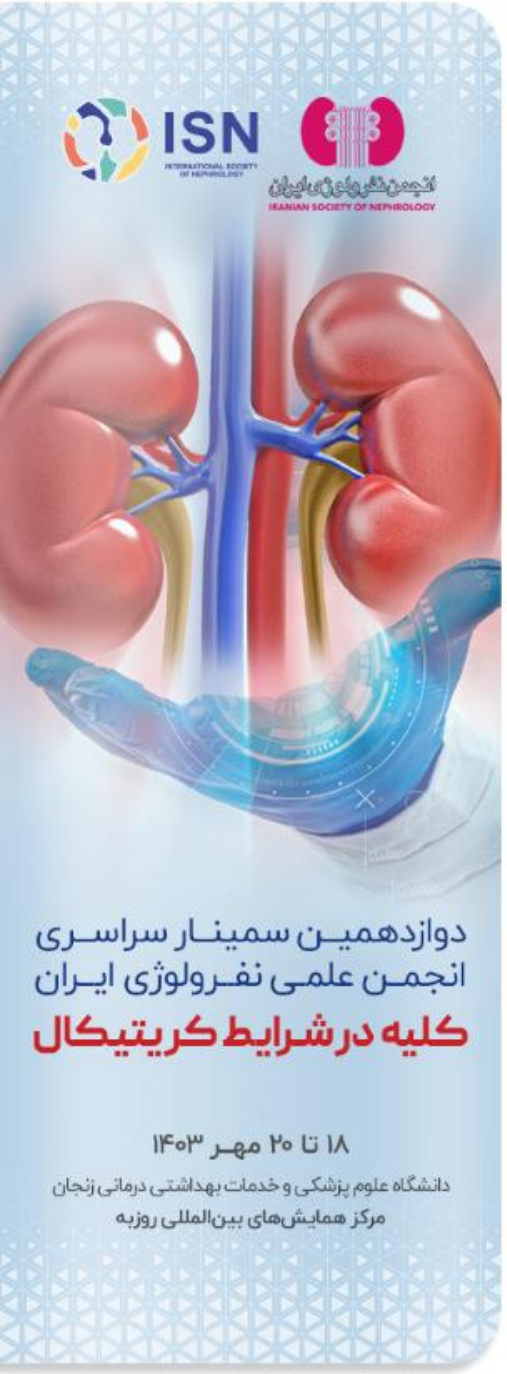
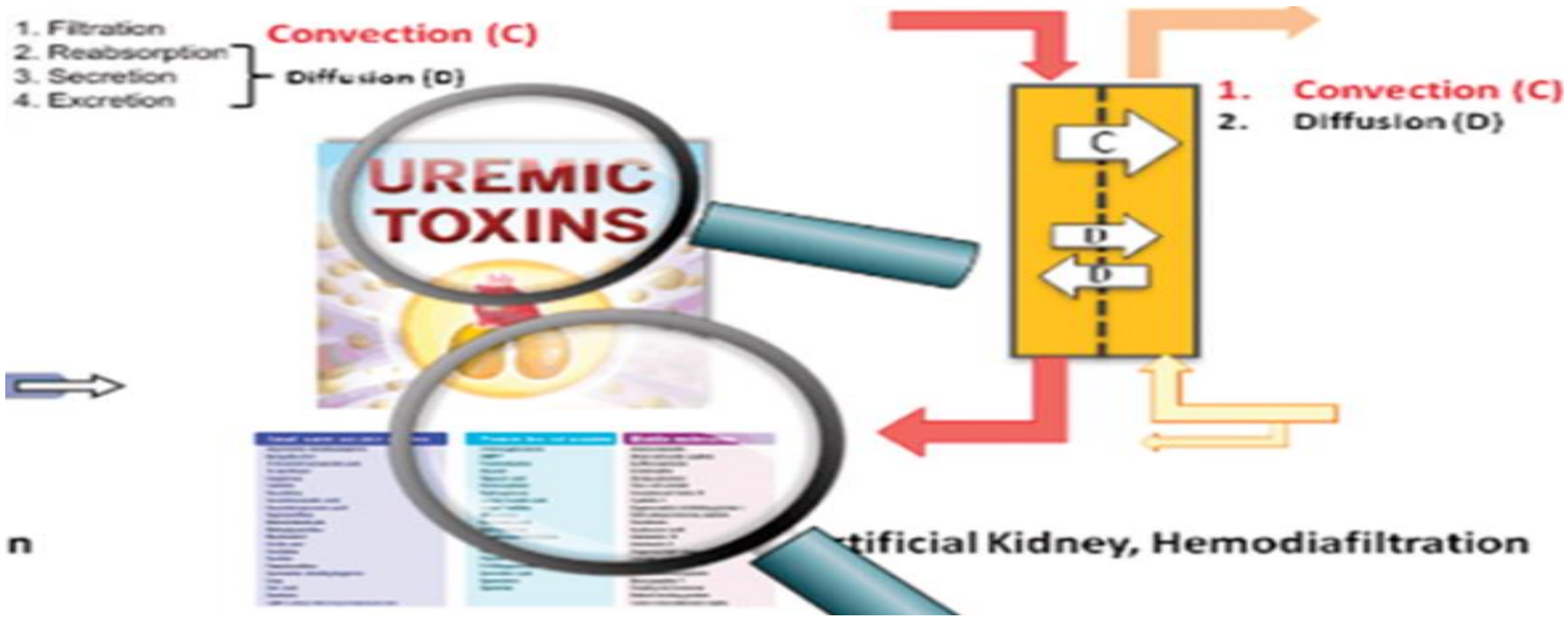


IN THE NAME OF GOD



Extracorporeal therapies in the management of poisoning and drug overdose

Dr: Farzaneh Futuhi

SBMU : Assistant Professor of Nephrology

Loghman Hakim Hospital

EPIDEMIOLOGY

In 2019, there were over 2.1 million human toxicologic exposure cases reported to the American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS) with 2048 associated deaths.

The retrospective study was conducted at Loghman Hakim hospital in Tehran between 2016 and 2020.

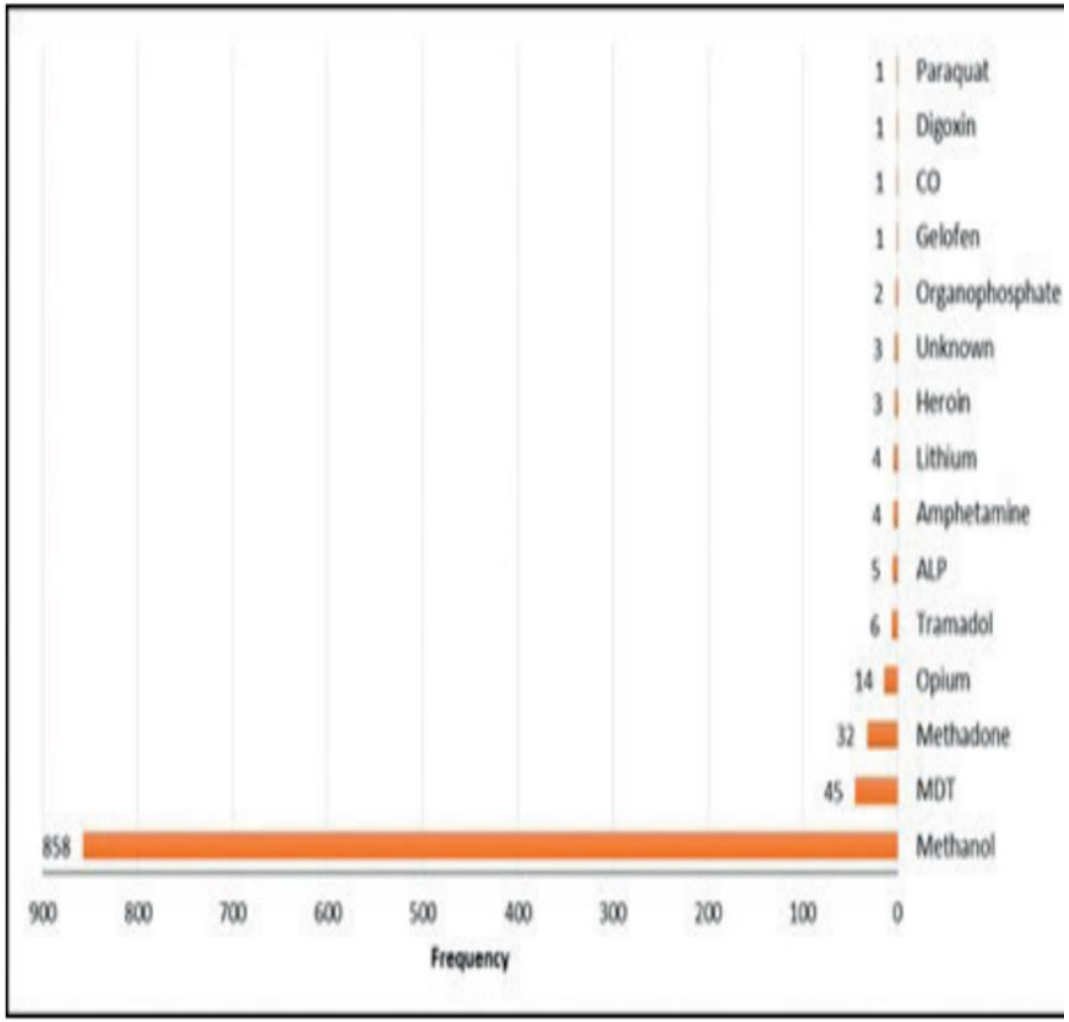
The study investigated all patients who were hospitalized and underwent hemodialysis at the poisoning center

Results:

Methanol consumption was the highest cause of poisoning (858 cases, 87.6%).

