



# Overview of Extracorporeal Removal of Toxic Ingestions

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# Objectives

- Outline early and basic management for poisonings
- Understand different extracorporeal treatments available
- Outline pharmacokinetics of substances amenable to extracorporeal removal
- In depth look at several toxic ingestions



# Financial Disclosures

- Unfortunately none



# History

- First published series of ECTR removing poisons published by Dr. Schreiner in the 1950s
- Minimal data due to lack of randomized controlled studies
- Parachute Bias
- Lack of standard of care
- Mostly case reports and case series with publication bias to positive outcomes
- Growing understanding of pharmacokinetics to hopefully guide therapy
- EXTRIP (Extracorporeal Treatments in Poisoning)



# Extracorporeal Techniques

- Hemodialysis
- Continuous Renal Replacement Therapy
- Hemoperfusion
- MARS (molecular adsorbent recirculating system)
- Peritoneal Dialysis



# Hemodialysis

- Toxins & other substances are cleared from the blood by diffusion across a semi-permeable membrane down a concentration gradient from blood to dialysate
- Toxin removal also with convection via ultrafiltrate removal independent of concentration gradient
- Toxic substance must be water soluble, have low MW, low protein binding, and low volume of distribution
- Clearance of the toxin depends on membrane surface area (& type), blood and dialysate flow rate
- High-flux membranes can also remove higher MW toxins
- Risk for post-HD “rebound” due to redistribution of toxin



# Continuous Modalities

- Continuous hemofiltration/hemodialysis (CVVH, CVVHD)
- CVVHDF uses both diffusion and convection
- CVVH uses large amounts of ultrafiltrate (removal via convection) and replacement fluid – may be more beneficial for middle molecule clearance
- Blood passes through large hollow pore fibers, allowing convective removal of molecules up to 40kDa.
- Useful in unstable patients
- Prolonged duration of therapy, minimizes rebound effects
- Disadvantages however include lower clearance vs. HD
- Clearance usually not  $> 4\text{L} / \text{hr}$  or  $67 \text{ ml}/\text{min}$  (vs.  $600\text{-}800 \text{ ml}/\text{min}$  in HD)

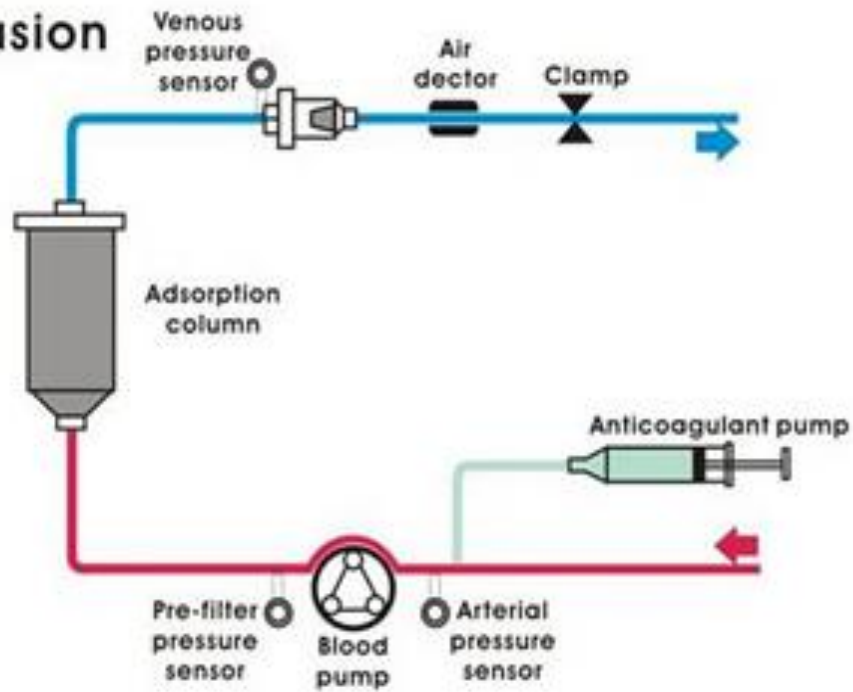


# Hemoperfusion

- Blood passes through a cartridge with sorbent material able to absorb the toxin
- Charcoal based, synthetic resins, anion exchange
- Toxic substance must have binding affinity to the sorbent & have a low volume of distribution
- Charcoal efficiently removes molecules in 1000-1500 kDa range, but doesn't remove protein-bound molecules
- Resins more effective with protein/lipid-bound toxins
- Generally declining modality due to limited use, poor life of cartridges (change q2-3hrs), more technically difficult to perform, unable to correct acid-base, fluid, electrolytes
- Could combine with HD however (in series)



