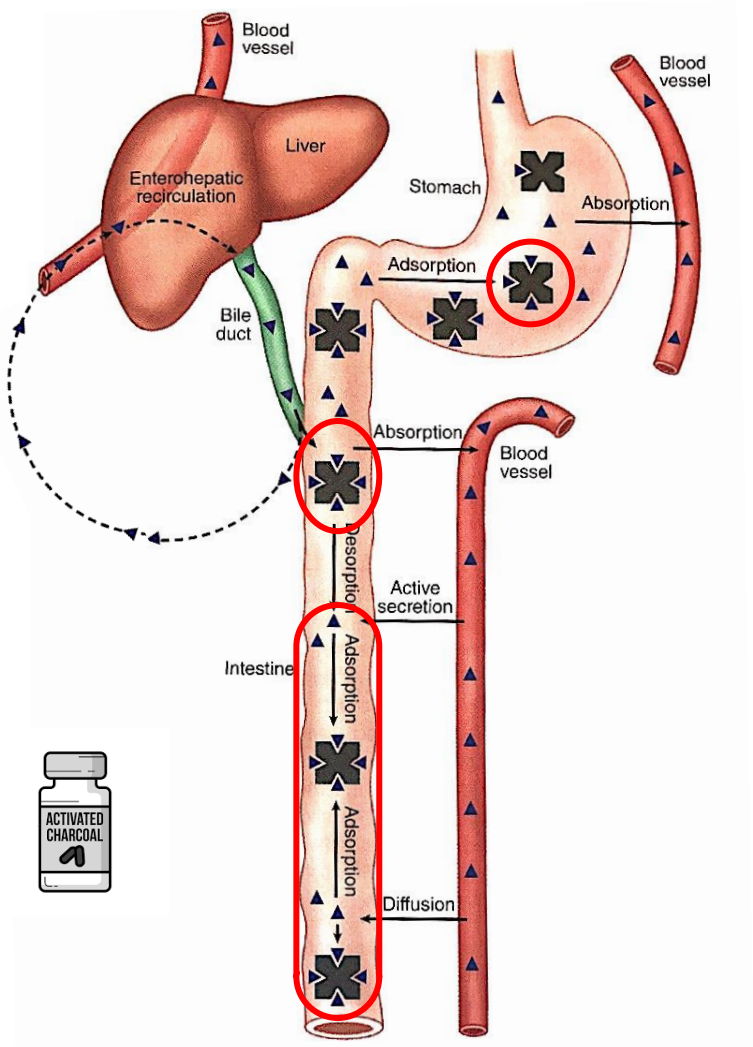
3

Can toxicity be minimized by a treatment that limits absorption or increases elimination?

Activated charcoal



II GI decontamination by activated charcoal



- Not for all exposures **= presumed toxic dose**
- **Carbo-absorbable toxins** i.e. soluble / not ions (lithium)
- **Contraindications :**
  - Compromised airways (disturbed consciousness +++) unless patient intubated
  - Hydrocarbons, foaming agents
  - Risk of digestive perforation/hemorrhage
  - Urgent endoscopy

Acute poisoning

Immediate release	Extended-release
1 dose within 1 hour of ingestion	**Repeated doses every 6 hours**

Position Paper: Single-Dose Activated Charcoal

American Academy of Clinical Toxicology & European Association of Poisons Centres and Clinical Toxicologists

Position Statement and Practice Guidelines on the Use of Multi-Dose Activated Charcoal in the Treatment of Acute Poisoning

American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists

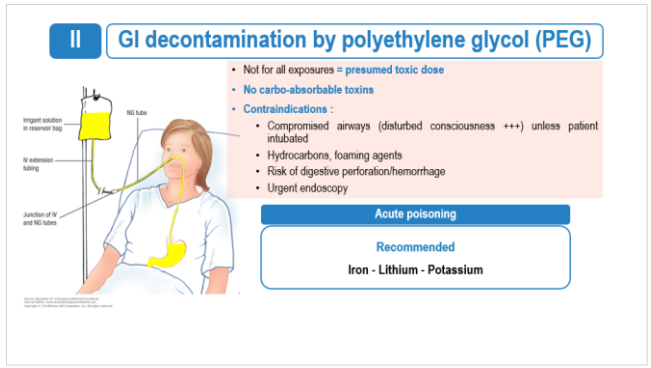
II Do I need ExtraCorporeal Toxin Removal (ECTR)

3

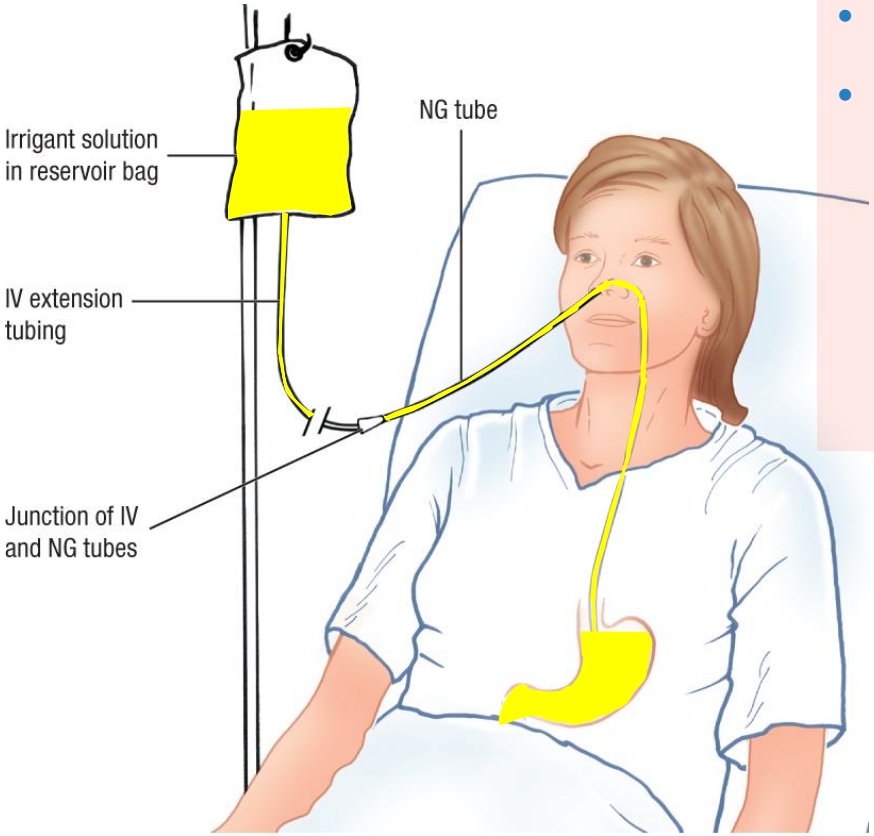
Can toxicity be minimized by a treatment that limits absorption or increases elimination?