Hemodialysis was the most widely used extracorporeal method (971 cases, 99.1%).

The mortality rate was 13.3%. Metabolic acidosis was observed in 823 cases (84%). Acute kidney injury (AKI) was present in 536 cases (54.7%).



Rahimi et al. Epid: A-Five-Year Study

1: Cause of intoxication in the studied patients. MDT= Multiple Drug Toxicity.

Introduction

Accidental or intentional poisoning and drug overdose are a significant source of morbidity, mortality and health care expenditure worldwide.

Treatment includes supportive care, prevention of poison absorption and, when appropriate, the use of antidotes or interventions to enhance the elimination of poison, as urine alkalinization or extracorporeal treatment, especially when natural elimination mechanisms are impaired.

Extracorporeal treatments (ECTRs) are required in 0.1% of intoxications.

Extracorporeal removal treatments have been used to treat poisoning for decades and different modalities are available, including hemodialysis, hemofiltration, hemoperfusion, continuous renal replacement therapy and therapeutic plasma exchange and ECMO.

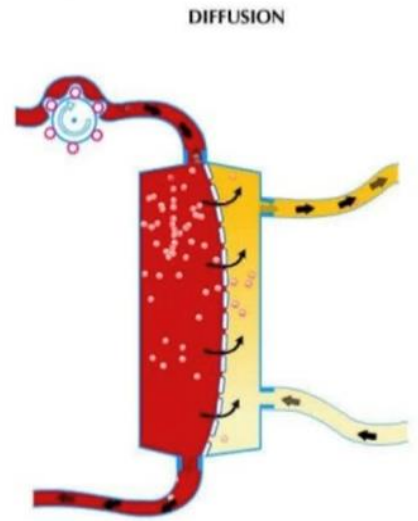
Indian J Crit Care Med. 2018 Dec; 22(12): 862–869.

Principles of renal replacement therapy (RRT)

There are two main transportation processes :Diffusion and convection

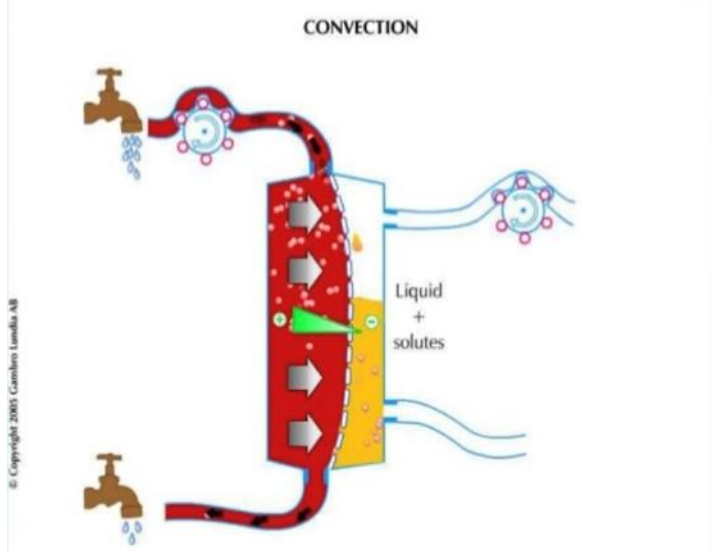
Diffusion

Factors affecting diffusion are concentration **gradients, molecular size and charge of the solutes, surface area, thickness, and solute permeability of the membrane**
Diffusion is the main determinant mechanism of small solute clearance in hemodialysis



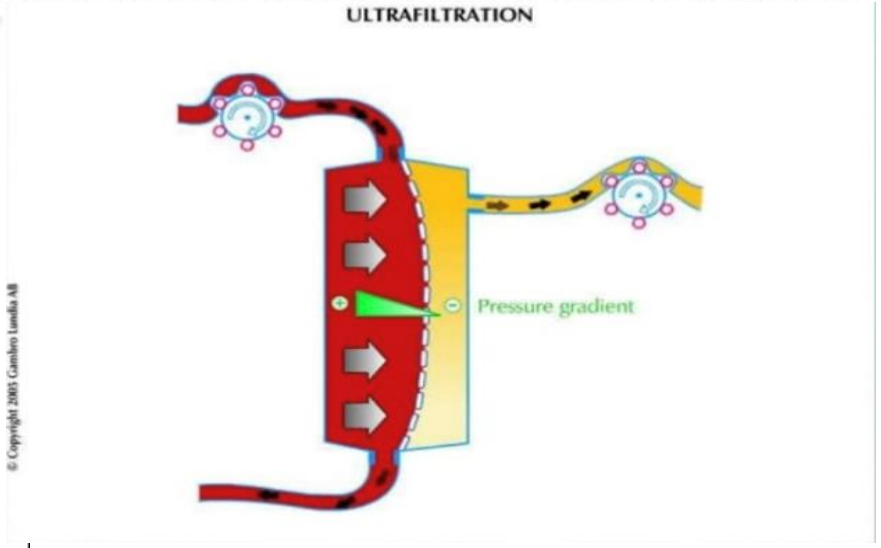
Convection

Convection which is the solutes migrate along with water flow (solvent) across the semipermeable membrane
There are many factors affecting the convection such **as solute concentration gradients, sieving coefficient, surface area, pore size, and the permeability of membran**e and ultrafiltration rate.
Convection is able to remove protein-bound uremic toxins and middle molecule solutes such as interleukins, complement, platelet-activating factors, and other cytokines.



Ultrafiltration: Movement of fluid (plasma water) through a semi-permeable membrane due to a pressure gradient

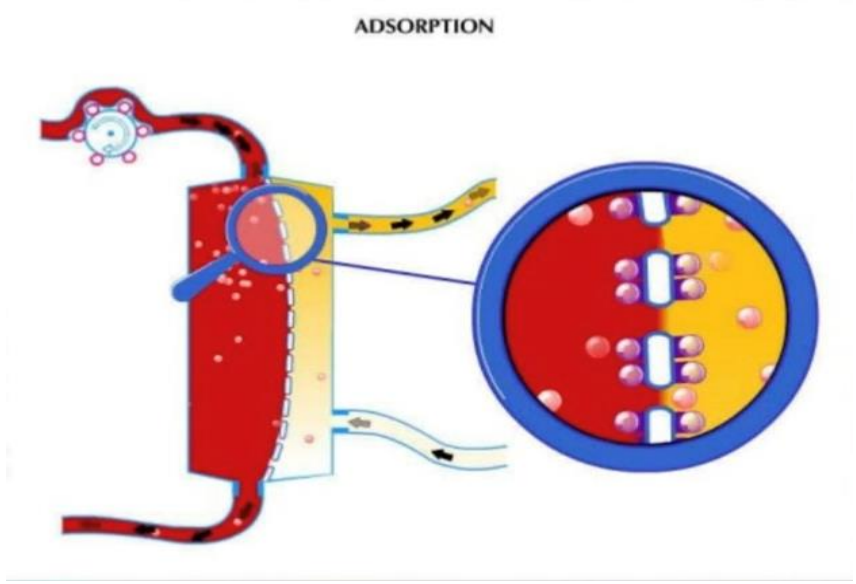
Adsorption: Molecules adhere to the surface of semi-permeable membrane, removing it from the circulation (can occur with TNF and other cytokines, beta-2 micro globulin)



RRT Molecular Transport Mechanisms

- Ultrafiltration → Fluid Transport
- Diffusion
- Convection
- Adsorption

} Solute Transport



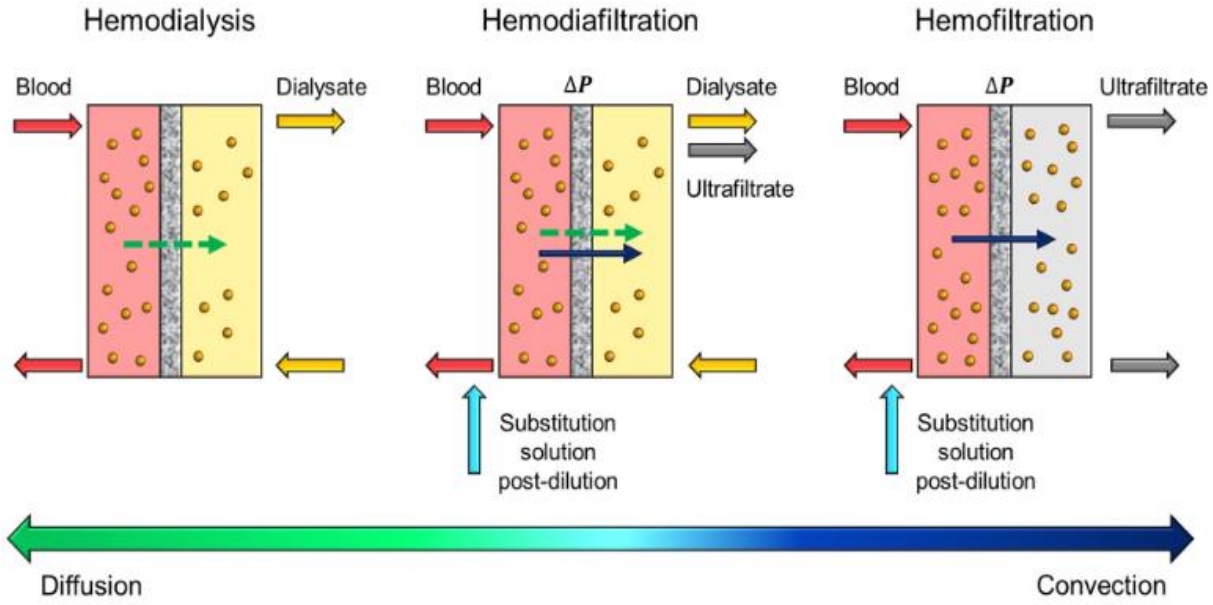
[NEJM Review Article on CRRT]