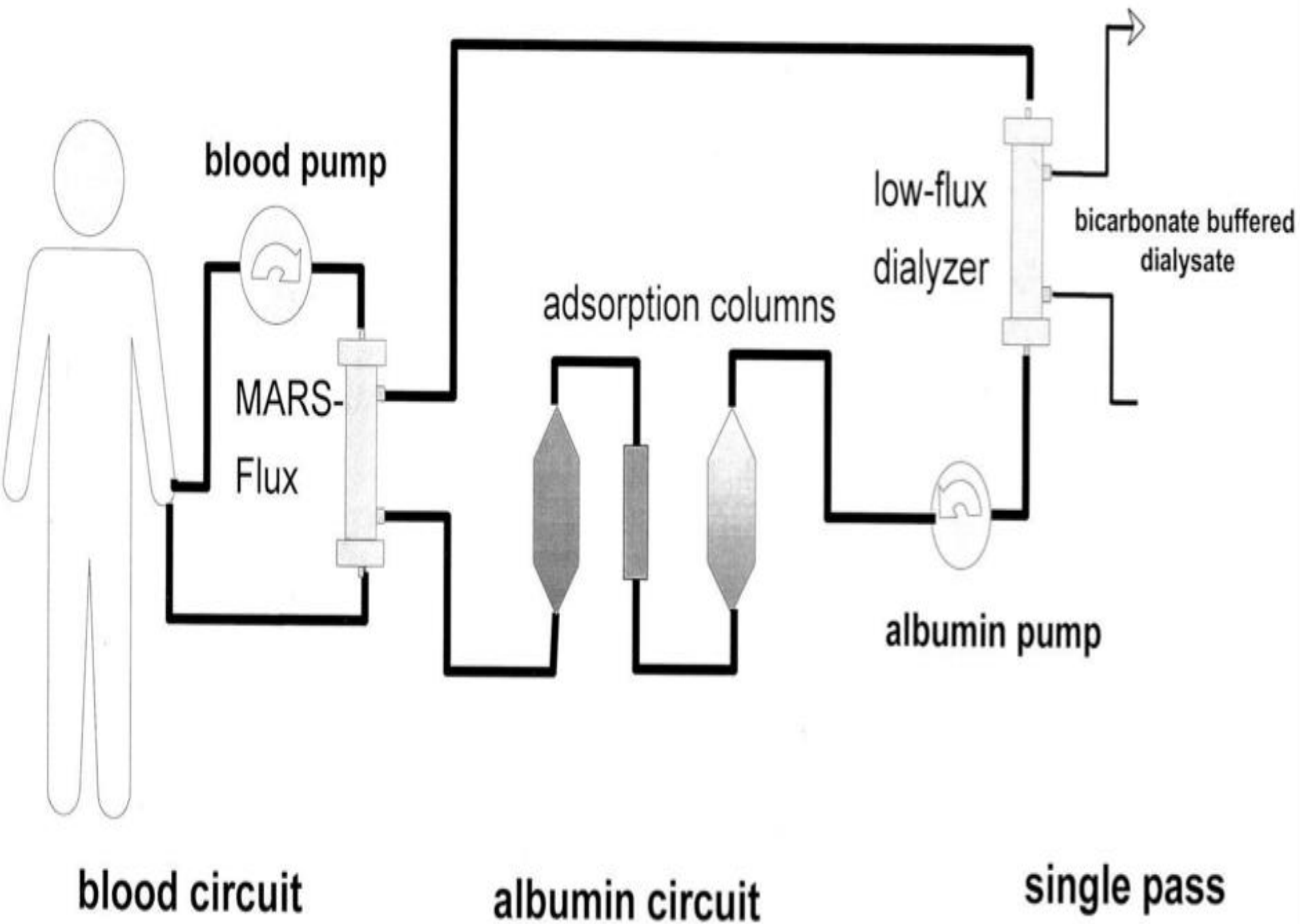
# Hemoperfusion

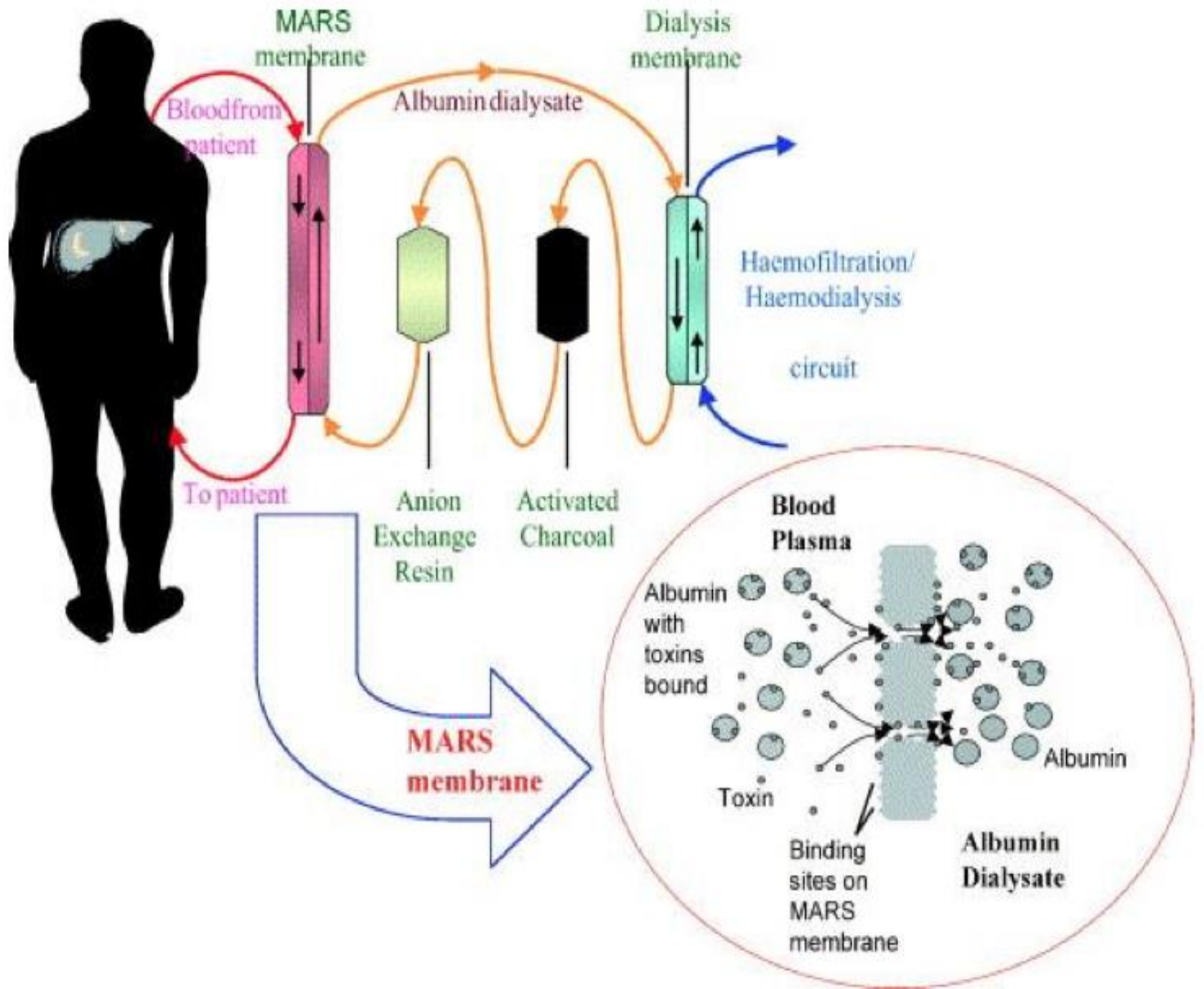




# MARS


- Molecular adsorbent recirculating system (MARS)
- Blood purification system aimed at removing albumin- bound toxins
- Three serial extracorporeal circuits: blood, albumin detoxification, hemodialysis