Activated charcoal

Polyethylene glycol (PEG)



II GI decontamination by polyethylene glycol (PEG)



Source: Reichman EF: *Emergency Medicine Procedures, Second Edition:* www.accessemergencymedicine.com

- Not for all exposures **= presumed toxic dose**
- **No carbo-absorbable toxins**
- **Contraindications :**
  - Compromised airways (disturbed consciousness +++) unless patient intubated
  - Hydrocarbons, foaming agents
  - Risk of digestive perforation/hemorrhage
  - Urgent endoscopy

Acute poisoning

Recommended

Iron - Lithium - Potassium

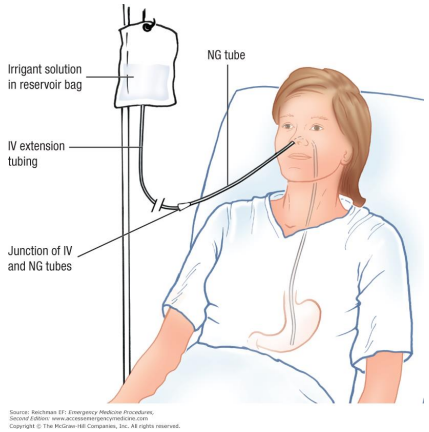
II Do I need ExtraCorporeal Toxin Removal (ECTR)

3

Can toxicity be minimized by a treatment that limits absorption or increases elimination?

Activated charcoal

Polyethylene glycol (PEG)



Alkaline diuresis

Greater elimination of salycilates at alkaline urine pH

II Do I need ExtraCorporeal Toxin Removal (ECTR)

1. **Can exposure or poisoning lead to serious complications or even death?**
   - No → No indication for extracorporeal toxin removal (ECTR)
   - Yes ↓
2. **Can this toxicity be prevented/reversed by administering an antidote?**
   - Yes → No indication for extracorporeal toxin removal (ECTR)
   - No ↓
3. **Can toxicity be minimized by a treatment that limits absorption or increases elimination?**
   - Yes → No indication for extracorporeal toxin removal (ECTR)
   - No ↓

I need ExtraCorporeal Toxin Removal

Outline

I Introduction

II Do I need ExtraCorporeal Toxin Removal (ECTR)

III Will ECTR using RRT benefit my patient?

IV Which RRT method(s) for ECTR?

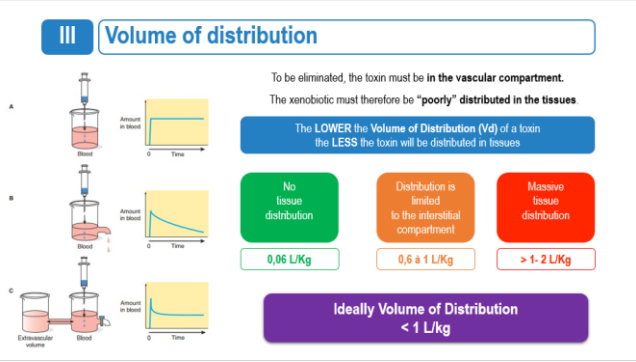
V Who should be dialyzed?

VI Conclusion

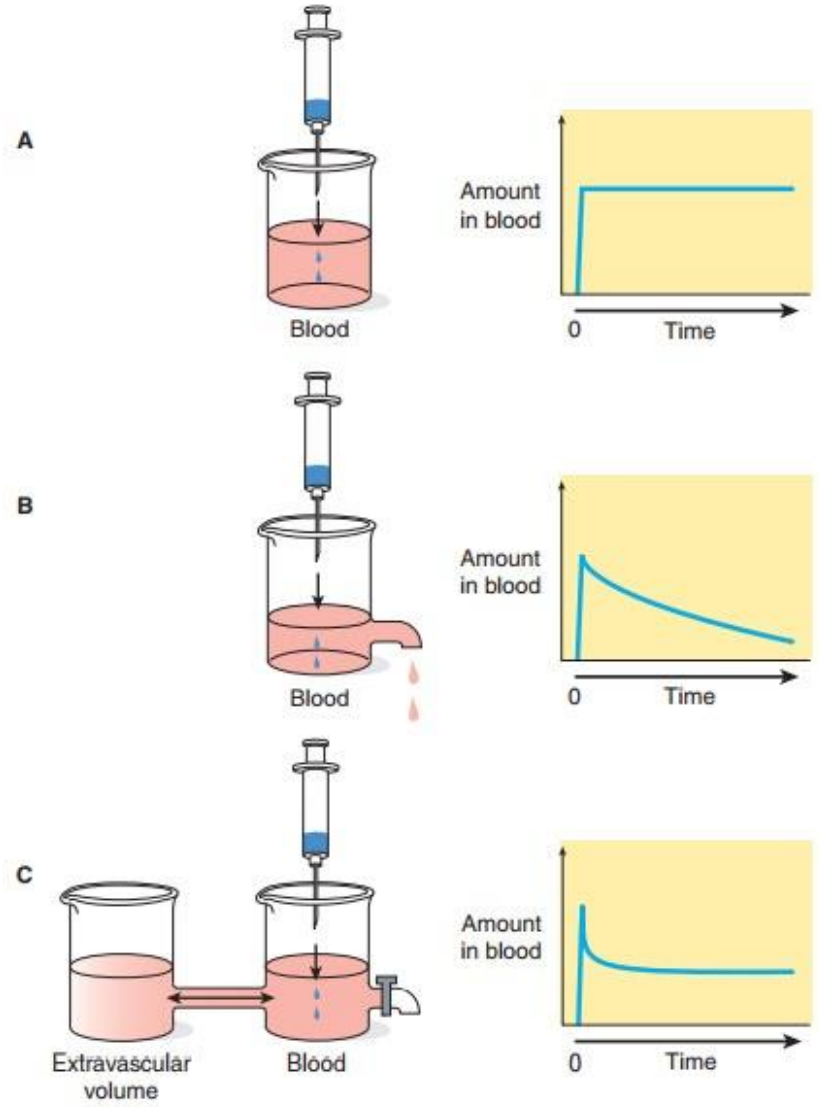
III Will ECTR using RRT benefit my patient?