HDF techniques

HDF is an RRT modality which combines diffusion and convection techniques to enhance the removal of middle molecule solutes and protein-bound uremic toxins by using high-flux dialyzer .
This technique requires not only dialysate fluid but also sterile substitution fluid for replacement.
There are various types of dilutional methods according to the site of replacement fluid infusion pre-dilution, post-dilution, mid-dilution, and mixed-dilution

Advantages of HDF:

- Enhanced small, middle and larger m removal
- Protein-bound uremic solute clearance
- Better intradialytic hemodynamic stability
- Reduced inflammation & infection
- Anemia correction
- Improved phosphate control
- Improved CV status



Membranes 2021, 11, 239

HDF and AKI

1.HDF and rhabdomyolysis-induced AKI

Rhabdomyolysis, is induced renal vasoconstriction, oxidative stress, direct tubular injury, and tubular obstruction.
It has a molecular mass of 17.9 KDa
Several studies also reported mass myoglobin removal on CVVHF with high-flux or HCO membranes

2.HDF and myeloma cast nephropathy

Myeloma cast nephropathy characterized by monoclonal light chain and uromodulin obstructions in distal tubules of the kidney.
supra-hemodiafiltration with endogenous reinfusion (supra-HFD) which is a subtype of HDF that utilizes separated convection, diffusion, and adsorption
The sorbent cartridge has a high affinity for both κ and λ free light chains without the drawback of albumin loss.

HDF and AKI

3.HDF and sepsis-induced AKI

CVVHDF might better control the cytokines and other uremic toxin accumulations and provided better survival outcome.

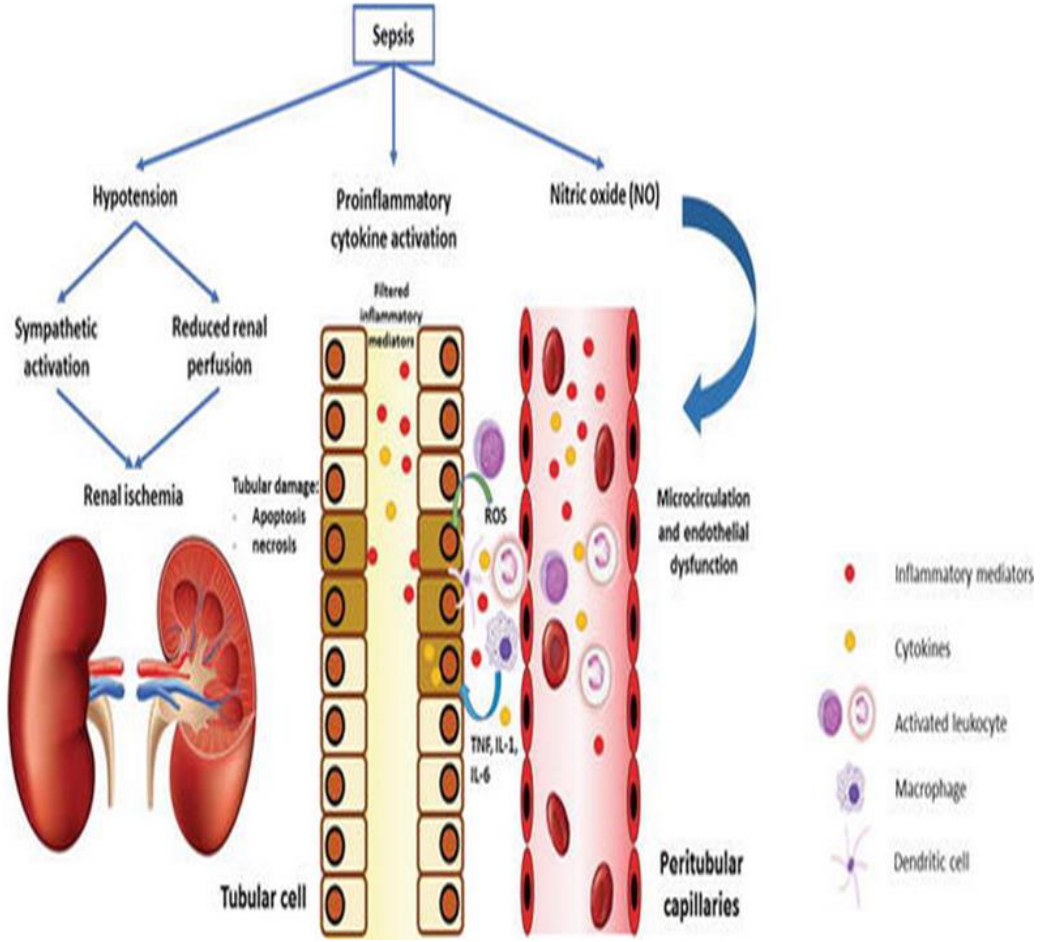
Dose prescription

KDIGO guidelines proposed the optimal dose of CRRT of 20–25 mL/kg/h in AKI

Effluent rate prescription should be increased by 20–25% to achieve an actual prescribed dose.

4.HDF and contrast-induced nephropathy (CIN)

Prophylactic HDF is likely to provide salutary benefit in patients with very high risks who are undergoing coronary interventions.



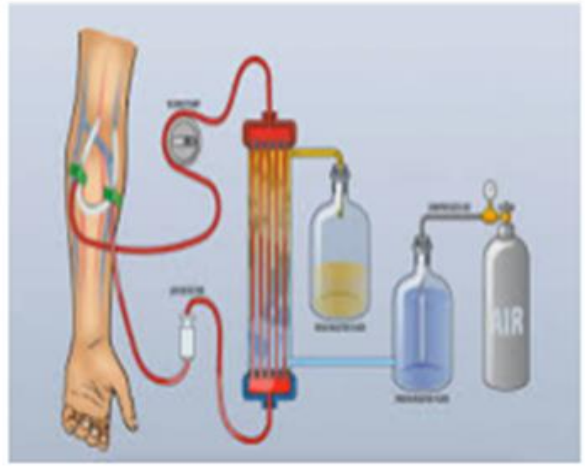
Principles of Hemodiafiltration: Rationale for Improved Patients' Survival

Indications for renal replacement therapy

Acute management of life-threatening complications of AKI:

A: Metabolic acidosis ;(pH less than 7.1)
E: Electrolytes; Hyperkalemia (K >6.5 m eq /L) or rapidly rising K)
I: Ingestion ;Certain alcohol and drug intoxications
O: Refractory fluid overload
U: Uremia, pericarditis, neuropathy, decline in mental status.

Table 2: Indications of extracorporeal treatment
Exposure to the poison likely to cause serious morbidity and mortality
Poison toxicity unlikely to be prevented or reversed by an antidote
Poison toxicity unlikely to be minimized by treatments that prevent absorption and/or enhance elimination
Poison's endogenous clearance <4 ml/min/kg
Volume of distribution <1-2 L/kg



Indian Journal of Critical Care Medicine ¦ Volume 22 ¦ Issue 12 ¦ December 2018

Modalities of Extracorporeal Therapy for Poisoning

- **Peritoneal dialysis (PD)**
- Is not very effective in removing drugs from the blood,
- When HD is difficult to institute quickly, such as in small children, . hypothermic poisoned patient, PD maybe useful.

- **Hemodialysis**
- Therapy of choice for *water-soluble drugs*, especially those of LMW along with a low level of protein binding,
- Examples - ethanol, ethyl glycol, lithium, methanol, and salicylates.
- HD not very useful in removing lipid-soluble drugs .

- **Apheresis :**

Plasma exchange have been utilized for rare poisonings not otherwise amenable extracorporeal removal, such as snake envenomation, iatrogenic poisoning with monoclonal antibodies, arsine gas, and *Amanita phalloides* (a highly poisonous basidiomycete mushroom) poisoning.

- **Albumin dialysis:**

It refers to HD (typically CRRT) against a dialysate that contains circulating albumin, and useful to remove protein-bound toxins, albumin dialysis typically is inferior to HD at clearing poisons, with clearances of a number of protein-bound drugs (*e.g.*, phenytoin, valproic acid)

- Clin J Am Soc Nephrol. 2019 Sep 6; 14(9): 1408–1415

Hemoperfusion

- More effective than hemodialysis in clearing the blood of many protein-bound drugs and lipid-soluble drugs
- **Continuous hemodiafiltration, hemoperfusion**. useful in drugs with moderately large volumes of distribution and slow intercompartmental transfer times to prevent post therapy rebound of plasma drug levels.
- **Continuous hemoperfusion** - in theophylline, and phenobarbital toxicity and
- **Continuous hemodiafiltration** -in ethylene glycol and lithium toxicity

Cerebrospinal fluid exchange

considerations

1. Molecular mass

- HD, conventional dialyzers may clear substances up to 15,000 Da
- Hemofilters may clear substances closer to 50,000 Da.
- Plasmapheresis may clear substances of any size

2.Phenomenon of "rebound,"

plasma levels of a given substance will increase hours after HD. Lithium is the best-known and other drugs metformin, methotrexate, vancomycin, dabigatran

3.Protein Binding

High degree of protein binding drugs, will have a low plasma concentration of unbound drug available for dialysis such as salicylates, valproic acid, carbamazepine, phenytoin . **Substances with <80% protein binding are removal HD.**

4.Water Solubility

Drugs with high water solubility will be dialyzed to a greater extent than those with high lipid solubility.