	Hemo-dialysis	Hemo-filtration	Hemo-perfusion
Solubility	Water	Water	Water or lipid
Molecular weight	< 500 Da	< 40 kDa	< 40 kDa
Protein binding	Low (< 80%)	Low	Low or high
Volume of distribution (Vd)	< 1 L/kg	< 1 L/kg	< 1 L/kg
Endogenous clearance	< 4 ml/min/kg	< 4 ml/min/kg	< 4 ml/min/kg
Distribution time	Short	Longer	Short

HD	CRRT	Hemoperfusion	Plasmapheresis
Lithium	Lithium	Carbamazepine	Phalloids
Ethylene glycol		Paraquat	
Methanol			
Salicylates			
Valproic acid	Valproic acid		
Metformin	Metformin		
Theophylline	Theophylline	Theophylline	



# Characteristics of toxins that affect removal

- Solute size
- Lipid solubility
- Protein Binding
- Volume of Distribution
- Blood flow rate
- Dialysate flow rate
- Dialyzer surface area
- Characteristics of the dialyzer membrane



## Ideal substances amenable to RRT

- Low molecular weight
- Water soluble
- Low protein binding (uremia shown to actually decrease protein binding of substances)
- Drug removal is limited by membrane surface area  $\times$  permeability





# Pharmacokinetics

- Absorption & bioavailability (% drug -> systemic circulation)
- Volume of distribution ( $V_d$ ) is the theoretical dispersion of the substance in the body.
  - Amount of drug in the body / concentration of the drug in plasma. Affected by obesity, ECF volume, CO, renal function, age, gender, etc. Low  $V_d$  is  $< 1$  L/kg
- Clearance is the theoretical volume of blood from which the substance is removed per unit time.
  - Native clearance depends on the ability of a molecule to pass across the GBM into the urine, a function of molecular size, charge, urine flow rate (ml / min). Solute removal is via convection (filtration) & modified by tubules.



# Case Presentation

- 70 year old Caucasian male with history of HTN, HLD, NIDDM and depression who presents after being found altered by wife after reported suicide attempt. Several empty medication bottles found at patient side. Noted to have very poor PO intake and diarrhea over the previous 3 days.
- Upon arrival patient was confused with diffuse abdominal pain – unable to give further history
- Pulse 110 Resp 28 Pulse ox 92% BP 92/62
- Ill appearing, tachycardic, non-focal exam, soft abdomen but with diffuse abdominal pain to palpation and voluntary guarding



# Case Presentation

- PH - 6.94 PCO<sub>2</sub> – 15 PaO<sub>2</sub> 98 Bicarbonate 5 meq/L
- AG 27
- Lactate 15 mmol/L
- Osmolar Gap - 6
- Noted to have AKI, SCr 2.5 mg/dL from baseline 1.1 mg/dL
- Upon speaking to wife, she found empty bottle of metformin (presumed over 20 tabs of 750 mg metformin)



# Metformin Toxicity

- Metformin is a biguanide which is the most frequently used oral antidiabetic in the world
- Toxicity in .03 per 1000 patients, far less receive extracorporeal therapy
- Associated with type B lactic acidosis (inhibits pyruvate dehydrogenase causing shift to anaerobic metabolism and therefore increased lactic acid production)

## Pathophysiological classification of lactic acidosis

<b>HYPOXIC</b>	<b>NON-HYPOXIC</b>
Ischemia	Delayed Clearance
Shock, severe anemia, cardiac arrest	Renal or hepatic dysfunction
Global Hypoxia	Pyruvate Dehydrogenase Dysfunction
Carbon monoxide poisoning	Sepsis, thiamine deficiency, catecholamine excess, alcoholic and diabetic ketoacidosis
Respiratory Failure	Uncoupling of Oxidative Phosphorylation
Severe asthma, COPD, asphyxia	Cyanide, salicylates, methanol & ethylene glycol metabolites, anti-retroviral drugs, valproic acid, biguanides, INH
Regional Hypoperfusion	Accelerated Aerobic Glycolysis
Limb or mesenteric ischemia	Increased effort, sepsis, seizures, large fructose loads, malignancies