1 Is the toxin theoretically eliminated by a RRT method?

Volume of distribution



III Volume of distribution



To be eliminated, the toxin must be **in the vascular compartment.**

The xenobiotic must therefore be **"poorly" distributed in the tissues**.

The **LOWER** the **Volume of Distribution (Vd)** of a toxin
the **LESS** the toxin will be distributed in tissues

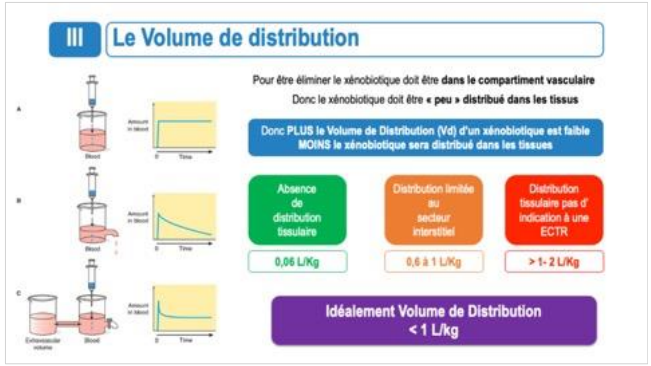
No tissue distribution	Distribution is limited to the interstitial compartment	Massive tissue distribution
0,06 L/Kg	0,6 à 1 L/Kg	> 1- 2 L/Kg

Ideally Volume of Distribution
< 1 L/kg

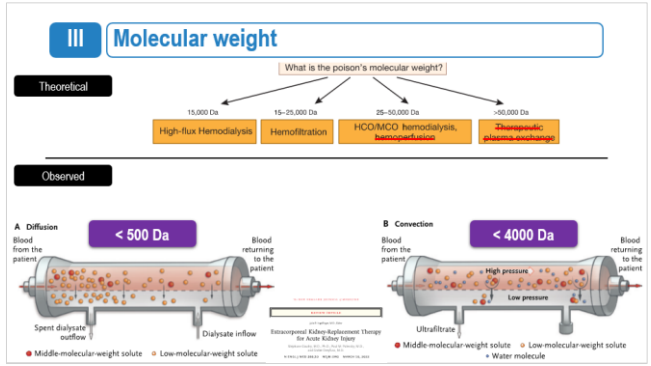
III Will ECTR using RRT benefit my patient?

1 Is the toxin theoretically eliminated an RRT method?

Volume de distribution



Molecular weight



III Molecular weight

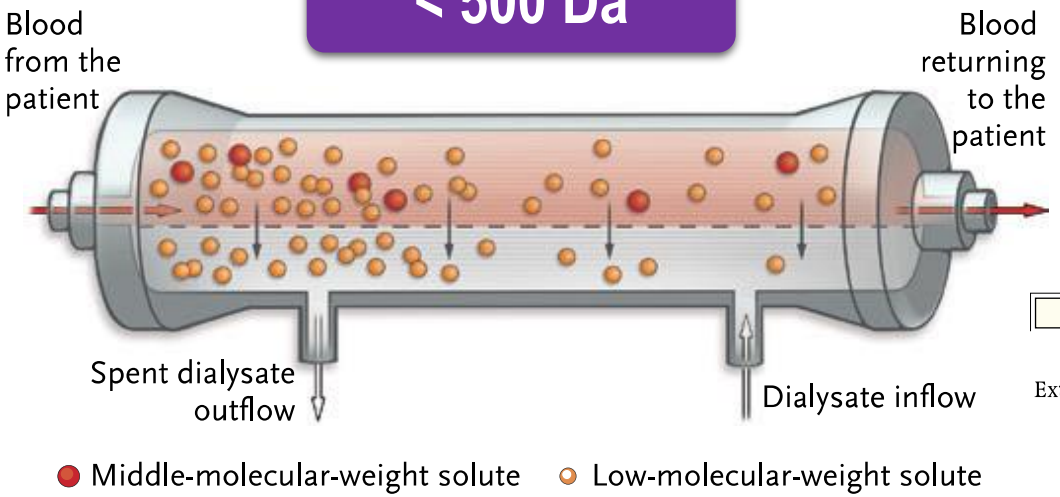
Theoretical

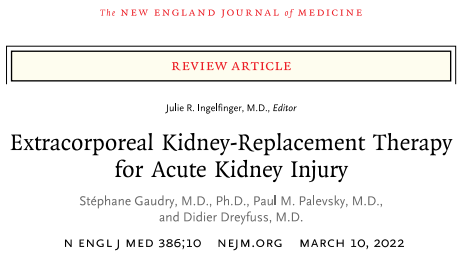
What is the poison's molecular weight?

15,000 Da	15–25,000 Da	25–50,000 Da	>50,000 Da
High-flux Hemodialysis	Hemofiltration	HCO/MCO hemodialysis, hemoperfusion	~~Therapeutic plasma exchange~~