5.Volume of Distribution

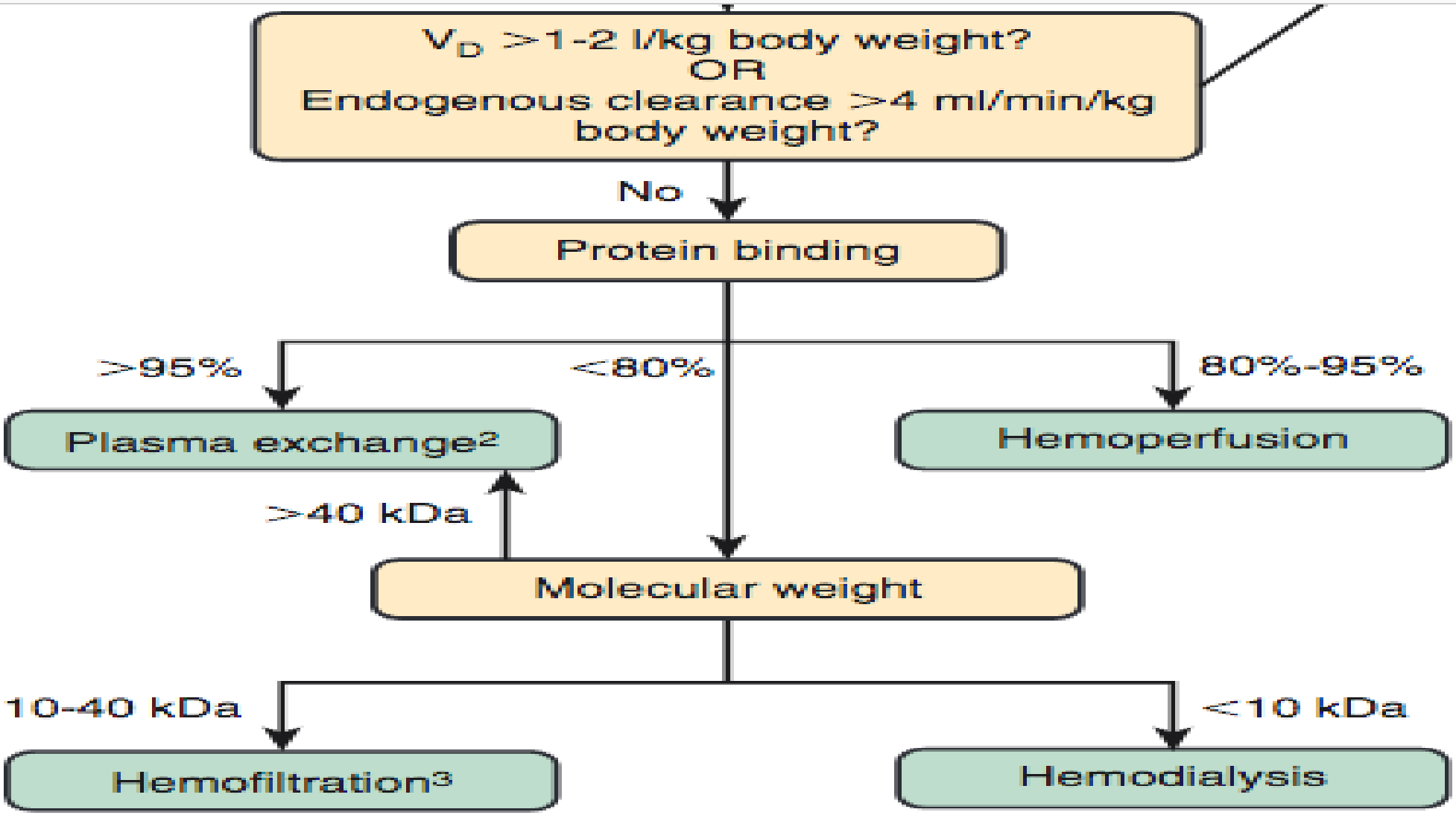
A large VD, implies that the drug is not readily accessible to hemodialysis

The drugs with large VD*(> 5 L/kg):*
Antidepressants, Antipsychotics, Verapamil.
Antimalarials, Opioids, Propranolol

Drugs with a relatively small VD (< 1 L/kg): ***salicylate, ethanol, phenytoin phenobarbital, lithium, valproic acid,*** so they are dialysis able

6.Endogenous Clearance

Dialysis will have a limited impact if the rate of drug removal is faster by endogenous routes (>4 mL/Kg/min).


V_D >1-2 l/kg body weight?
OR
Endogenous clearance >4 ml/min/kg body weight?
No
Protein binding
>95%
<80%
80%-95%
Plasma exchange²
Hemoperfusion
>40 kDa
Molecular weight
10-40 kDa
<10 kDa
Hemofiltration³
Hemodialysis

considerations for the time of toxin removal with RRT

When Should Extracorporeal Removal Be Considered?

- Molecular weight
- Protein binding
- Volume of distribution
- Solute compartmentalization
- Contribution of extracorporeal toxin removal relative to endogenous clearance

Box 67.1 Factors That May Enhance Poison Clearance During Hemodialysis

Larger surface area of dialysis membrane
High-flux dialyzer
High blood and dialysate flows
Increased ultrafiltration rate (with replacement solution)
Increased time on dialysis
Reduced recirculation
Two dialyzers in series
Two distinct extracorporeal circuits

CJASN September 2019, 14 (9)1408-1415

Table 1: Important parameters for optimizing clearance with the different extracorporeal therapies

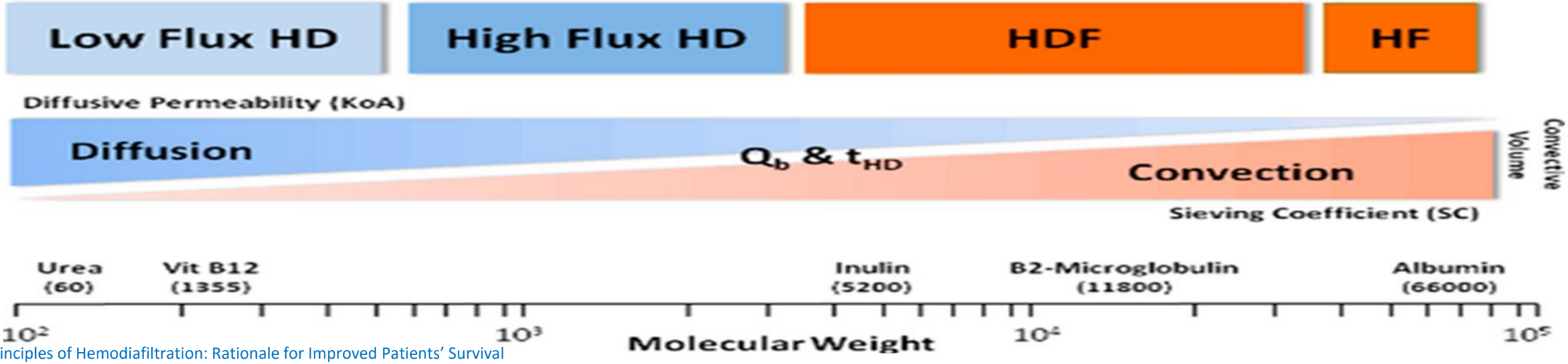
	For small molecules (MW<500-1000 Da)	For middle-sized molecules	For protein-bound molecules (>80%)
Intermittent hemodialysis	High Qb (up to 400 ml/minute) Ratio Qd: Qb ≥2.5 High-efficiency filter	High-flux filter with a large surface area High Qb Adding a second filter	High Qd Filter with a large surface area
Intermittent hemofiltration	High Qb, High Q_{UF} Maximize postdilution then add predilution	High Qb, High Q_{UF}, Maximize postdilution then add predilution High-flux filter	High-flux filter Predilution
CRRT	High Qeffluent (Qd > Q_{UF}) High Qb Maximize postdilution then add predilution High-efficiency filter Filter changed<48 h	High Qeffluent (Q_{UF} > Qd) Maximize convection: CVVH > CVVHDF (because replacement fluid is greater) High Qb High-flux filter, Filter changed <48 h	
Hemoperfusion	Charcoal vs. resin column (depending on poison) High Qb (max 350 mL/min) Filter change <4 h		
Therapeutic plasma exchange	Centrifugation or filtration ≥2 plasma volumes exchanged, Central catheter High Qb (100-200 ml/min for filtration and 100 ml/min for centrifugation) Replacement fluid tailored to the poison Heparin vs. citrate anticoagulation		
For all processes	Right jugular catheter ≥ femoral. For a femoral site, use catheter >20 cm long. Subclavian site probably equivalent to jugular but avoid in patients at risk for end-stage renal disease.Both subclavian and jugular sites may require X-ray confirmation of placement		

Indian J Crit Care Med. 2018 Dec; 22(12): 862–869

Table 3: Extracorporeal treatment options

>95% of poison is protein bound at current concentration - therapeutic plasma exchange
80%-95% of poison is protein bound - hemoperfusion
<80% of poison is protein bound
Poison's MW - 1500 Da - high-flux HD
Poison's MW - 15-20,000 Da - hemofiltration
Poison's MW - 20-50,000 Da - high cutoff/middle cutoff HD, hemofiltration
Poison's MW - >50,000 Da - therapeutic plasma exchange