**TABLE 1. Metformin: Physicochemical and Toxicokinetic Data**

Molecular weight	165 Da
Volume of distribution	1–5 L/kg
Protein binding	Negligible
Oral bioavailability	55%
Time to peak concentration	Immediate release: 1–3 hr  Extended release: 6–8 hr
Endogenous half-life (therapeutic use, normal GFR)	2–6 hr
Endogenous clearance (therapeutic use, normal GFR)	400–650 mL/min
Therapeutic concentration	0.5–3 mg/L
Lethal plasma concentration	> 50 mg/L
Toxic dose	> 100 mg/kg (pediatrics)  > 5 g (adults)

GFR = glomerular filtration rate.



# Metformin Dosing

- Recently changed from SCr dosing recommendations to eGFR
- Currently 18 products with metformin on the market
- Can start metformin until eGFR  $< 45$  mL/min/1.73 m<sup>2</sup>
- Will continue metformin until eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>
- Unclear evidence about dose reductions with eGFR  $< 45$



# Clinical Course

- Given profound acidemia, altered mental status and AKI decided to initiate extracorporeal therapy
- Decided on CVVHD given hemodynamics.
- Qb 300 Qd 4L/hr, continued until PH > 7.35 and lactate < 3 mmol/L
- Clinical assay for metformin not widely available or standardized
- Patient clinically improved after 36 hours of RRT and volume administration and remained off dialysis, transferred to psychiatry service





# Prevalence

- American Association of Poisonings reported 3 million human poison exposures in 2013
- Over 2000 deaths in 2013
- Some form of treatment/decontamination for over 1 million cases
- Extracorporeal therapy in about 3000 cases



## Basic/Early Management

- Enteric decontamination to prevent absorption (emetics, gastric lavage, irrigation, charcoal)
- Antidotes (naloxone, flumazenil, NAC, **fomepizole**, sodium bicarbonate, digibind, glucagon, etc)
- Supportive care and monitoring



# Ion Trapping

- Many drugs and toxins are weak acids or bases that diffuse back into tubular cells into neutral form, but are poorly absorbed as anions or cations
- Dissociation constant (pKa) determines ionization of drug
- Anionic drugs best excreted at higher urine pH and conversely cationic drugs excreted best at low urine pH
- Urine pH can convert drug to ionized form making it nonreabsorbable and give greater net excretion
  - i.e salicylate excretion quadrupled if urine pH > 7.5



# Features of severe toxicity

- Ingested quantity associated with toxic levels
- Ingestion of toxin with severe delayed effects
- Natural removal mechanism impaired
- Clinical condition deteriorating
- Clinical evidence of severe toxicity – hypotension, coma, metabolic acidosis, respiratory depression, dysrhythmias or cardiac decompensation



## Case 2

- 22 yo male with history of depression comes in after being found down at home next to bottle of anti-freeze
- Ill appearing, intubated in field
- 110/72 Pulse 110 Temp 36.7 C resp 28
- Found to have large anion gap (22) and oliguric AKI
- Osmolar Gap 35
- ETOH level 0
- Ethylene glycol level pending

# Urine Microscopy





# Ethylene Glycol

- Dialysis indications:
  - Severe metabolic acidosis, pH < 7.2
  - AKI with electrolyte imbalances that are medically refractory
  - Unstable hemodynamics
  - EG level > 50 mg/dL (unless fomepizole is administered and patient is asymptomatic with normal pH)
- Can also help metabolism of toxic metabolites to nontoxic byproducts with pyridoxine (B6) and thiamine (B1) (promotes conversion of glyoxilic acid to glycine rather than oxalate)