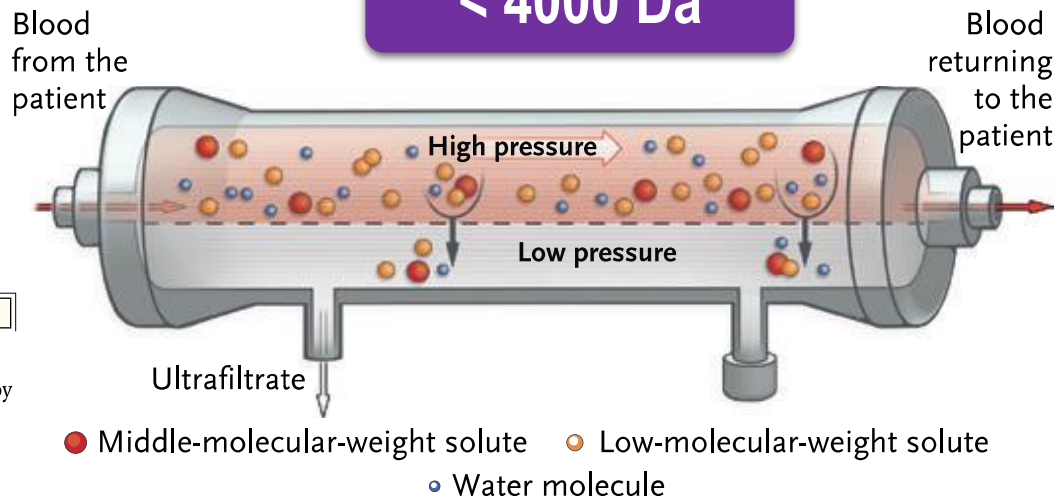
Observed

A Diffusion — **< 500 Da**





B Convection — **< 4000 Da**

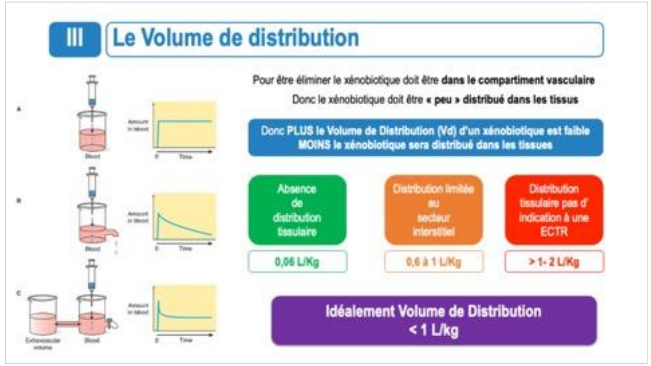


III Will ECTR using RRT benefit my patient?

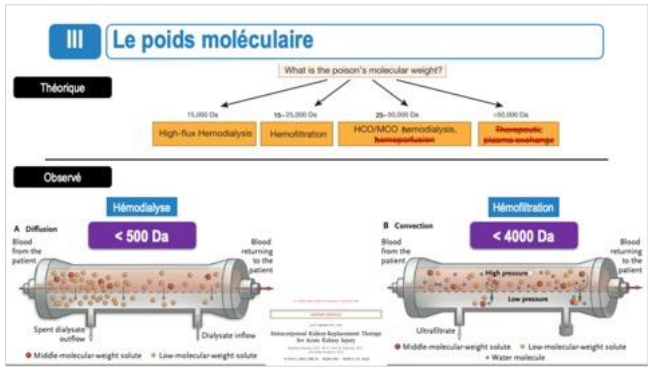
1

Is the substance theoretically eliminated by an ECTR technique?