MW: Molecular weight; HD: Hemodialysis



Principles of Hemodiafiltration: Rationale for Improved Patients' Survival

Utility of extracorporeal modalities in poisoning

Modality	Toxin Molecular Mass (Da)	Toxin Volume of Distribution (L/kg)	Protein Binding of Toxin	Examples of Toxins Amenable to Therapy	Primary Limitations of Therapy
Hemodialysis	Up to 10,000–15,000	≤1.5–2	≤80%	Salicylates, toxic alcohols, lithium	Hemodynamic stability
HCO filter HD	Up to 50,000	≤1.5–2	≤80%	Small peptide therapeutics; any therapy amenable to HD	Limited availability Limited role in poisoning
CRRT	Up to 15,000–25,000	≤1.5–2	≤80%	Lithium	Slow toxin clearance (excepting toxins with slow redistribution)
Hemoperfusion	Unclear, but high	≤1 L/kg	Any	Valproic acid, carbamazepine	Limited availability Clotting Hypocalcemia
Plasma exchange	No limit	≤1 L/kg	Any	Monoclonal antibodies, arsine	Limited availability Very slow clearance

CJASN™

Dialyzability of selected toxins by therapeutic class

Therapeutic Class/Group of Poisons	Examples	General Pharmacokinetic Properties	Selected Agents Amenable to Extracorporeal Removal	Selected Agents Not Amenable to Extracorporeal Removal
Antiarrhythmics	Amiodarone, flecainide, lidocaine, sotalol	Lipophilic with high volume of distribution, protein binding	Sotalol (HD)	Amiodarone, flecainide, lidocaine
Anti-diabetic medications	Insulin, metformin, sulfonylureas	Varied	Metformin (HD)	Insulin, sulfonylureas
Antidepressants and antipsychotics	Amitriptyline, haloperidol, quetiapine, sertraline	Lipophilic with high volume of distribution, protein binding	Lithium (HD, CRRT)	SSRIs/SNRIs, TCAs, antipsychotics
Antiepileptics	Barbiturates, benzodiazepines, carbamazepine, phenytoin	Varied; generally at least moderately lipophilic	Barbiturates (HD); after massive ingestion, carbamazepine, phenytoin, valproic acid (HD)	Benzodiazepines, lamotrigine
Antimicrobials	Antifungals, antivirals, β-lactams,	Varied	Cefepime, vancomycin (HD)	Amphotericin

Hemodialysis in Severe Poisoning Cases

01

Hemodialysis in Severe Poisoning

Recommended when NAC is not administered or serum concentrations of toxic substances are elevated.

Acetaminophen

02

Considerations for Hemodialysis

Altered mental status

Metabolic acidosis

Elevated lactate

Serum concentrations exceeding specific thresholds (e.g., >100 mg/dL or >70 mg/dL

alcohol

03

Valproic Acid Poisoning

Severe toxicity (serum levels >130 mg/dL)

Shock

Cerebral edema

Respiratory depression

Coma

valproic acid

04

Cisplatin Overdose

Therapeutic plasma exchange is crucial for removing the drug from the plasma.

Rapid binding of cisplatin to plasma proteins.

cisplatin

05

Duration of Hemodialysis

Continue until clinical improvement is observed.

Serum concentrations reach appropriate levels for each specific poisoning scenario.

Not amenable to ECTR removal

β-blockers:

some β-blockers like atenolol are removed by ETCR, although others such as propranolol, timolol and metoprolol are not, considering their molecule characteristics

Tricyclic antidepressants:

ECTRs are not likely to have any clinical benefit in poisoning by tricyclic antidepressants as amitriptyline and its use is not recommended. Some case reports defend the use of therapeutic plasma exchange but evidence is modest

Digoxin:

Digoxin has a very effective antidote – digoxin immune Fab and a very high Vd (6.1 ± 2.6 L/kg) so ECTR are not useful in overdose and its use is not recommended

Isoniazid:

Treatment should focus on supportive care and pyridoxine administration, therefore, ECTR are not recommended.

Calcium channel blockers:

It was considered that the risks and costs associated with ECTR surpassed any potential benefit in calcium channel blockers poisoning like amlodipine, diltiazem and verapamil.

Methotrexate:

An expected benefit from ECTR is very limited and in rare circumstances. Although it might accelerate elimination of plasma methotrexate, its use is not supported as addition to standard care, as an alternative to glucarpidase (methotrexate antidote)

What is hemoperfusion?

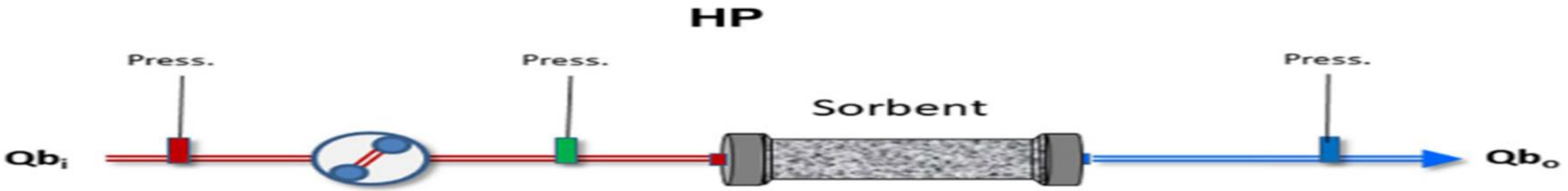
There is no dialysis membrane or dialysate , so blood is passed through a sorbent.

It can absorb effectively **the fat soluble ,medium and large molecular, and high protein binding rate medicine and poison as well as low volume of distribution** for example **theophylline overdose, as well as paraquat** poisoning.

Hemoperfusion can be combined with dialysis/CRRT

Blood flow may vary according to the size of the cartridge (100–250 ml/min)

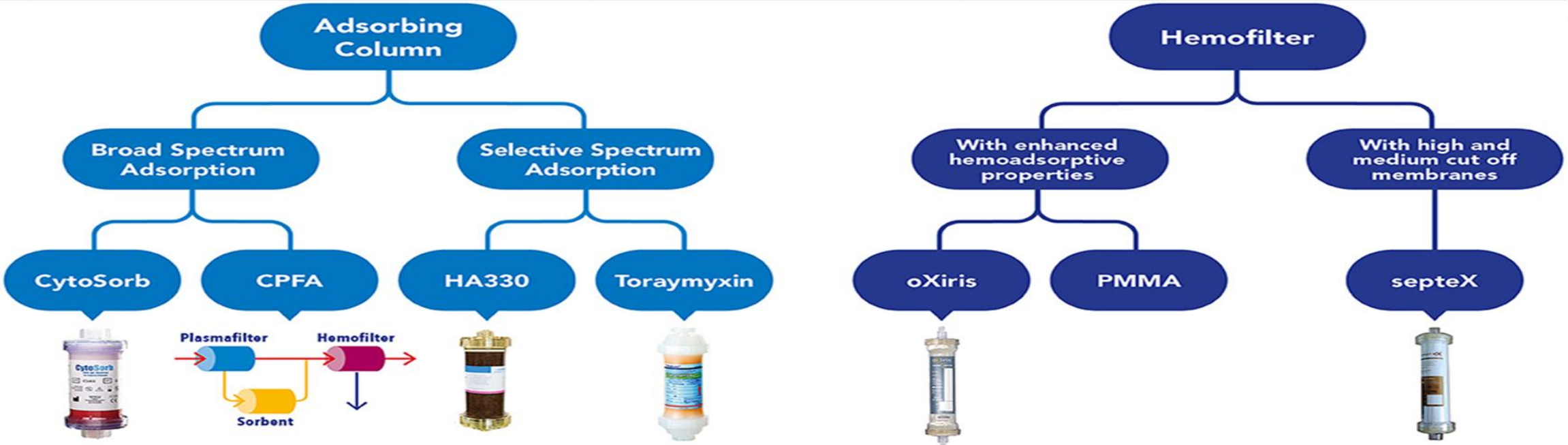
The extracorporeal circuit is anticoagulated with heparin or citrate.



Qb_i = 100 – 250 ml/min
Q_f^{Net} (ml/min) = 0 ml/min

Schematic configuration of direct hemoperfusion (HP). Qb_i = Blood flow at the inlet of the unit; Q_f^{Net} = net ultrafiltration

Available sorbents



Sorbent polymer	Commercial name (manufacturer)	Amount of sorbent	Coating
Norit charcoal	Adsorba (Gambro)	100–300 g	Cellulose acetate
Polymyxin B	Toraymyxin (Estor)	–	–
Spherical charcoal	Hemosorba (Asahi)	170 g	Polyhema
Polystyrene divinyl benzene	HA 130/230/330 (Jafron)	–	None
Polystyrene divinyl benzene	Cytosorb (Aferetica)	300 g	None
Ultra-high molecular weight polyethylene beads with end-point-attached heparin	Seraph-100 (ExThera Medical)	–	–

Available sorbents

Charcoal adsorption or resins:

The blood flow for efficient drug removal is 300 mL/min, up to 450 mL/min , so it is performed for 4 h.

It is used in detoxification *Amanita phalloides* mushroom intoxication, overdose barbiturates, valproic acid, theophylline, aluminum, and carbamazepine as well as paraquat ingestion.