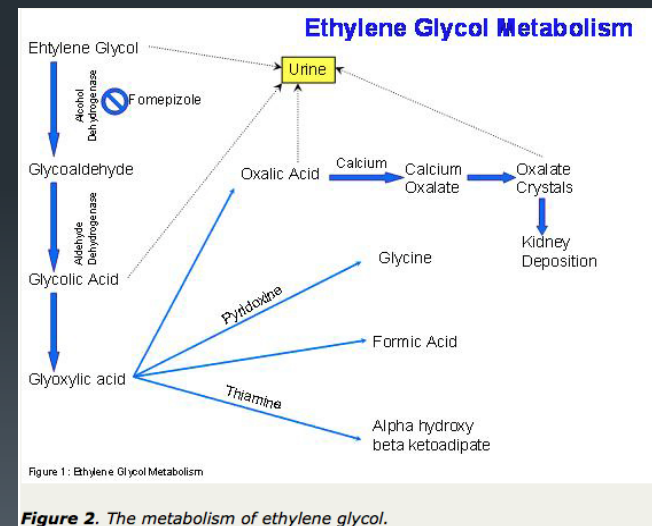
# Ethylene Glycol

- HD until the level is  $< 20$  mg/dl or without a level, recommend HD x 8+ hrs repeated BID
- Glycolic acid has long half-life and slow elimination rate but also low MW (76 Da), water-soluble, and low  $V_d$  (0.55 L/kg)
- Therefore, a low EG level with increased AG denotes high glycolic acid levels and therefore should perform HD



# Ethylene Glycol

- Mechanism of AKI is through toxic metabolites causing calcium oxalate precipitation throughout renal cortex (and other tissues throughout body)
- Can cause clinically significant hypocalcemia





## Case Continued

- Patient with 2 6-hour dialysis sessions
- Moved to ICU for management
- Improved metabolic acidosis and mental status
- Improved renal function to baseline within 4 days
- Admitted 3 months later with recurrent intoxication and unfortunately passed away.
- EG level > 200 mg/dL at time of death



# Fomepizole (4-methyl-pyrazole)

- Blocks metabolism of alcohols to their toxic metabolites (alcohol dehydrogenase = AD) just like ethanol does
- Has > 8000 fold higher affinity for AD than EG, > 800 than EtOH
- Recommended use:
  - Ingestion of alcohol, concentration > 20 mg/dl
  - Recent ingestion with osmolar gap > 10 mOsm/L
  - Strong clinical suspicion of ingestion of alcohol and 2 of the following: arterial pH < 7.3, tCO<sub>2</sub> < 20, osmolar gap > 20 mOsm/L (or urinary oxalate crystals if ethylene glycol)
- Loading dose (10-15 mg/kg), 10 mg/kg q12hrs x 4 doses, then 15 mg/kg q12hrs until EG < 20, asymptomatic, normal pH
- Most effective prior to onset of AG metabolic acidosis
- Dialyzable so will need to be dose adjusted

# Metabolism of the Alcohols

Ethylene glycol  
"antifreeze"



Glycoaldehyde



**Glycolic acid**



Glyoxylic acid



**Oxalic acid**

Methanol  
"wood alcohol"



**Formaldehyde**



**Formic acid**

**Ethanol**



Acetaldehyde



Acetate

**Isopropanol**  
"rubbing alcohol", "antifreeze",  
windshield, de-icing



Acetone

Toxic alcohols & **toxic metabolites**.  
AD = alcohol dehydrogenase)



# Methanol

- Fatal intoxicant that may be ingested, inhaled or absorbed through skin
- Presents with inebriation and stupor – osmolar gap may be present
- If very high levels may need HD x 18-21 hours, repeated q24hrs if there is rebound toxicity.
- Avoid heparin given risk of ICH, particularly basal ganglia.
- Folate (folinic acid) helps increase the metabolism of formic acid to  $\text{CO}_2 + \text{H}_2\text{O}$ .
- Fomepizole for levels  $< 20$  mg/dL may be sufficient
- Dialysis for levels  $> 50$  mg/dL



# Isopropyl Alcohol

- De-icing solvents, cleaning products, hand sanitizer
- Large osmolar gap, less likely anion gap unless hypotension and type A lactic acidosis
- Toxic metabolites are not of principal concern as with ethylene glycol and methanol
- Fomepizole can inhibit metabolism of isopropyl ETOH to acetone
- Hemodialysis indicated when levels > 400 mg/dl or CNS depression