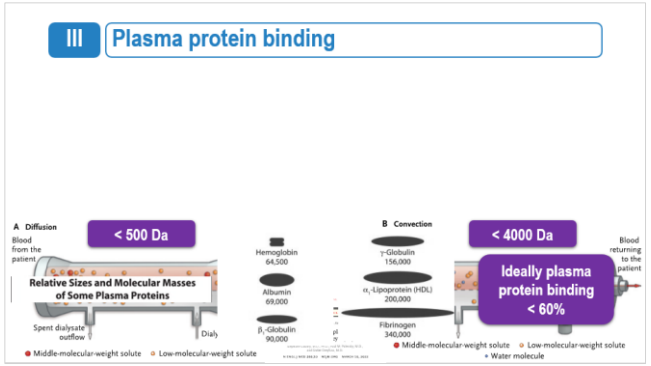
Volume de distribution



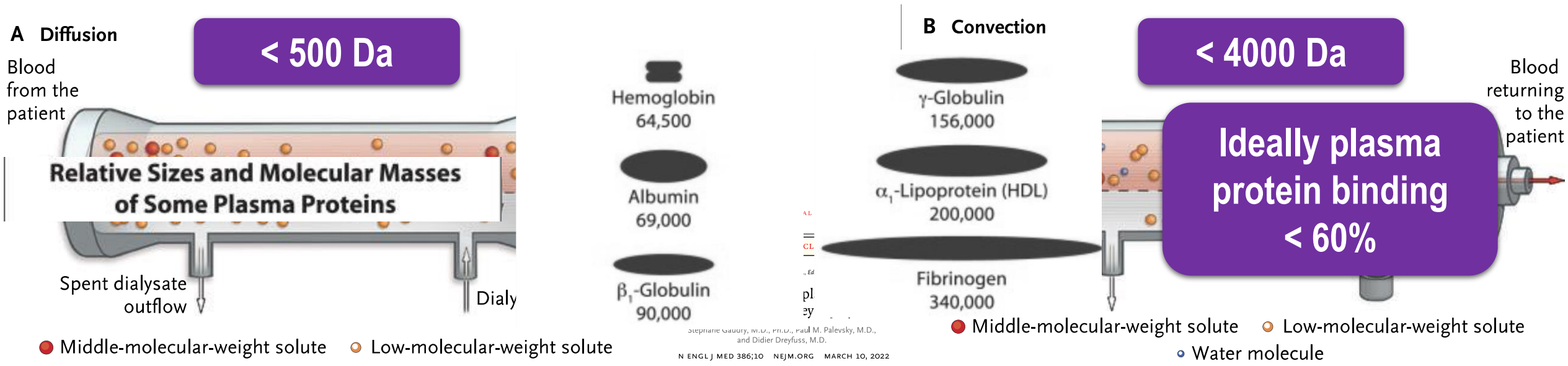
Molecular weight



Plasma protein binding



III Plasma protein binding



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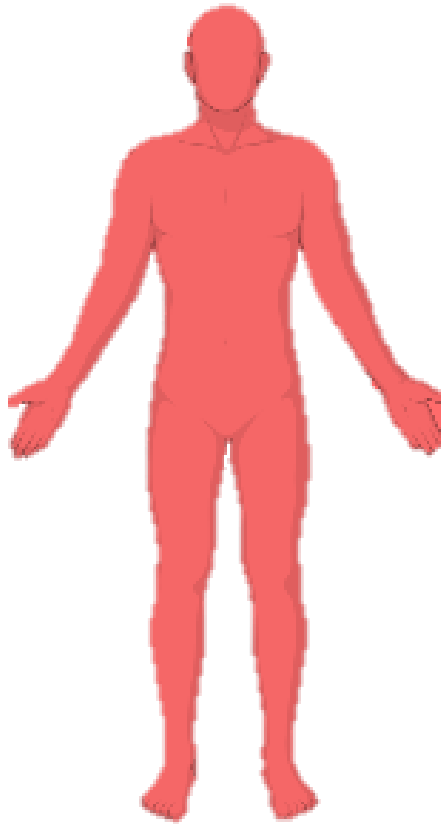
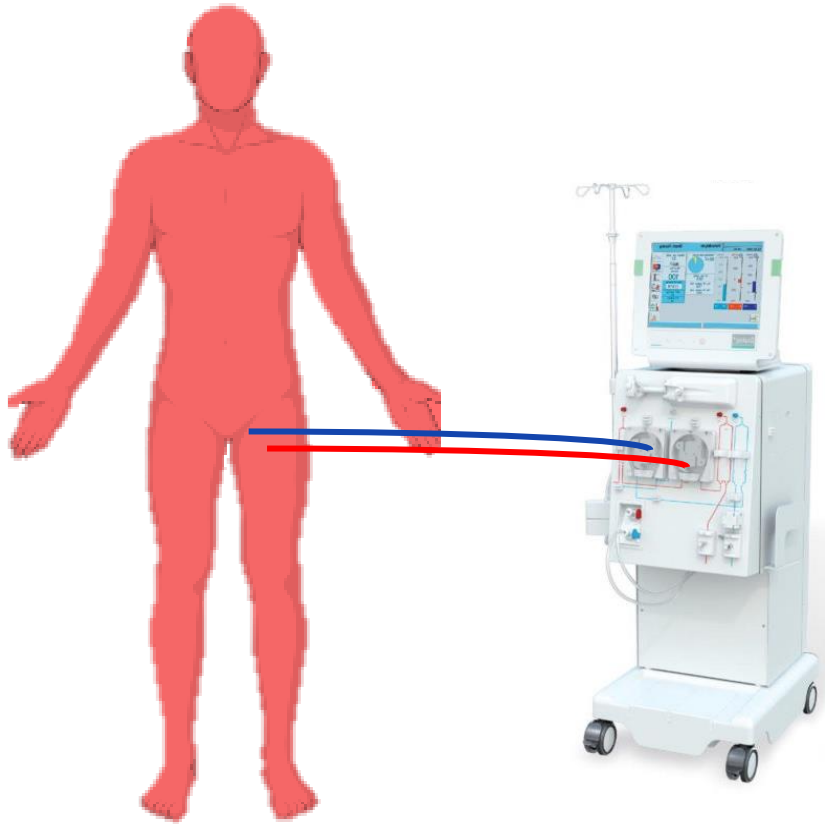
N ENGL J MED 386;10 NEJM.ORG MARCH 10, 2022

III Will ECTR using RRT benefit my patient?

2

Is the endogenous clearance of the toxin < 4 ml/min/kg?





III Will ECTR using RRT benefit my patient?

2 **Is the endogenous clearance of the toxin < 4 ml/min/kg?**

Metformine

Type of ECTR	ECTR Clearance (mL/min)		
	Median	Range	*n*
Endogenous (normal glomerular filtration rate, therapeutic dose)	500		
Hemodialysis	148	68–228	10

III Will ECTR using RRT benefit my patient?

3 Does ECTR improve clinical symptoms and/or outcome?

Eliminating the toxin is all well and good, **but it must improve the patient's clinical condition.**

No randomized controlled trial in clinical toxicology = case reports / retrospective series

Not all patients will benefit **= which patients will benefit from ECTR? = what criteria = clinical? dosage? biological abnormalities?**

Lithium

Xenobiotic	MW (Da)	Vd(L/kg)	Protein Bound (%)
Lithium	6.94	0.6-0.9	0

III Will ECTR using RRT benefit my patient?

3 Does ECTR improve clinical symptoms and/or outcome?

EXTRIP — THE EXTRACORPOREAL TREATMENTS IN POISONING WORKGROUP

Blood Purification in Toxicology:
Reviewing the Evidence and Providing Recommendations

General Recommendations

- ECTR is recommended in patients with severe Li poisoning (1D)

Indications

ECTR is recommended

- If kidney function is impaired and the [Li+].>4.0 mEq/L (1D)
- In the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias irrespective of [Li+] (1D)

ECTR is suggested

- if the [Li+].>5.0 mEq/L (2D)
- If confusion is present (2D)
- If the expected time to obtain a [Li+]<1.0 mEq/L with optimal management is >36 h (2D)

If EXTRIP+ criteria has been strictly followed

Finally, 101/128 patients would have been treated with ECTR if *All-EXTRIP$_{int}$* has been strictly followed; 22 were actually treated with ECTR

N=101	ECTR +	ECTR -
N (%)	22 (22)	79 (78)
Severe poisoning, N (%)	18 (81)	29 (36)***
Death, N (%)	1 (5)	3 (4)
Persistent neurological impairment on ICU discharge, N (%)	3 (14)	20 (26)
Both, N (%)	4 (19)	23 (30)
Length of ICU stay, days	14 [7; 21]	6 [3;11]**

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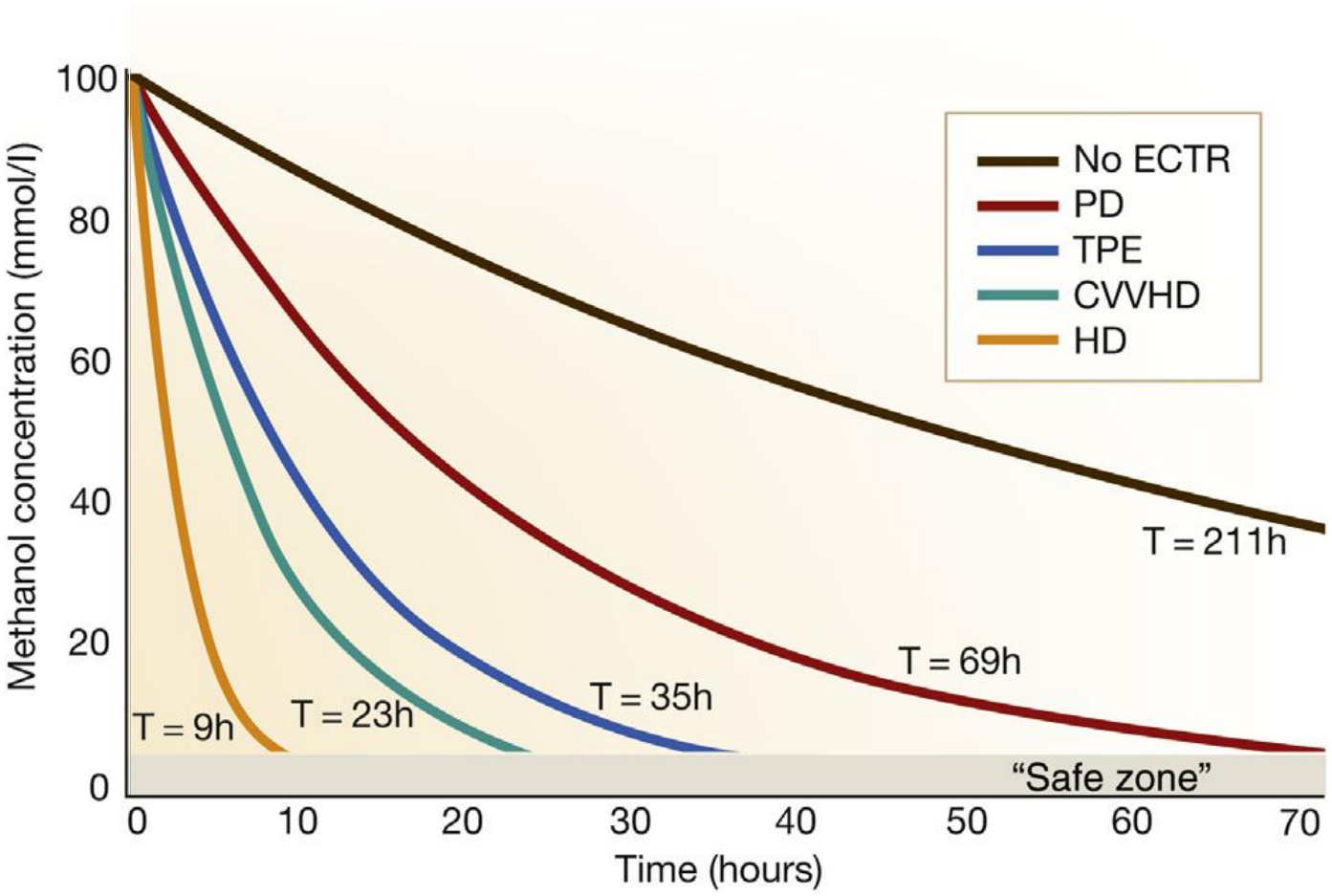
IV Which RRT method(s) for ECTR?