Polymyxin B hemoperfusion:

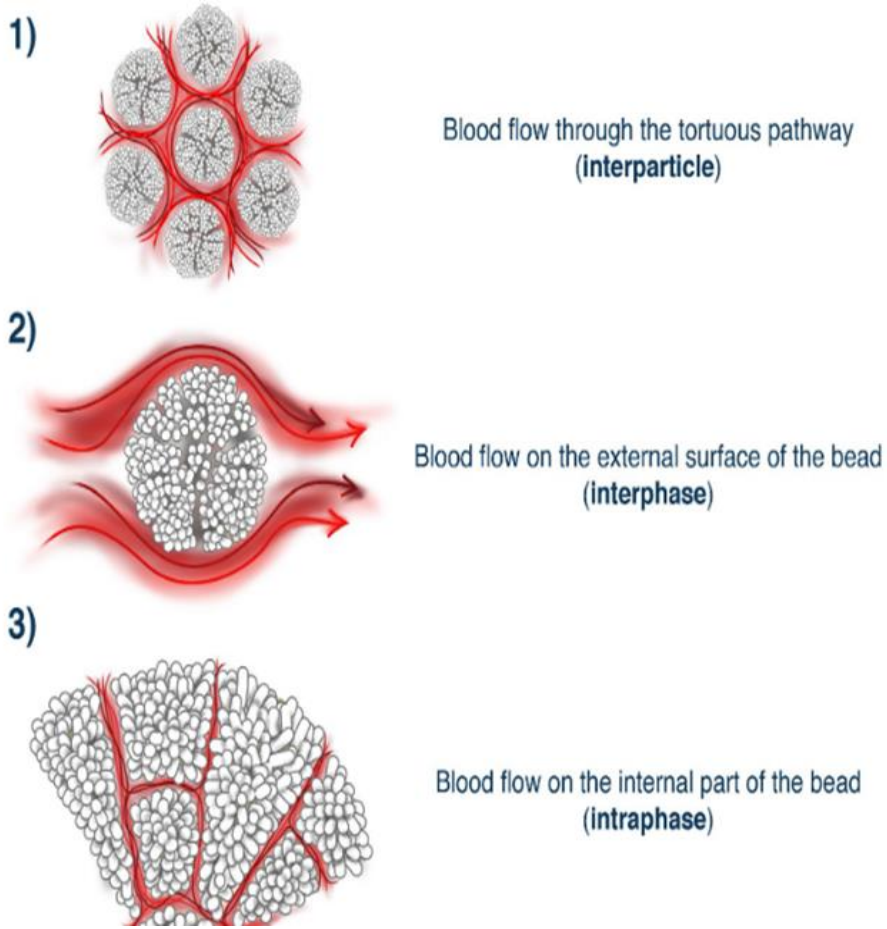
It removed endotoxins during sepsis and septic shock .

This treatment requires sessions of 2 h of by blood flow **rate rang 80 - 120 mL/min.**

Coupled plasma filtration adsorption:

It is not currently recommended in septic shock or hyperinflammation after the negative results of the COMPACT and COMPACT-2 trials

Ronco Critical Care (2022) 26:135



Macro-porous (Pore size > 500 Å),
Meso- porous (Pore size 20–500 Å)
Micro-porous (Pore size < 20 Å)

Available sorbents

CytoSorb hemoperfusion:

It is composed of polystyrene divinylbenzene and polyvinylpyrrolidone copolymers.

Maximum effectiveness in terms of sorbent saturation has been reported at around 12 h

Both in children and in adults, Cyto Sorb® has been used to reduce bilirubin and myoglobin serum concentrations

Jafron HA series for hemoperfusion/plasma perfusion:

Neutro macro porous resins made of styrene–divinylbenzene copolymer, HA130, HA230,HA330

Seraph-100 micro affinity pathogen binder:

It contains ultra-high molecular weight polyethylene beads with end-point-attached heparin

Blood flow rates range from 150 to 350 mL/min and treatment time may be extended up to 24 h.

Multi-modal approach to the treatment of dysregulated inflammation, removing cytokines as well as bacteremia and viremia .

Blood Purif 2019;47:94–100 DOI: 10.1159/000493523

Jafron HA series for hemoperfusion/plasma perfusion

HA130 is mainly used in chronic conditions in combination with hemodialysis
It significant benefit in symptoms such as pruritus, muscular weakness, appetite, and anemia

HA230 is mostly indicated in acute intoxications especially in cases of a drug overdose, pesticides, and industrial toxin

HA330 and HA380 cartridges are mostly indicated in acute inflammatory conditions such as sepsis, trauma, burns, pancreatitis and various cytokine release syndromes severe COVID-19, hemophagocytic syndrome.

DPMAS (double plasma filtration molecular adsorption system)
This sorbent has been used alone or in combination with the HA330-II cartridge to the removal of cytokines and bilirubin /bile acids in acute liver failure and fulminant hepatitis in adults and children

Blood Purif 2019;47:94–100 DOI: 10.1159/000493523

When to consider hemoperfusion?

There are no established indications for hemoperfusion.

Intoxication

Intoxication with a drug (valproate, carbamazepine) a toxic chemical (paraquat or organophosphates) as well as toxic natural products (mushroom-related toxins)

Liver disease

There is very limited information or research in severe liver failure (either acute or acute on chronic) even though there is a robust rationale for targeting ammonia or bilirubin as well as treatment of intractable cholestatic pruritus

Renal disease

A variety of end-stage renal failure-associated toxins are not adequately removed during dialysis justifying the combined use of resins in selected patients such as beta-2 micro globulin removal or uremic pruritus

Ronco and Bellomo *Critical Care (2022) 26:135*

Technical aspects of hemoperfusion

- **Plasma filtration-adsorption**:

  Plasma is separated from blood, circulated through the sorbent and reinfused into the circuit.

  This technique can be performed for a few hours

  PFAD = plasma filtration-adsorption) or

  CPFA = continuous plasma filtration absorbent (over a prolonged period)

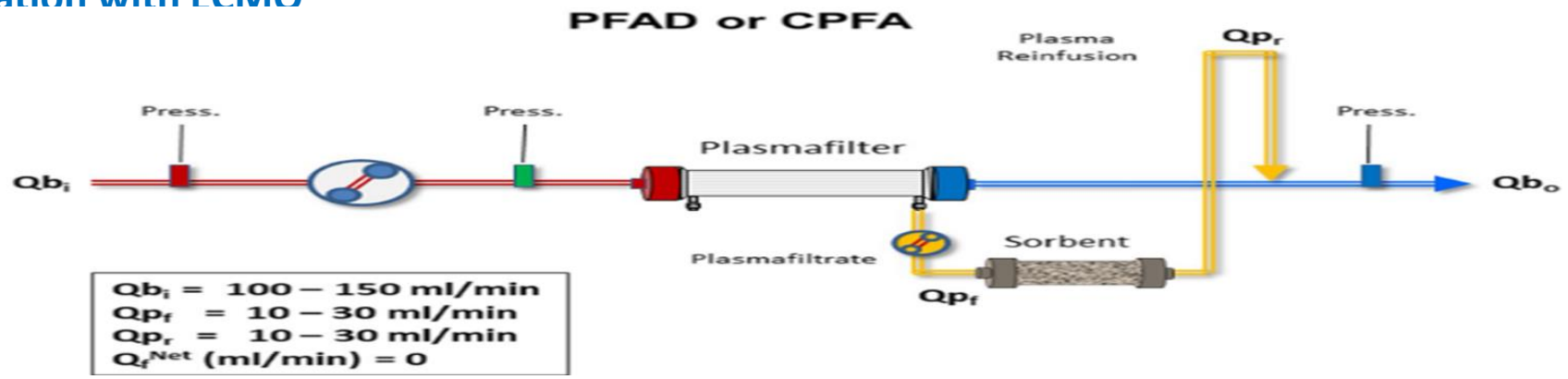
(PFAD-HD) or CRRT (CPFA-CRRT) can be combined with hemodialysis or CRRT

The efficiency of the treatment to small solutes such as urea and creatinine are increased .

DPMAS: Double plasma filtration molecular adsorption system

It uses in combined kidney and liver failure, by different sorbent units with specific characteristics.

Hemoperfusion in combination with ECMO



Non-selective hemoperfusion

A multicenter randomized trial compared Cyto Sorb therapy with conventional care 100 ventilated patients with sepsis or septic shock and either acute lung injury or ARDS.

The primary outcome was the change in IL-6 during study day 1 to 7.

There were no significant differences in IL-6 levels.

Cyto sorb based therapy was tested in COVID-19 patients on ECMO

In a single- randomized trial, 17 ECMO patients were treated with Cyto sorb for 72 h and 17 without.

The decrease in IL-6 levels was similar but survival after 30 days was 18% with CytoSorb therapy and 76% without .

JAFRON HA cartridge series in sepsis that case series non randomized study

They involved 24 treated patients and 20 controls.
It reported hemodynamic benefits, reduced IL8 and IL6 levels, and beneficial effects on ICU length of stay but no effect on mortality

Ronco and Bellomo Critical Care (2022) 26:13

Potential clinical applications of hemoperfusion and ongoing trials

Extracorporeal therapies for drug or chemical intoxication are indicated when there is life-threatening toxicity, an inadequate response to standard supportive measures, or the poison's endogenous clearance is <4 mL/min/kg and the poison's volume distribution is <1–2 L/kg

Side effect:

HP requires greater systemic anticoagulation;
Flows that do not exceed 350 mL/min so to avoid the risk of hemolysis;
nonselective adsorbs platelets, calcium, glucose, and white blood cells
The higher cost and the need to replace the cartridge every 2 hours due to saturation

Positive effect:

While HP use for poisoning has declined to roughly 1% of HD utilization in the United State

HP seems to be more effective than HD for paraquat poisoning achieves enhanced clearance of paraquat, leading to higher survival rates compared to high-flux HD . paraquat poisoning being an important concern mostly in Asia.

Currently, the strongly recommended method by the EXTRIP (Extracorporeal Treatments in Poisoning) group for the removal of most drugs is intermittent HD. HP is an alternative option (1C or 1D) when HD cannot be performed

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Kidney Res Clin Pract. 2023 May; 42(3): 298–311.