# Propylene Glycol

- Commercially sold as coolant
- Iatrogenic administration with prolonged IV administration of lorazepam (also seen with valium, phenytoin, penobarbital, etomidate)
- Causes ATN
- Large osmolar gap noticed
- Hemodialysis with refractory acidosis
- Can efficiently remove propylene glycol



<b>Drug (MW)</b>	<b>Toxic level</b>
Methanol (32)	>50
Ethanol (44)	>400
Ethylene glycol (62)	>25
Isopropanol (100)	>350





# Osmolar Gap

- Calculated Osm - Measured Osm =  
Osmolar gap  
Measures Osm =  $2 (\text{Na}) + \text{Glu} / 18 + \text{BUN} / 2.8$   
Significant OG if  $> 15$  mOsm/L  
Can correct for ethanol:  $\text{EtOH level} / 4.5$

# Salicylates

- Dialysis indications:
  - CNS depression at level  $> 50$  mg/dl
  - Salicylate level  $> 80$  mg/dl
  - Salicylate-induced pulmonary edema • Continue HD until level  $< 10$  mg/dl
- Pharmacokinetics
  - MW = 38-180 Da
  - Vd = 0.17 L/kg (? Enteric coated ASA)
  - At therapeutic levels, 90% salicylates are protein-bound, but unbound % increases as the total concentration increases
- 50% protein-bound drug is removed with IHD
- Should supplement with decontamination (activated charcoal and urinary alkalinization)



# Barbiturates

- Overdose initially treated through supportive measures – decontamination
- High flux hemodialysis and hemoperfusion both are effective with extracorporeal drug clearance
- Urinary alkalization to pH 8



## Case 3

- A 32 year old woman ingested 20 lithium carbonate 300 mg tablets in a suicide attempt
- She is drowsy and her speech is slurred
- Her serum  $\text{Li} = 6 \text{ mEq/L}$
- BP 110/78 Pulse 76 Resp 28 Pox 98%



# Lithium Toxicity

- Alkali metal (like Na, K)
- Widely used for bipolar disorder
- Therapeutic range 0.6-1.2 mEq/L
- Toxicity = mainly CNS
  - Tremor, slurred speech, muscle twitching
  - Confusion, delirium, seizures, coma
  - Recovery may take weeks
- Toxicity may occur as a result of *acute* overdose or *chronic* use



# Lithium Toxicity

- Sodium polystyrene can be used as exchange resin to enhance lithium elimination
- Clearance increased with volume expansion, loop diuretics and interruption of distal reabsorption with amiloride or triamterene
- Levels can rebound due to high volume of distribution, dialysis with CNS symptoms and level  $> 2.5$ , asymptomatic and level  $> 4$  also can warrant extracorporeal treatment



# Lithium

- Completely absorbed orally
  - Volume of distribution approx 0.8 L/kg
  - Slow entry into CNS
  - Initial serum levels do NOT reflect brain levels
- Eliminated entirely by the kidneys
  - Half-life 14-20 hours
  - Prolonged in patients with renal insufficiency
  - Promoting saline excretion hastens Li removal



# Lithium

- Acute:
  - High levels, drops rapidly
  - Absent symptoms
- Chronic:
  - Often associated w/ renal insufficiency, DI
  - Occurs gradually
  - Symptoms more severe, even with lower levels (eg, 2 - 2.5 and above)





# Dabigatran

- Oral direct thrombin inhibitor
- Small (471 Da), lipophilic molecule (large Vd), 35% protein bound, > 80% renally cleared.
- No effective reversal agent
- Case reports:
  - • NYU: 80 y/o male, hemoptysis, s/p 2 units FFP, INR 7-8. HD x 1, and level went from 1100 -> 18 ng/ml over 4 hrs, rebounded to 100ng/ml 20 minutes after HD. No further bleeding.
  - • UC-Davis: 94 y/o male, fall, large SDH with midline shift, alert but hesitant for invasive NSx procedure. INR 1.5. Level 312 ng/ml. HD x 1, level fell to 29, rebounded to 43.



# Other Medications

- Theophylline
- Procainamide
- MTX
- Valproic Acid
- Amanita Mushrooms
- Carbamazepine



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