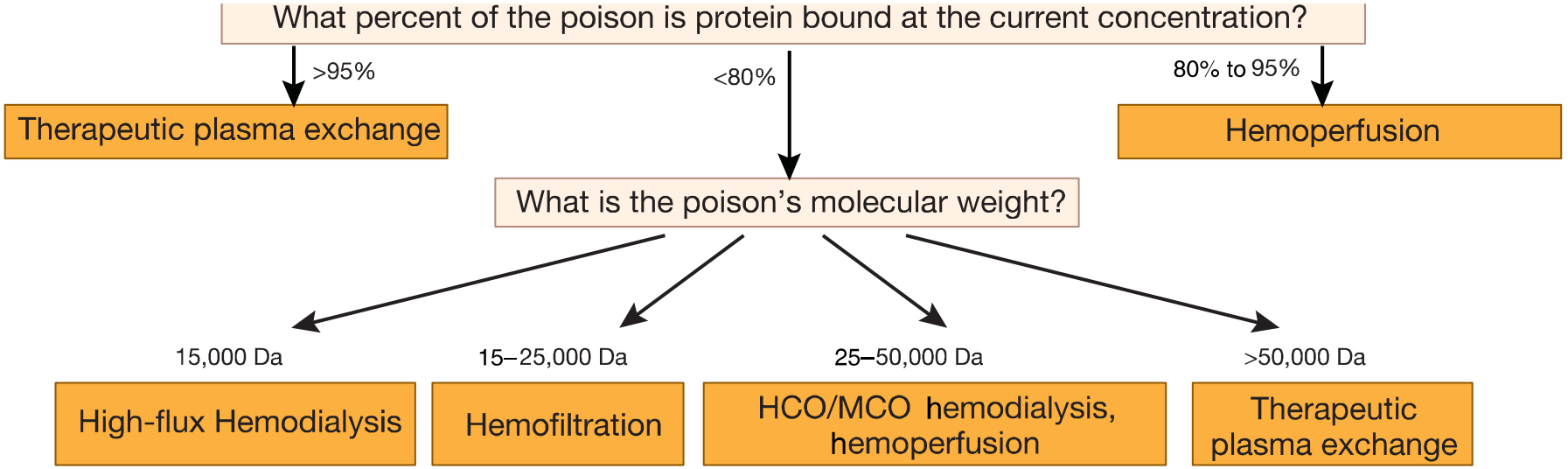
Methanol

Xenobiotic	MW (Da)	Vd(L/kg)	Protein Bound (%)
Methanol[23]	32	0.6-0.7	0

Intermittent



IV Which RRT technique(s) for ECTR?



REVIEW Open Access

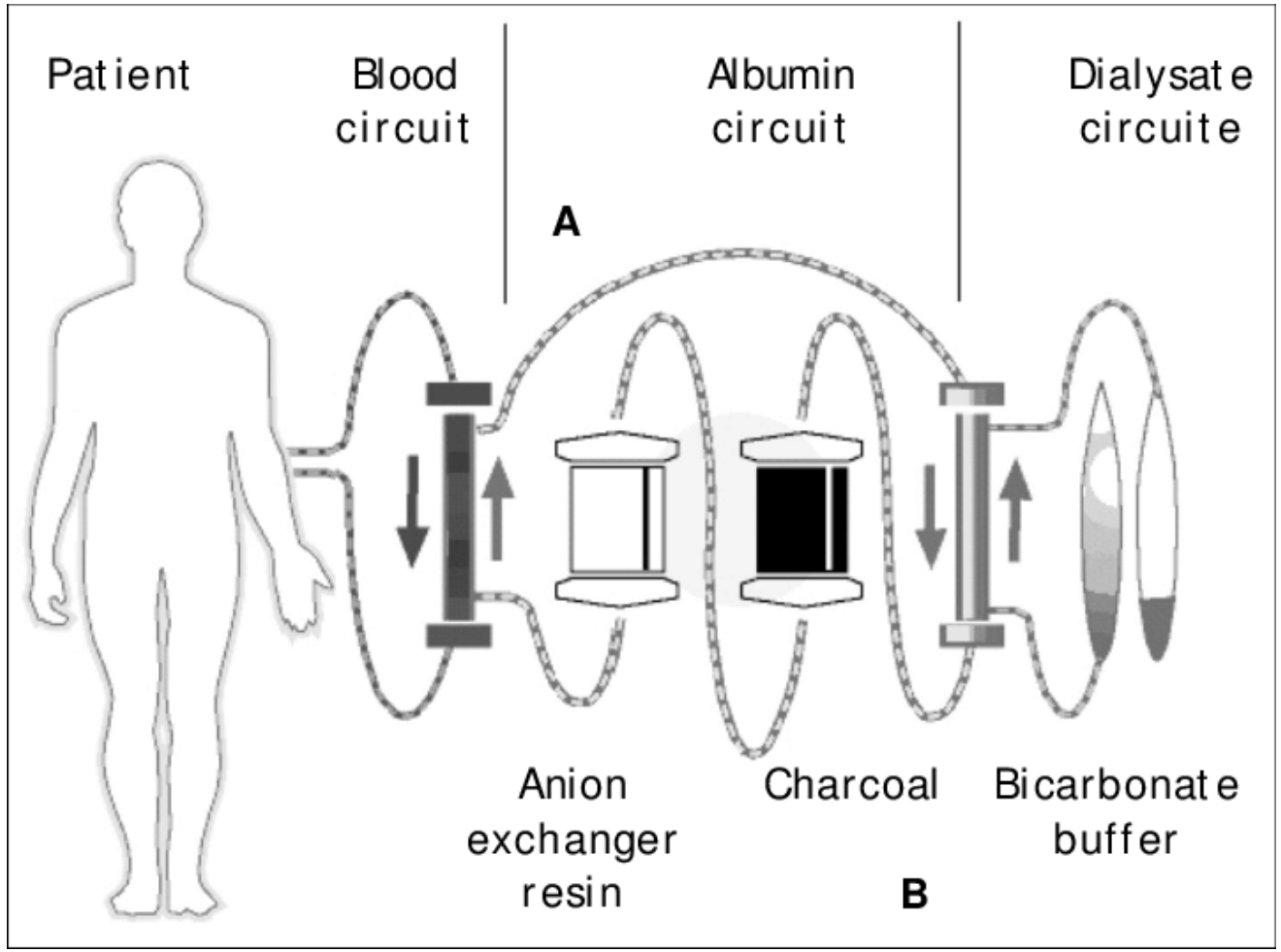
Management of pharmaceutical and recreational drug poisoning