Hemoperfusion in Overdose

Barbiturates	*Antimicrobials/ anticancer*	*Cardiovascular*
amobarbital	(adriamycin)	digoxin
butabarbital	ampicillin	diltiazem
hexabarbital	carmustine	(disopyramide)
pentobarbital	chloramphenicol	metoprolol
phenobarbital	chloroquine	n-acetylprocainamide
quinalbital	clindamycin	procainamide
secobarbital	dapsone	quinidine
thiopental	doxorubicin	(aluminum)*
vinalbital	gentamicin	(iron)*
Nonbarbiturate hypnotics, sedatives, tranquilizers	isoniazid	*Miscellaneous*
carbromal	(methotrexate)	aminophylline
chloral hydrate	thiabendazole	cimetidine
chlorpromazine	*Antidepressants*	(fluoroacetamide)
(diazepam)	(amitryptiline)	(phencyclidine)
diphenhydramine	(imipramine)	phenols
ethchlorvynol	(tricyclics)	(podophyllin)
glutethimide	*Plants, animals, herbicides, insecticides*	theophylline
meprobamate	amanitin	*Solvents, gases*
methaqualone	chlordane	carbon tetrachloride
methsuximide	demeton sulfoxide	ethylene oxide
methyprylon	dimethoate	trichloroethanol
promazine	diquat	
promethazine	methylparathion	
Analgesics, antirheumatic	nitrostigmine	
	organophosphates	

Notable drugs:

- -Theophylline
- -Barbiturates
- -Tricyclics (incl. Carbamazepine)
- -Digoxin
- -Salicylates
- -Paraquat
- -Organophosphates

Optimal physicochemical properties for extracorporeal removal of drugs.

	Hemodialysis	Hemofiltration	Hemoperfusion
Molecular weight	<500 Da	<40 KDa	<40 KDa
Protein binding	Low (<80%)	Low	Low or high
Volume of distribution	<1 L/Kg	<1 L/Kg	<1 L/Kg
Solubility	Water	Water	Water or lipid
Endogenous clearance	<4 mL/Kg/min	<4 mL/Kg/min	<4 mL/Kg/min

The Individualized Management Approach for Acute Poisoning",, vol. 2021

Toxin	Molecular Mass (Da)	Volume of Distribution (L/kg)	Protein Binding	Speed of Distribution from Plasma to Tissue	Dialyzability	Optimal Extracorporeal Modality for Removal
Amitriptyline	277	19	95%	Fast	Not dialyzable	None
Colchicine	399	5–8	40%	Fast	Not dialyzable	None
Ethylene glycol	62	0.6–0.8	Little to none	Fast	Dialyzable	HD
Lithium	7	0.6–0.9	Approximately 10%	Slower, may have rebound after HD	Dialyzable	HD; CRRT (nonemergent cases)
Metformin	129	1–5	None	Slower, may have rebound after HD	Moderately dialyzable	HD
Methotrexate	454	0.8–2	35%–50%	Slower, may have rebound after HD	Moderately dialyzable	HD
Rituximab	144,000	<0.2	None	Not applicable	Not dialyzable	Plasma exchange
Vancomycin	1449	<0.4–1	<60% (varies)	Slower, may have rebound after HD	Moderately dialyzable	HD

Introduction to Extracorporeal Membrane Oxygenation (ECMO) in Poisoning Cases

Introduction to Extracorporeal Membrane Oxygenation (ECMO) in Poisoning Cases

ECMO is utilized to provide circulatory or respiratory support in poisoned patients with refractory shock, cardiac arrest, or severe respiratory failure.

Poisonings can lead to shock, cardiac arrest, and respiratory failure, which may be refractory to traditional therapies.

ECMO allows for respiratory or circulatory stability, aiding in effective drug clearance and organ recovery in poisoned patients.

In 2019, over 2.1 million human toxicologic exposure cases were reported in the US, with 2048 associated deaths.

ECMO has been increasingly used in poisoned patients, showing reduced mortality rates compared to non-ECMO treated cases, especially in instances of refractory shock, cardiac arrest, or respiratory failure.

Extracorporeal membrane oxygenation use in poisoning: a narrative review with clinical recommendations

Types of ECMO and Clinical Utility in Poisoned Patients

Types of ECMO

Venoarterial (VA) ECMO

Venovenous (VV) ECMO

Clinical Utility in Poisoned Patients

VA ECMO for refractory shock or cardiac arrest

VV ECMO for severe respiratory failure

Benefits of ECMO in Poisoning Cases

Providing circulatory or respiratory support

Facilitating toxicant metabolism and clearance

Considerations

Short-term ECMO support

Combining ECMO with extracorporeal removal therapies

Recommendations

VA ECMO for acute poisoning with refractory cardiogenic shock

Role of VA ECMO in drug intoxication

It can use in cardiotoxicity as well as case of refractory shock not responding to conventional measures.

VA ECMO may be useful in providing adequate cardiac output and maintaining tissue perfusion, which helps in redistribution of the toxic substances and their metabolites from central circulation and facilitates the metabolism and excretion of drugs by improving hepatic and renal blood flow.

Bridge to recovery

The duration of VA ECMO support depends on several factors such as severity of toxicity and recovery cardiac dysfunction, half-life of toxin, and organ dysfunction at the time of initiation of VA ECMO.
Veno-arterial (VA) ECMO reduced cardiac oxygen consumption and provided both hemodynamic and respiratory support as a bridge to recovery .

Published case reports	Ingested agent	The duration of ECMO (hours
Goodwin et al. 1993	Desipramine	60
Williams et al. 1994	Imipramine	7
Kobayashi et al. 2011	Nortriptyline	14
Kejiri et al. 2021	Amitriptyline	27

- **VA ECMO and Drug Intoxication**

Mohamed Nassef and Nashat Abdulhalim

Submitted: 29 December 2023 Reviewed: 04 June 2

TCA-induced cardiac toxicity

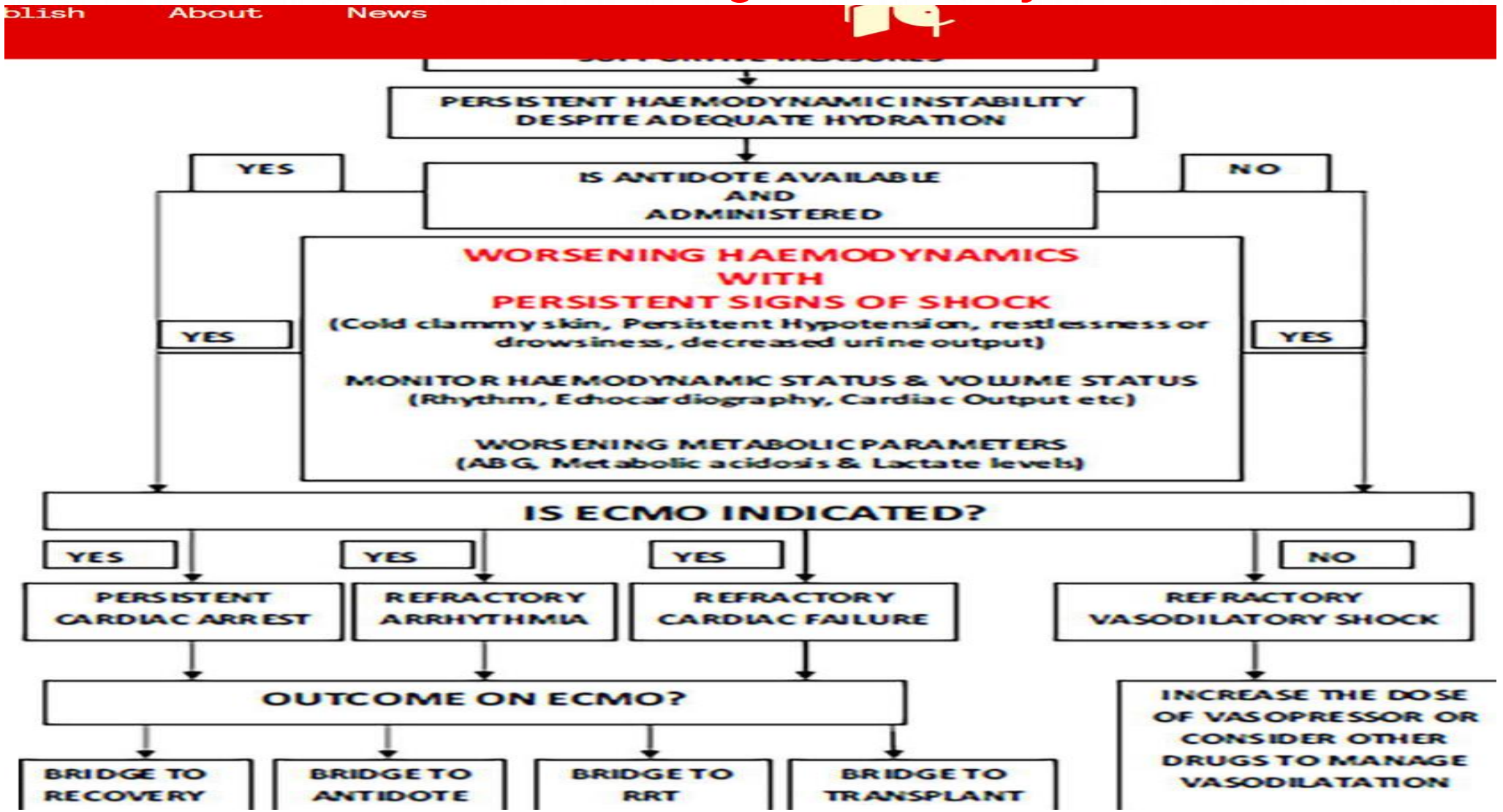
Drugs with Membrane Stabilizing Activity (MS