Mégarbane *et al. Ann. Intensive Care* (2020) 10:157

However, at the present time, **there is no scientific evidence to support the superior efficacy of these techniques** in terms of elimination of the toxin or decreased severity of the clinical features or morbidity and mortality.

IV Which RRT method(s) for ECTR?

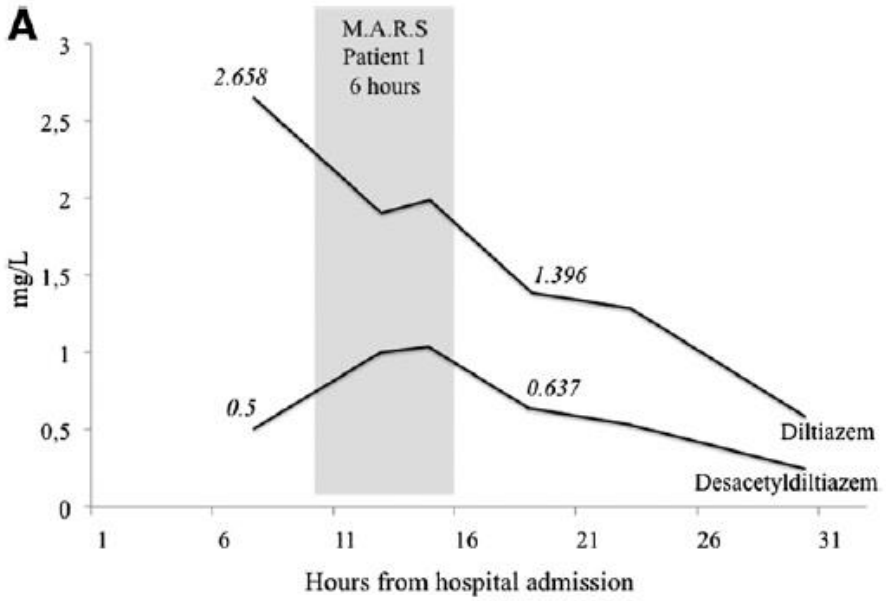
Albumine dialysis

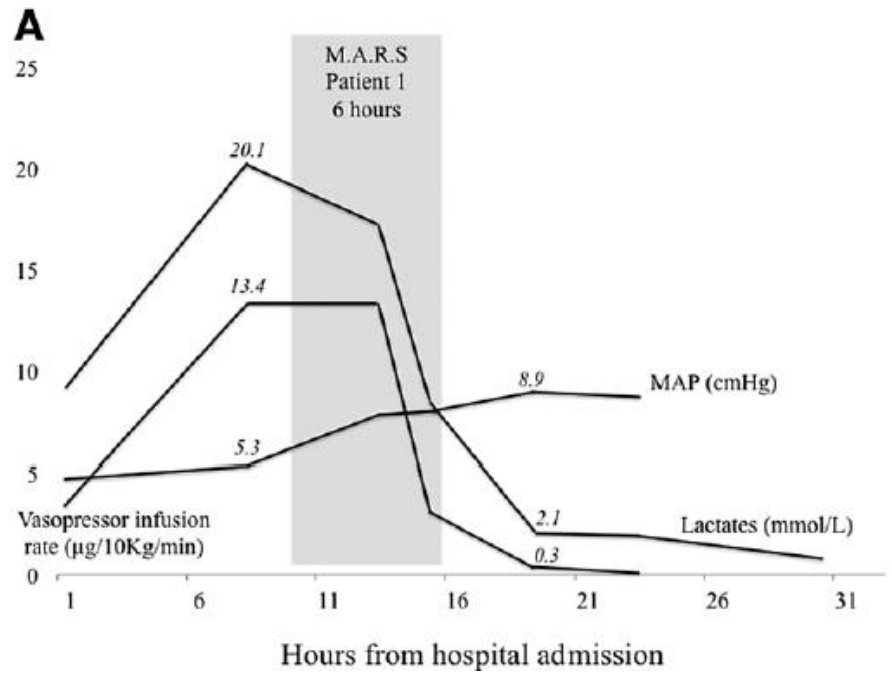


IV Which RRT method(s) for ECTR?