1.Calcium channel blockers
2.Meprobamate
3.Colchicine
4.Cardiac glycosides (digoxin)
5.H1 Antihistaminic
6.Beta Blockers (not associated with membrane stabilizing activit

- cardiotoxic

1.Anti-arrhythmic agents (Vaughan Williams class I)
2.Beta Blockers
3.Dopamine and norepinephrine uptake inhibitors (bupropion)
4.Anti-epileptics (Phenytoin/Carbamazepine)
5.Antimalarial agents (Quinine/Chloroquine)
6.Polycyclic antidepressants (Imipramine, Desipramine, etc.)
7.Opioids (dextropropoxyphene)
8.Recreational Agents such as Cocaine

ECMO Bridge to recovery



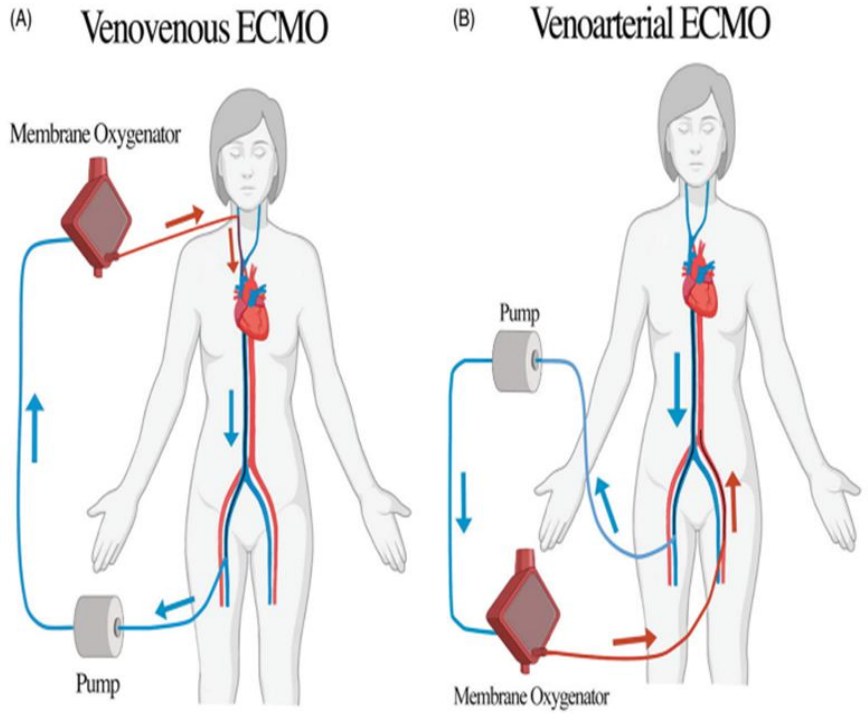
Contraindications ECMO

Patients with pre-existing comorbidities with low expected survival or recovery.

Relative contraindications vary based on each center’s experience but often include:

severe brain injury; advanced age; unrepaired aortic dissection or severe aortic regurgitation

In VA ECMO; irreversible organ injury; contraindication to systemic anticoagulation, such as severe hemorrhage.



1. Extracorporeal membrane oxygenation (ECMO) overview. (A) venovenous (VV) ECMO, and (B) venoarterial (VA) ECMO.

VA ECMO and Drug Intoxication
Published: 27 June 2024

Summary

- Hemoperfusion is preferred to hemodialysis for the removal of chemicals that are lipid soluble or are highly protein bound(paraquat, mushroom).
- Hemodialysis is preferred for water-soluble, low-molecular weight compounds.
- In humans, in view of the difficulties in conducting controlled prospective clinical trials
  - a reduction in coma time or overall mortality has not been conclusively demonstrated with hemoperfusion

Summary

- Hemoperfusion combined with hemodialysis is a promising option in patients with MODS and sepsis.
- Concurrent hemodialysis and hemoperfusion is a safe option in poisoning patients.
- Hemofiltration has a role only in patients with severe hypotension and in poisoning agents with large volume of distribution.

List of drugs and the recommended extracorporeal therapy in case of acute poisoning

Drug	The first choice of extracorporeal modality	Acceptable alternatives
Acetaminophen	Intermittent HD (1D)	Intermittent HP (1D), CRRT (3D)
Baclofen	Not recommended (1D)	
Barbiturates	Intermittent HD (1D)	HP (1D) or CRRT (3D)
B-blockers		
Propranolol	Not recommended (1D)	
Atenolol	Intermittent HD (1D) only in severe poisoning with kidney impairment	
Sotalol		
Calcium channel blockers	Not recommended (1D)	
Carbamazepine	Intermittent HD (1D)	Intermittent HP (1D), CRRT (3D)
Digoxin	Not recommended (1D)	
Gabapentin/pregabalin	Intermittent HD (1D) only in severe poisoning with kidney impairment	
Isoniazid	Not recommended (2D), consider extracorporeal therapy where pyridoxine cannot be administrated (2D)	
Lithium	Intermittent HD (1D)	CRRT (1D)
Metformin	Intermittent HD (1D)	CRRT (2D)

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Recommendations for ECTR in selected poisonings

Agent	Characteristics	Preferred modality (other accepted)	Main indications (Strength of recommendation and level of evidence)	Cessation (Strength of recommendation and level of evidence)
Atenolol	MW 266 Da PB 0%-5% Vd 1.0-1.2 L/kg	HD (CRRT)	Extreme bradycardia resistant to supportive measures if kidney function is impaired (2D)[25]	Clinical improvement (1D)[25]
Baclofen	MW 213.7 Da PB 30%-35% Vd 0.4-0.8 L/kg	HD	Coma requiring mechanical ventilation if kidney function is impaired (1D)	Clinical improvement (1D)
Barbiturates (Phenobarbital)	MW 232 Da PB 20%-60% Vd 0.25-1.2 L/kg	HD (HP, CRRT)	Prolonged coma, shock, respiratory depression (1D); toxicity persists after supportive measures (activated charcoal) (1D)[26]	Clinical improvement (1D)[26]
Carbamazepine	MW 236 Da PB 75% Vd 0.8-1.4 L/kg	HD (HP, CRRT)	Seizures refractory to treatment or life-threatening dysrhythmias (1D); prolonged coma or respiratory depression (2D)	Clinical improvement (1D); Carbamazepine [] < 1 mg/dL (2D)
Cisplatin	MW 301 Da PB 96%-98% Vd 16 L/kg	TPE	Non-defined. Avoid therapy side effects (neuro-, nephro-, myelo- and ototoxicity)[24]	Clinical improvement [24]
Ethylene glycol	MW 62 Da PB 0% Vd 0.6 L/kg	HD (CRRT)	Ethylene glycol [] > 50 mg/dL without antidotal treatment; depression of CNS, severe metabolic acidosis or AKI	Clinical improvement
Gabapentin	MW 171 Da PB <5%	HD	Severe poisoning and coexisting kidney impairment (1D)[28]	Clinical improvement (1D) [28]

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	Vd 0.7-0.9 L/kg		(2D)	
Metformin	MW 165 Da PB 0% Vd 1-5 L/kg	HD (CRRT, HF)	Lactate level > 20 mmol/L, pH < 7.0 or failure of supportive therapy (1D)	Lactate level < 3 mmol/L AND pH > 7.35 (1D)
Methanol	MW 32 Da PB 0% Vd 0.6-0.8 L/kg	HD (CRRT)	Methanol [] > 50 mg/dL in the absence of fomepizole; Coma, seizures, visual impairment, severe metabolic acidosis (1D)	Methanol [] <20 mg/dL; clinical improvement (1D)
Paracetamol	MW 151 Da PB 25% Vd 0.8-1.0 L/kg	HD (HP, CRRT)	Paracetamol [] > 100 mg/dL when NAC is not administered (1D) or > 90 mg/dL if NAC is administered and altered mental status or metabolic acidosis are present (1D)	Clinical improvement (1D)
Phenytoin	MW 252 Da PB 90% Vd 0.6-0.8 L/kg	HD (HP)	Severe poisoning refractory to supportive measures, as prolonged coma (2D)[29]	Clinical improvement (1D)[29]
Salicylates (Acetylsalicylic acid)	MW 180 Da PB 30% (overdose) Vd 0.2-0.5 L/kg	HD (HP, CRRT)	Salicylate [] > 100 mg/dL (1D); [] 90 mg/dL with impaired kidney function (1D); altered mental status or hypoxemia (1D)	Clinical improvement (1D); salicylate [] < 19 mg/dL (1D); ≥ 6h of ECTR if the [] is not available (2D)
Thallium	MW 204 Da PB 0% Vd 3-10 L/kg	HD (HP, CRRT)	Any poisoning – ingestion, contact or inhalation (2D)[30]	Thallium [] 0.1 mg/L for ≥ 72 hr (2D)[30]
Theophylline	MW 180 Da PB 50% Vd 0.5 L/kg	HD (HP, CRRT)	**Acute:** Theophylline [] > 10 mg/dL (1C); seizures, arrythmias, shock (1D) | **Chronic:** [] > 6 mg/dL (2D)[31]	Clinical improvement; theophylline [] 1,5 mg/dL (1D)[31]
Valproic Acid	MW 144 Da	HD (HP, CRRT)	Valproic acid [] > 130 mg/dL (1D) or > 90 mg/dL (2D); cerebral edema	Clinical improvement (1D)


Thank you for
your attention