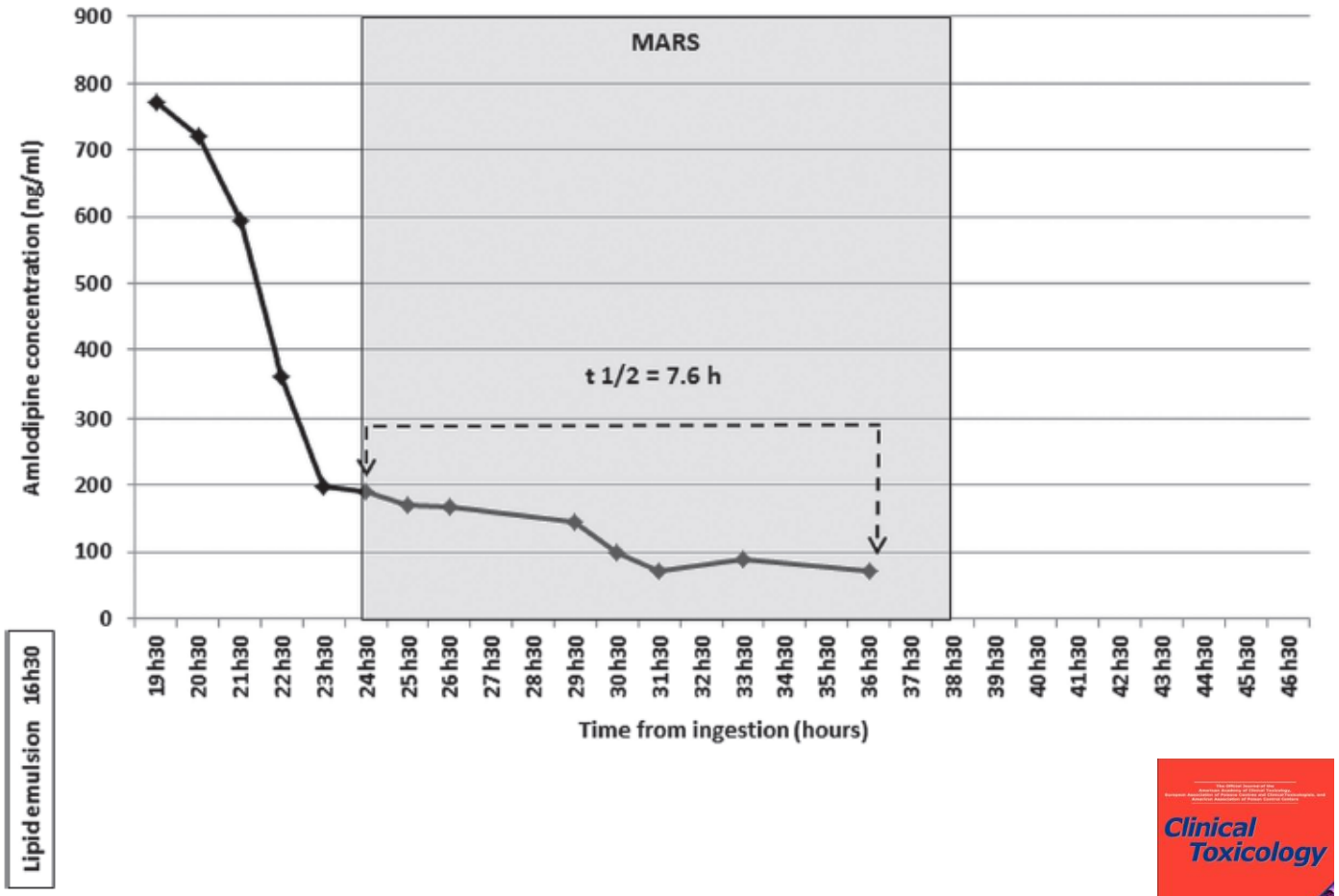
Extracorporeal Albumin Dialysis in Three Cases of Acute Calcium Channel Blocker Poisoning With Life-Threatening Refractory Cardiogenic Shock

Nicolas Pichon, MD, Anthony Dugard, MD, Marc Clavel, MD, Jean Bernard Amiel, MD, Bruno François, MD, Philippe Vignon, MD, PhD





IV Which RRT method(s) for ECTR?



1,5 mg eliminated

1 tablet = 5 or 10 mg !

Mixed amlodipine/valsartan overdose treated by the molecular adsorbent recirculating system (MARS™)

Ludovic Gérard, Anne-Cécile Galloy, Arnaud Capron & Philippe Hantson

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V Who should be dialyzed?

Recommendations from international experts

Based on a highly rigorous methodology

Most recommendations are based
on a low level of evidence

All require optimal treatment prior to initiation of hemodialysis

V Who should be dialyzed?

	Clinique	Biologique	Analytique	Durée
Lithium (Li)	Coma **OR** Seizures **OR** Dysrythmia	AKI KDIGO 2 **AND** [Li+] > 4	[Li+] > 5 mmol/l	[Li+] < 1 mmol/l Hemodialysis duration at least 6 hours
		Decrease in [Li+] elimination over 36 hours		
Metformine	Shock **OR** coma	Lactate > 20 mmol/L **OR** pH ≤ 7.0 **OR** AKI **OR** ALF		Lactate < 3 mmol/L **AND** pH > 7.35
Salycilates	Decrease in consciousness **OR** hypoxemia		[salicylates] > 7.2 mmol/L	Clinical improvement **AND** [salicylate] < 1.4 mmol/l **OR** Hemodialysis duration at least 6 hours
		AKI KDIGO 2 **AND** [salicylates] > 6.5 mmol/L		
		pH ≤ 7.2		
Phenobarbital	Prolonged coma **OR** Shock Respiratory depression requiring intubation		[phénobarbital] stagnates or increases despite repeated administration of CA	Clinical improvement
Valproate (VPA)	Shock **OR** Cerebral oedema Chest tube insertion for coma	pH ≤ 7.1 Hyperammoniemia	[VPA] > 1300 mg/L	Clinical improvement
			[VPA] > 900 mg/L	**OU** [VPA] entre 50-100 mg/l

VI Conclusion

1. **Do I need an ECTR?**
   - No → No indication for extracorporeal toxic removal (ECTR)
   - Yes ↓
2. **Will ECTR using RRT benefit my patient?**
   - No → No indication for extracorporeal toxic removal (ECTR)
   - Yes ↓

Intermittent hemodialysis is always recommended as first-line treatment

6 xenobiotics for which hemodialysis may be indicated

- Lithium
- Phenobarbital
- Salycilates
- Valproate
- Theophylline
- Metformine

EXTRIP
THE EXTRACORPOREAL TREATMENTS IN POISONING WORKGROUP

Expert centres

Thank you for your attention

dominique.vodovar@aphp.fr

Fédération de Toxicologie de l'Assistance Publique des Hôpitaux de Paris

Hôpital Lariboisière
Fernand-Widal

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

UFR de
Médecine

Université Paris Cité